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THE SYNTHESIS AND PROPERTIES OF [1,2,3]TRIAZOLO[1,5-a]PYRIDINES.

a thesis submitted to the University of Keele
in part fulfilment of the requirements for
the Degree of Doctor of Philosophy

by

Drago. R. Sliskovic

Department of Chemistry
University of Keele
Staffordshire

September 1982

To my Parents.

"Ako mu Vi to pravo ne date i toga ne priznate, narod će si tu prilikue i to pravo dati sam bez Vas i protive Vas." .....

.... STJEPHAN RADIĆ (1918).

The work in this thesis, unless otherwise stated, was carried out by the author under the supervision of Dr. G. Jones.

Contents

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Abstract

Chapter one describes the electrophilic substitution reactions of [1,2,3]triazolo[1,5-a]pyridine, and the reactions in which nitrogen extrusion are characteristic. It also describes the attempts to functionalise the pyridine ring. A review on the synthesis and properties of triazolopyridine is also presented.

Chapter two describes further efforts to functionalise the pyridine ring of the triazolopyridine molecules by the use of directed lithiation reactions. The 7-lithiotriazolopyridine derivative was found to react with a variety of electrophiles to produce 7-substituted triazolopyridines. Bromination of these compounds provided a convenient route to 2,6-disubstituted pyridines, and possibly bipyridyls. Introduction of a second lithium directing group led to some competitive lithiation studies. The N,N-diethylamide group was introduced to position 3 and the methoxy group at position 5. Pertinent reviews on directed lithiation reactions of similar heterocyclic systems and on the synthesis of 2,6-disubstituted pyridines and bipyridyls are also presented.

Chapter three describes attempts to apply directed lithiation reactions to other fused [1,2,3]triazole systems, namely the triazolo-[1,5-a]pyrazine and triazolo[1,5-c]pyrimidine systems.

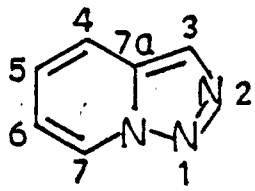
Chapter four discusses the spectral properties of the 3- and 7-substituted triazolopyridines. Carbon-13 resonance assignment studies were undertaken on triazolopyridine, all resonances but those due to C4 and C6 have been assigned. The mass spectral fragmentation patterns of certain triazolopyridin-7-yl methanols were investigated. Some showed a new fragmentation pathway involving loss of HCN and NO, rather than the more usual loss of nitrogen.

CHAPTER ONE

SYNTHESIS AND REACTIONS OF [1,2,3]TRIAZOLO[1,5-a]PYRIDINE

(1.1) Introduction

The [1,2,3]triazolo[1,5-a]pyridine ring system (1) has not been extensively studied. This is in direct contrast to the [1,2,4]triazolo[4,3-a]- (2) and [1,2,4]triazolo[1,5-a]pyridine (3) systems. These ring systems are shown along with their numbering systems in (Scheme 1.1).



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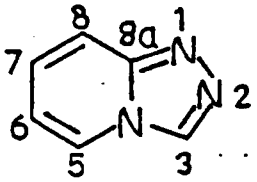

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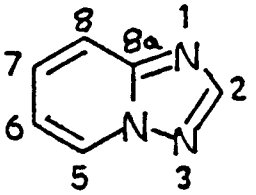


(3)

Scheme 1.1

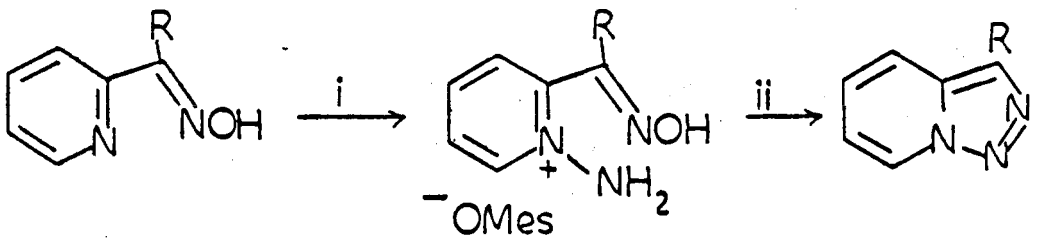
Review literature on the triazolopyridines (1)-(3) is scarce, there has only been one review[1] dealing with systems (1)-(3), up to 1961, however a much more comprehensive review covering all triazolopyridines is in the press.[2]

(1.2) Review of [1,2,3]triazolo[1,5-a]pyridines

(1.2a) Synthesis of [1,2,3]triazolo[1,5-a]pyridines

A. Formation of the five-membered ring by the forming of one bond

There are no syntheses in which the bond is formed between the positions 2 and 3. Cyclisation of the N-amino-pyridinium oxime mesylates (4) by polyphosphoric acid gives good yields of 3-substituted triazolopyridines (5).[3] (Scheme 1.2)

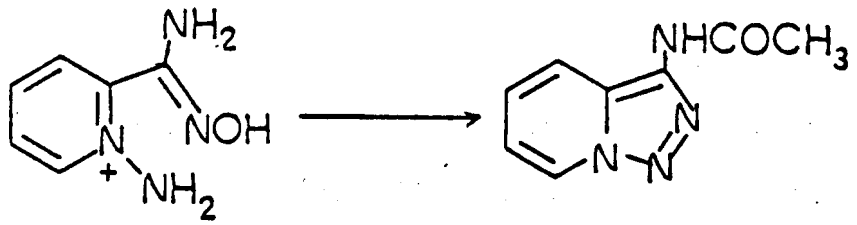


Mes = mesityl (4) (5), R=H, Me or Ph

(i) O-mesitylinesulphonylhydroxylamine (MSH)

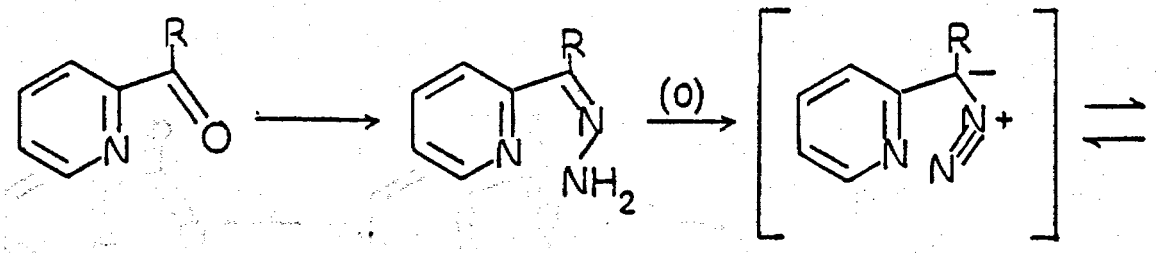
(ii) Polyphosphoric acid, 70-110°C. Scheme 1.2

The related amidoxime (6) is cyclised by acetic anhydride to give 3-acetylaminotriazolopyridine (7).[4]



(6) (7)

The majority of [1,2,3]triazolo[1,5-a]pyridines have been prepared by closure between a pyridine nitrogen atom and a side chain nitrogen (bond 7a-1), making use of the observation that the equilibrium (8) ⇌ (1) is almost completely displaced to the right. The most straightforward route involves some oxidation of the hydrazone of a 2-pyridyl carboxaldehyde or ketone as shown in Scheme 1.3. Thus for the production of the parent heterocycle (1), the hydrazone of pyridine-2-carboxaldehyde is oxidised by silver oxide[5] or potassium ferricyanide.[6] Nickel peroxide[7,8] and manganese dioxide[9] have also been used to produce 3-substituted triazolopyridines (5). Some doubt is cast on the intermediacy of the simple diazonium salt (8), since attempts to diazotise 2-aminomethylpyridine gave only 2-hydroxymethylpyridine.[5]



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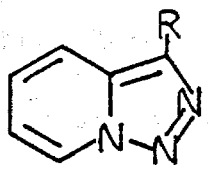
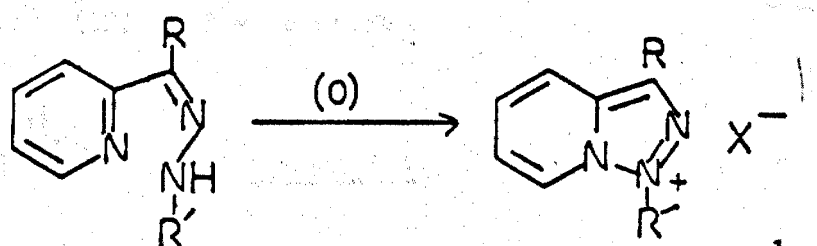


(1) R^1 = H

(5) R^1 = Me, Ph

Scheme 1.3

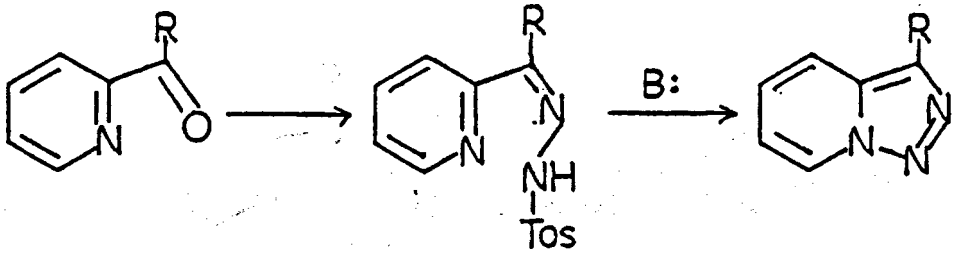
If an N-substituted hydrazone is used, the quaternary 1-substituted triazolopyridinium salt (9) is produced. Such oxidations have been performed with lead tetraacetate[10], N-bromo-succinimide[11], or electrochemically[12]. A further variant on this



(9) R^1 = Me, Ph

R^2 = Ph, Ph

synthesis makes use of tosylhydrazones (10), which on treatment with a base (aqueous alkali[13], morpholine[14], sodium ethoxide[15]) gave the triazolopyridines (5) and (11).

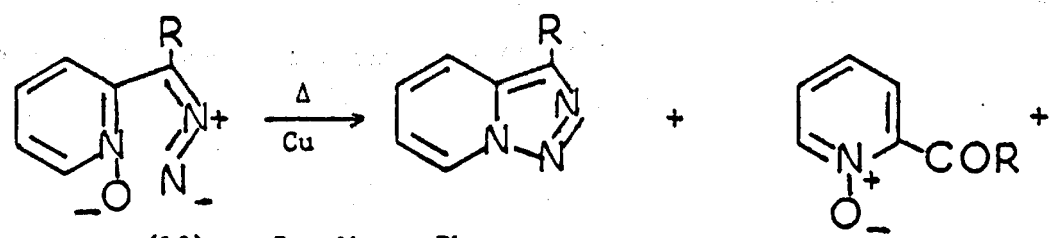


Tos = Tosyl (10) (5) R = H, Ph

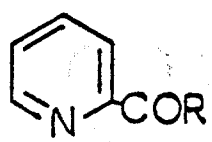
(11) R = 2-pyridyl

It has been shown that heating or irradiating such tosylhydrazones in basic media gives triazolopyridines[16].

Pyridyldiazoalkane N-oxides (12) give triazolopyridines among other products when pyrolysed, with or without copper catalysis[17]. (Scheme 1.4).



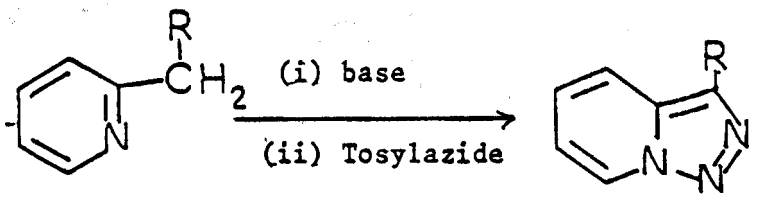
(12) R = Me or Ph



Scheme 1.4

B. Formation of the five-membered ring by forming two bonds

Regitz has shown[18,19] that diazo groups can be directly introduced at active methylene positions under basic conditions using tosyl azide as the source of the diazo group. Substituted 2-methylpyridines (13) are sufficiently activated to undergo such diazo group transfers. Thus have been prepared a number of 3-acyltriazolo[1,5-a]pyridines (14) and the phosphine oxide (15). In most cases a sodium alkoxide has been used as the base. In the synthesis of 3-cyanotriazolopyridine (16), the diazo group was derived from 2-azido-3-ethylbenzthiazolium tetrafluoroborate[20].



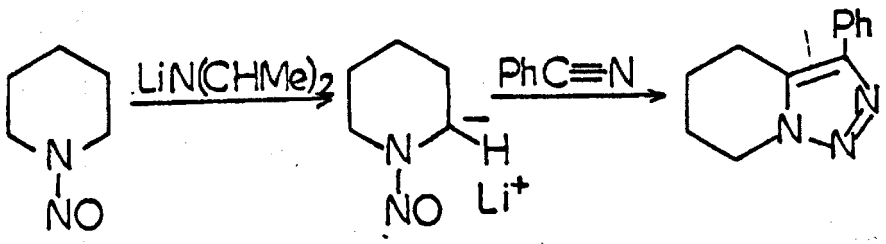
(13) (14) R = Pr^nCO, Bu^tCO, PhCO, 2-furyl

(15) R = $P(O)(Ph)_2$

(16) R = CN

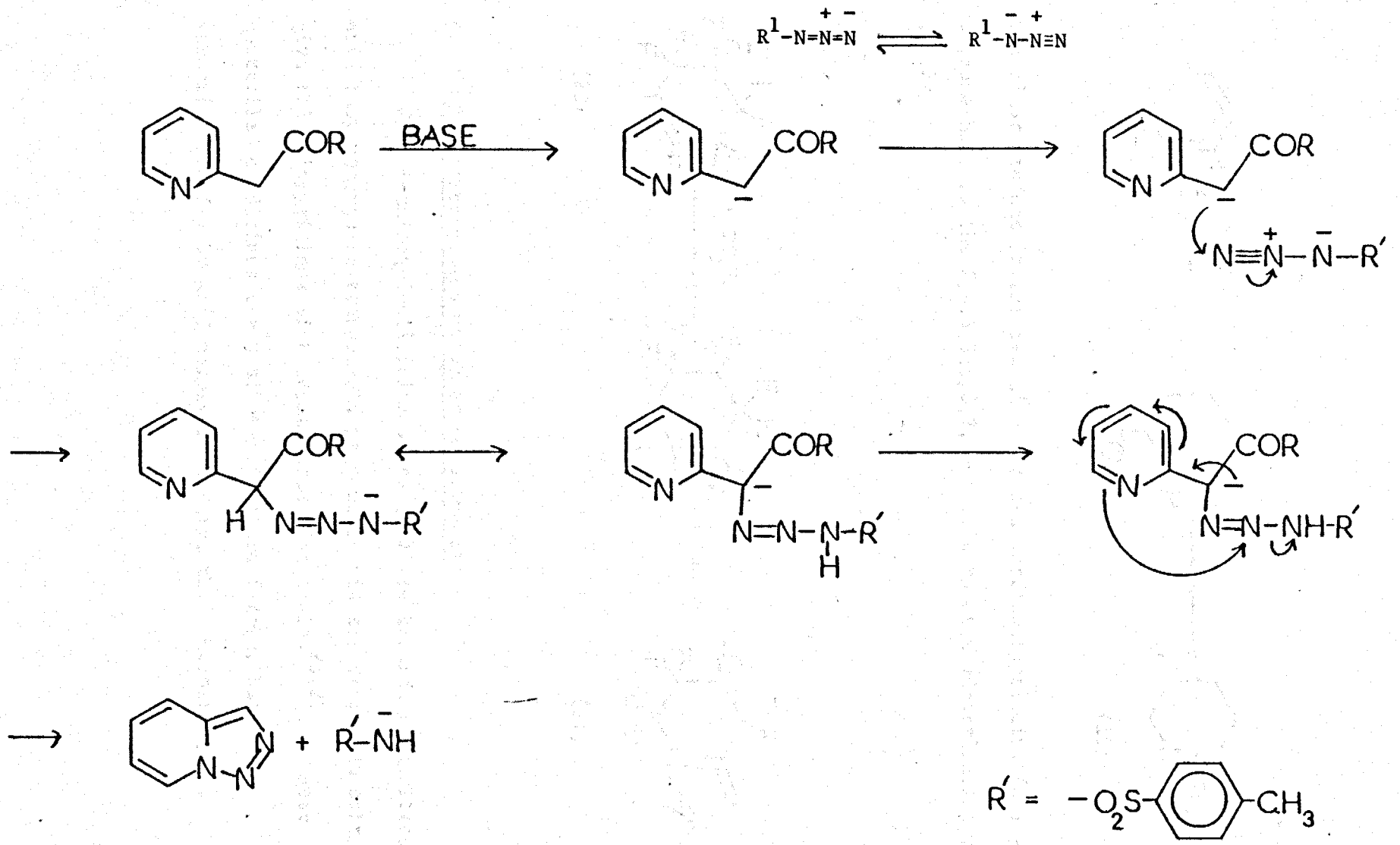
The mechanism is shown in scheme 1.5

Three methods for making 4,5,6,7-tetrahydrotriazolopyridines involve the formation of the triazole ring from two fragments.. The lithium derivative of N-nitrosopiperidine (17) reacts with benzonitrile to give the 3-phenyl derivative (18)[21].

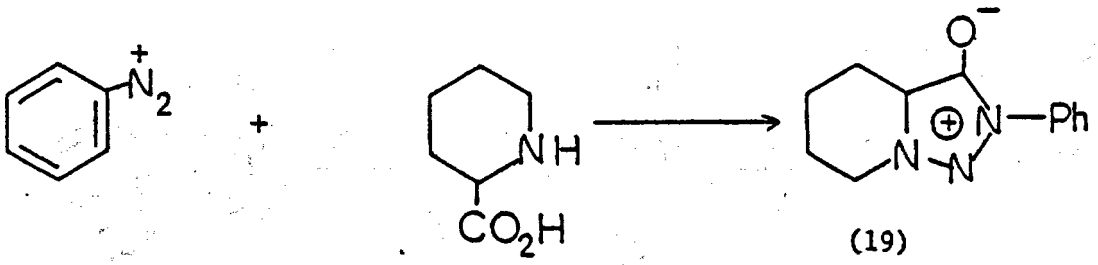


(17) (18)

Diazonium salts react with α-aminoacids to give mesoionic triazole oxides; if pipecolic acid is used the product is a tetrahydrotriazolopyridine oxide (19)[22,23].

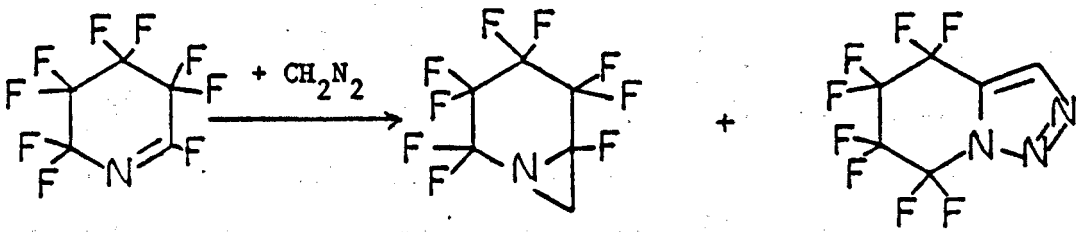


Scheme 1.5



(19)

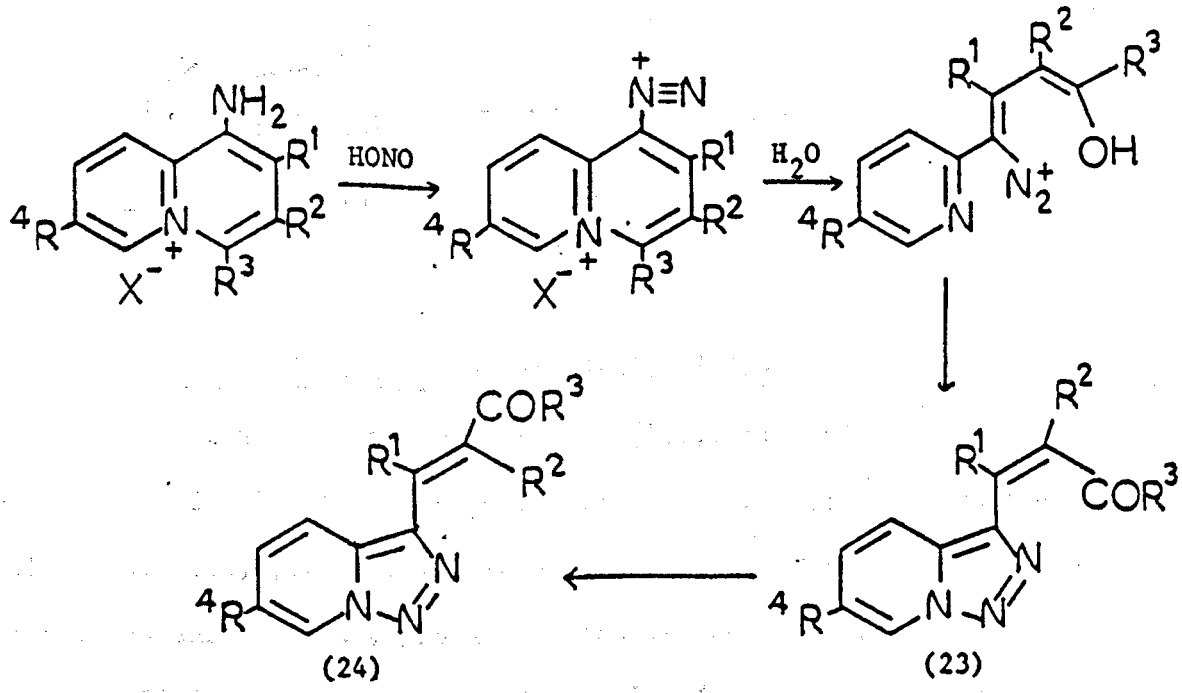
The minor product in the reaction between perfluoropyrideine (20) and diazomethane is the 4,4,5,5,6,6,7,7-octafluorotetrahydrotriazolopyridine (21)[24].



(20) (21)

C. By rearrangement of other heterocycles

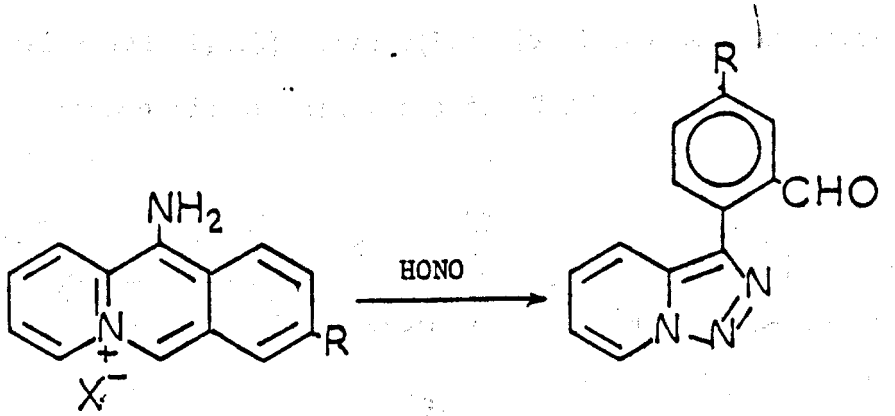
When 1-aminoquinolizinium salts (22) are treated with nitrous acid they undergo rearrangement, presumably via the diazonium salt to give triazolopyridines with unsaturated side chains[25,26]. Under controlled conditions the Z alkenes (23) are formed, but these isomerise rapidly by acid catalysis to give the E isomers (24).



(24) (23)

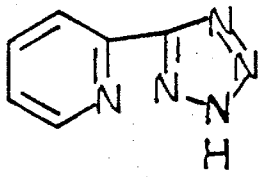
R^1 H, H, Br, ^{2}H, H, H
R^2 H, Me, Me, ^{2}H, Me, Me
R^3 H, H, H, Me, Co_2Et, H
R^4 H, H, H, H, H, Me

In a similar reaction the aminobenzo[b]quinolizinium salts (25) give 3-(2-formylphenyl)triazolopyridines (26)[27].



(25) (26) R = H, OMe

Flash vacuum pyrolysis of 5-(2-pyridyl)tetrazole (27) gives triazolopyridine (1) in low yield, presumably via the diazoalkane[28].

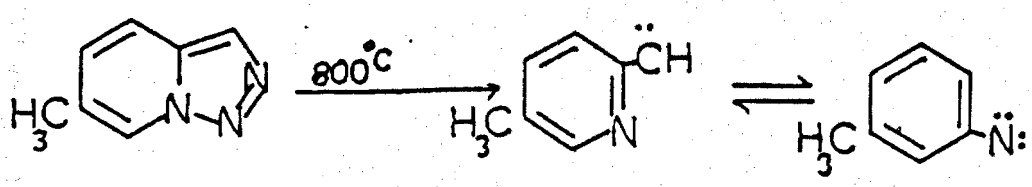


(27)

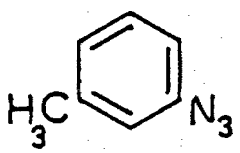
Compound (1)

(1.2b) Reactions of [1,2,3]triazolo[1,5-a]pyridine

Most of the reactions reported of [1,2,3]triazolo[1,5-a]pyridines involve loss of molecular nitrogen. Crow and Wentrup[29] report the pyrolysis of [1,2,3]triazolo[1,5-a]pyridine at 500°C to yield aniline (4%) and azobenzene (77%), products which are characteristic of phenyl nitrene. Similarly the 6-methyl derivative (28) gave m-toluidine and 3,3'-dimethylazobenzene. At 800°C the reaction products were very similar to those from the violent pyrolysis of m-tolyl azide (31). Thus 2-pyridyl carbene (29) was thermally interconverted to phenylnitrene (30). This was confirmed by the fact that the mass spectra of phenyl azide and [1,2,3]triazolo[1,5-a]pyridine were identical suggesting a common set of structures for $C_6H_5N^*$.

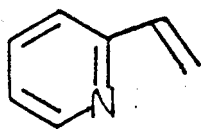


(28) (29) (30)



(31)

Pyrolysis of 3-methyl-[1,2,3]triazolo[1,5-a]pyridine at 800°C also resulted in loss of nitrogen and gave a quantitative yield of 2-vinylpyridine (32), while the corresponding phenyl derivative isomerised thermally at 500°C to give carbazole (33).



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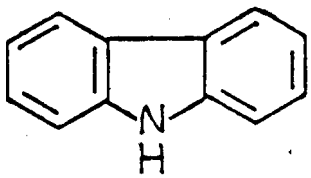


(33)

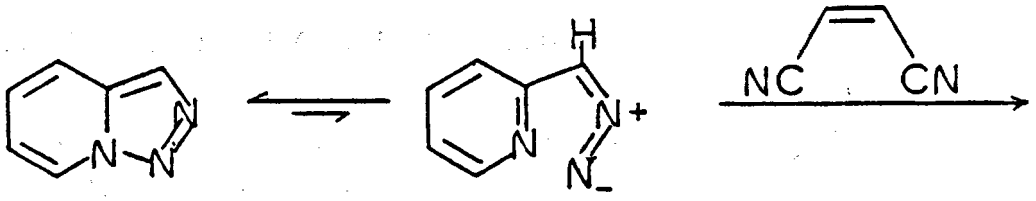
Wentrup has since expanded on this work in an effort to determine the mechanism for phenylnitrene ↔ pyridylcarbene interconversion[30-33]. Chapman and coworkers[34-35] have devoted much effort to the study of 1-aza-1,2,4,6-cycloheptatetraene (34), which is thought to be the key intermediate in the pyridylcarbene ↔ phenylnitrene interconversion.

(34)

Thermolysis of 3-phenyl[1,2,3]triazolo[1,5-a]pyridine and other substituted phenyl derivatives (substituents include Me, MeO, Cl, NO_2 and CN) gave carbazoles in yields up to 100%[36].

Wentrup[28] has presented evidence for the valence tautomeric equilibria of (1) with the diazomethylpyridine (8). [1,2,3]Triazolo-[1,5-a]pyridine (1) decomposed in diphenyl ether solution in the temperature range of 180-220°C. The rate of nitrogen evolution followed first order kinetics. When the decomposition of compound (1) was carried out in the presence of fumaronitrile, 3-(2-pyridyl)-1,2-cyclopropanedicarbonitrile (36) was isolated in 32% yield as a mixture of

two geometric isomers. The mechanism shown is consistent with the observations. The concentration of (8) was too low for direct



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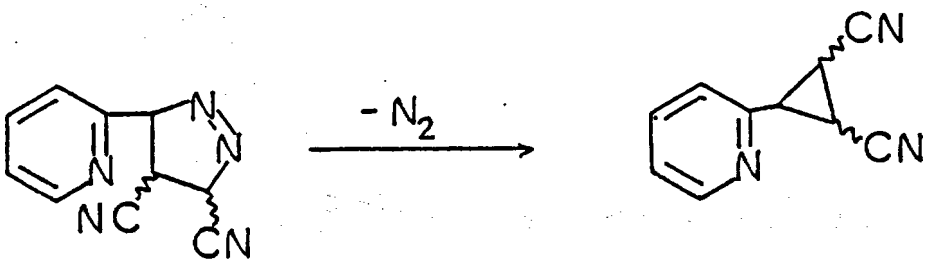
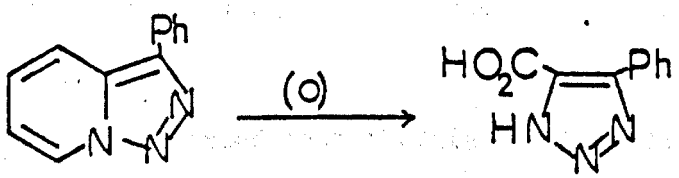


(35) (36)

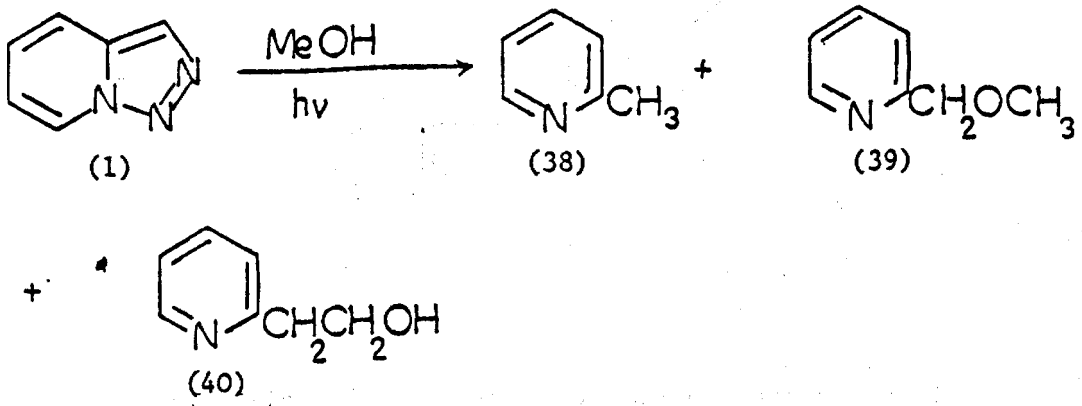
detection, a 1,3 dipolar cycloaddition of compound (8) to fumaronitrile would be rapid at the reaction temperature. The resulting 1-pyrazoline (35) decomposed under the reaction conditions yielding the observed product (36). Since the reaction shown is faster than the decomposition of compound (1) in the absence of fumaronitrile, a carbene route can be excluded.

Reimlinger and co-workers[15] have reported the oxidative degradation of 3-phenyl-[1,2,3]triazolo[1,5-a]pyridine (5, R = Ph) to 4-phenyl-[1,2,3]triazole-5-carboxylic acid (37).



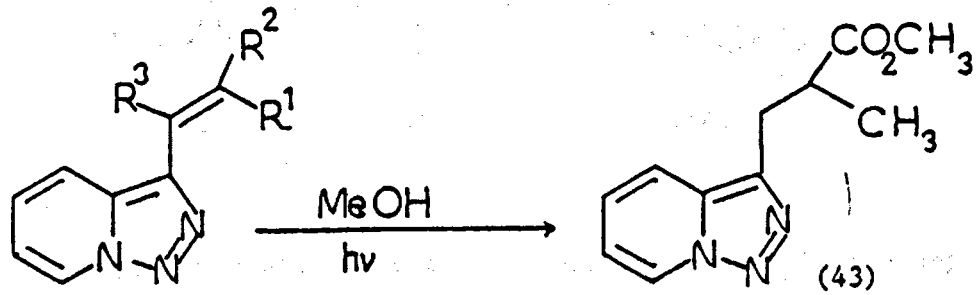
(5) (37)

The irradiation of [1,2,3] triazolo[1,5-a] pyridine (1) in methanol[37] or acetic acid[38] was found to yield 2-methylpyridine (38) and its derivatives (39) and (40) in low yield.



(1) (38) (39) (40)

Jones and Davies[39-40] have found that some 3-(triazolopyridyl) acraldehydes add methanol in high yield to give the corresponding propionates when irradiated through quartz or pyrex. Irradiation of either the E (41) or Z (42) acraldehyde gave the same product (43).



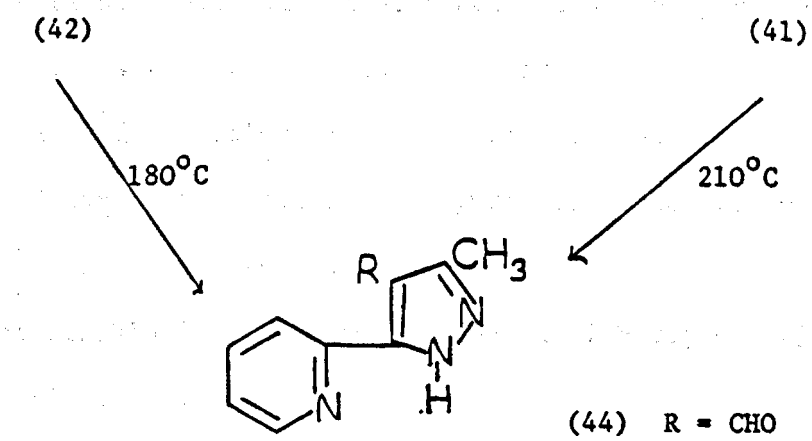
(43)

(41) R^1 = Me, R^2 = CHO R^3 = H

(42) R^1 = CHO, R^2 = Me, R^3 = H

Other hydroxylic solvents such as water and t-butylalcohol also added to the acraldehydes giving the corresponding propionic acid or t-butyl ester.

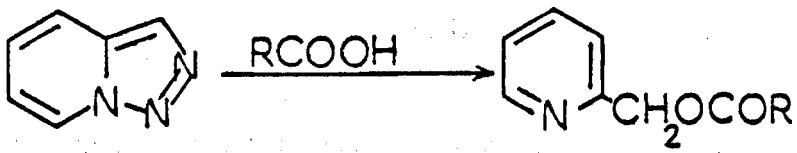
It has also been reported that the cis acraldehyde (42) undergoes thermal rearrangement to 3-methyl-5-(2-pyridyl)pyrazole-4-carbaldehyde (44); 3-methyl-5-(2-pyridyl)pyrazole (45) is also produced. The trans acraldehyde (41) gives only the pyrazole (45)[41-42].



(44) R = CHO

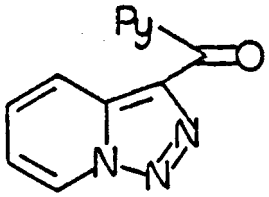
(45) R = H

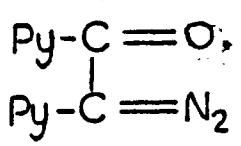
In carboxylic acids, cleavage occurs on heating (70–100°C) yielding esters of the corresponding 2-pyridylcarbinols (46)[43].



(1) (46)

Triazolopyridines with electron withdrawing groups in the 3-position, for example 3-(2-picolinoyl)-[1,2,3]triazolo[1,5-a]pyridine (47), were found to be resistant to the attacks of carboxylic acids[44]. Bromine, iodine or boiling aniline transformed compound (47) into (48) which further reacted with elimination of nitrogen to give dihaloketones or di(2-pyridyl)acetanilide.

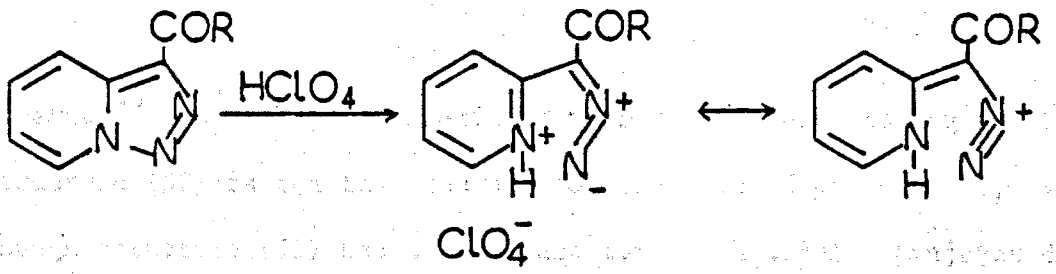




(47) (48)

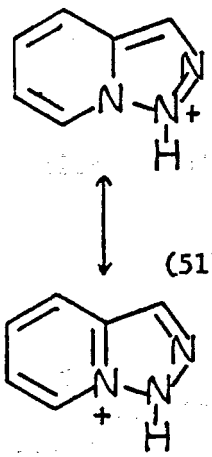
Py = 2-pyridyl

Regitz has reported[45] that treatment of 3-acyl-[1,2,3]triazolo-[1,5-a]pyridines (49) with perchloric acid in dioxan resulted in ring cleavage and led to yellow-orange perchlorates of the diazo stage (50) which could not be isolated in the synthetic procedure involving diazo group transfer to the ketones (see page 4). The salts were cyclised by loss of perchloric acid even in ethanol with regeneration of the triazolopyridines (49).

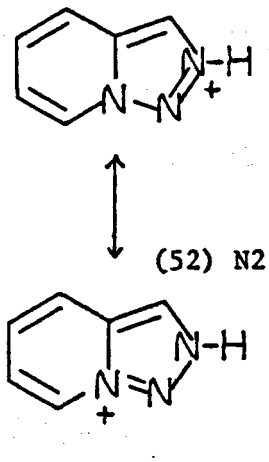


(49) (50)

With aqueous silver nitrate [1,2,3]triazolo[1,5-a]pyridine (1) gives a silver salt complex[6] and with methyl iodide it gives a methiodide[6]. Protonation with dilute acid[43] gave a stable conjugate acid. It can be seen that protonation can take place on either of the two non-bridgehead nitrogen atoms : (1) can form two possible cations (51) or (52).



(51) N1 Protonation

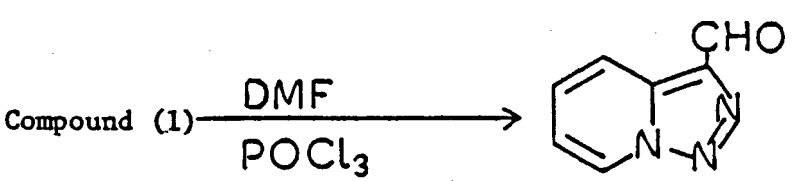


(52) N2 Protonation

Armarego[46] has used pK_a comparisons with diazaindenes to suggest that structure (52) is the favoured one for the site of protonation, even though structure (51) has a resonance form with a fully conjugated pyridine ring.

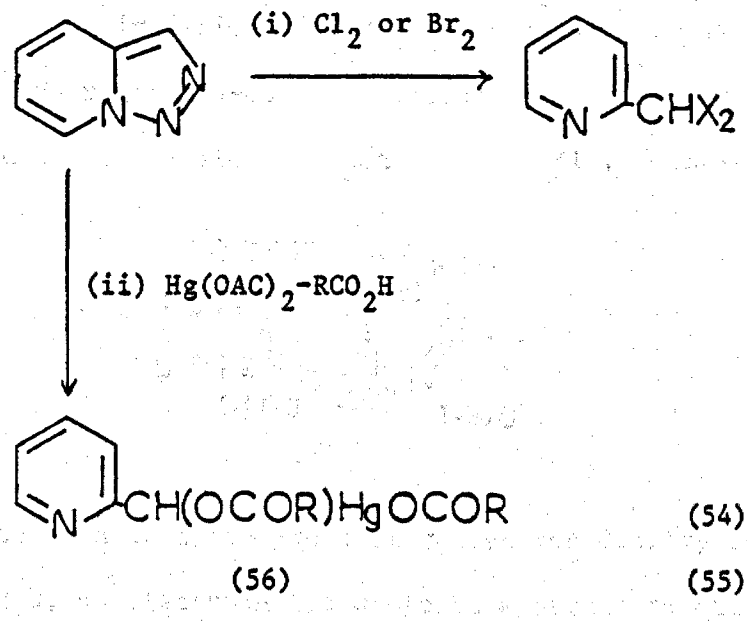
There have only been two recorded cases of a simple substitution of the [1,2,3]triazolo[1,5-a]pyridine ring system (1).

Heating (1) in D_2O solution above 100°C caused exchange of H3 for deuterium[28]. On long exposure, a slower exchange of H7 was also observed. The authors suggest that the exchange of the triazole ring proton may take place via the (diazomethyl)azines, or by a carbanion mechanism in the triazoles themselves. Exchange of the six-ring protons probably occurs via a carbanion mechanism. Vilsmeier-Haack formylation gave the 3-formyl derivative (53) in 8% yield.[26]



(53)

Triazolopyridine (1) also reacts with chlorine and bromine to give the dihalomethylpyridines (54) and (55). Reaction with mercuric acetate in glacial acetic acid gave the substituted mercuriacetate (56). These reactions were carried out as undergraduate projects at this university and they will be discussed in more detail in the next section.



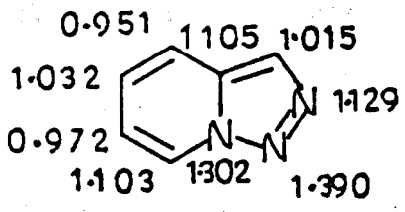
(56)

(54) X = Cl

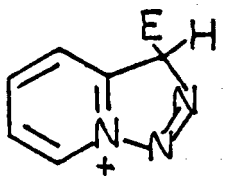
(55) X = Br

Discussion

The bulk of this chapter deals with the reactivity of the triazolopyridine nucleus, with reactions with electrophiles and with attempts to increase the reactivity of positions on the nucleus. [1,2,3]Triazolo[1,5-a]pyridine can be synthesised in many ways. The method used in the course of this research involves oxidation of the hydrazone (or tosylhydrazone) of pyridine-2-carboxaldehyde with potassium ferriycyanide[6] (or morpholine)[14]. The yields obtained were in the region 75-80%. Galasso[47] has used the SCF-LCAO-MO method to calculate the π electron densities of (1). These are as shown.



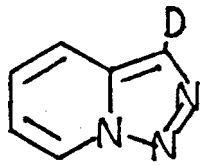
It can be seen that the greatest π electron density occurs at positions 7, 5 and 3, so electrophiles would be expected to attack these positions. However, consideration of the valence tautomers available for this molecule, in the attack of an electrophile, shows that position 3 would be the preferable side of attack, structure (57) has a fully conjugated pyridine ring which confers greater stability.



(57)

Experimental results agree with this observation. As mentioned in the Introduction, triazolopyridine undergoes Vilsmeier-Haack formylation to yield the 3-formyl derivative[26]. Base catalysed hydrogen-deuterium

exchange occured on heating with D_2O at 100°C to yield the 3-deuterio derivative (58).[28]

Compound (1) $\xrightarrow[\text{Sealed tube}]{100^\circ C/D_2O}$ 

(58)

Attempts to repeat these experiments under acid catalysis were not successful. Deuterium chloride and deuteriosulphuric acid (D_2SO_4) were used at various temperatures (40–100°C) and reaction times (30 mins → 4 days). The reaction was followed by n.m.r. spectroscopy. No reduction in the size of the singlet due to H3 at δ8.0 ppm was observed, however it was moved downfield (as were all other signals) and appeared at δ9.0 ppm. Obviously either N1 or N2 of the triazole ring was being deuterated. When dry hydrogen bromide gas was passed into a cooled solution of triazolopyridine, the hydrogen bromide salt of triazolopyridine was deposited. The n.m.r. was identical to those mentioned previously. Armarego[46] has used pK_a considerations to suggest that protonation occurs on N2. By running the spectrum in trifluoroacetic acid (a strong protonating medium) a spectrum identical to those above was obtained, and by shaking the sample with sodium bicarbonate, regeneration of triazolopyridine was achieved.

Many attempts to repeat the Vilsmeier-Haack formylation of triazolopyridine failed. A variety of conditions were used including:

(1) Mixing of the DMF and $POCl_3$ at room temperature and refluxing after addition of triazolopyridine[48]

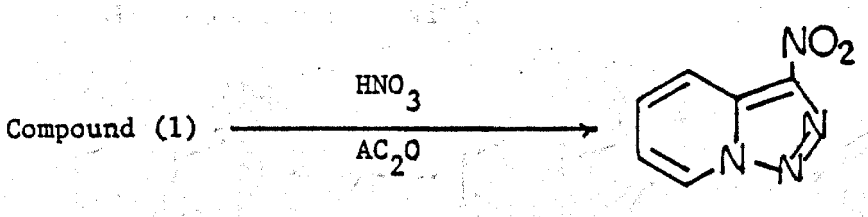
(2) Addition of finely divided calcium carbonate after addition of triazolopyridine, followed by refluxing[26]

(3) Mixing of the DMF and $POCl_3$ at 0°C.

(4) By using a modified Vilsmeier reagent.

N-formyl morpholine was prepared[52] and was used in place of dimethylformamide. Rate enhancement with unreactive substrates has been reported[52]. In all cases triazolopyridine was recovered.

Nitration gave 3-nitrotriazolopyridine (59). The reagent was a mixture of fuming nitric acid with acetic anhydride and the temperature was kept below 10°C. The position of the nitro-substituent was easily established by the ^1H n.m.r. spectrum which showed only four signals at δ7.4 (dd, J6.5 and 7 Hz, H-6), 7.9 (dd, J7 and 9 Hz, H-5), 8.5 (d, J9 Hz, H-4) and 8.95 p.p.m. (d, J6.5 Hz, H-7). These coupling constants compare well with those recorded for the parent triazolopyridine[28].

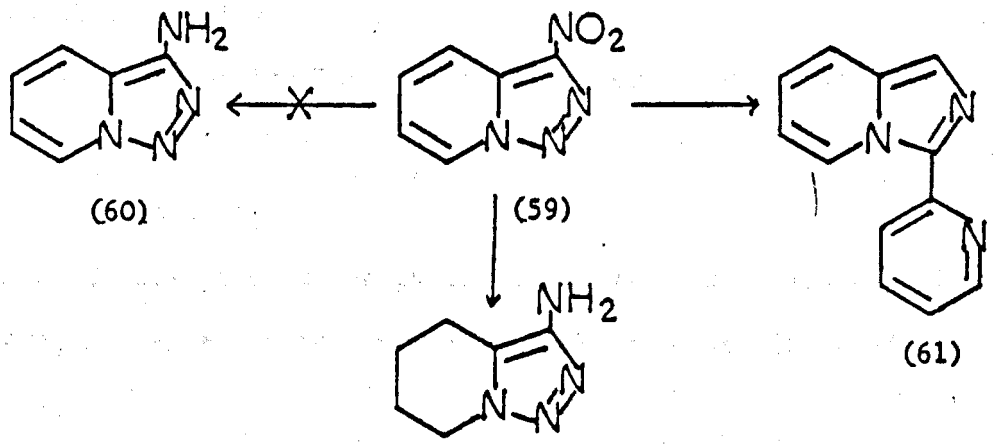


(59)

Attempts to reduce the 3-nitrotriazolopyridine (59) to 3-aminotriazolopyridine (60) were unsuccessful. The most abundant product from transfer hydrogenation was a colourless compound of molecular weight 195 and molecular formula $C_{12}H_9N_3$. In the ^1H n.m.r. spectrum all nine protons could be distinguished and by selective decoupling separated into three groups. Most prominent was a singlet (1H) at δ7.58 p.p.m. One series of four protons at δ8.62(H^A), 7.16 (H^B), 7.75 (H^C), and 8.33 p.p.m. (H^D) represented a sequence with coupling constants $J_{A,B}$ = 5.1 Hz, $J_{B,C}$ = 7.6 Hz, $J_{C,D}$ = 8.0 Hz, characteristic of an α-substituted pyridine. The remaining four protons showed a

similar sequence δ9.94 (H^E), 6.70 (H^F), 6.86 (H^G), and 7.48 (H^H) p.p.m., with $J_{E,F}$ = 6.8 Hz, $J_{F,G}$ = 7.1 Hz and $J_{G,H}$ = 6.9 Hz. The structure which best matched these data was that of 3-(2-pyridyl)imidazo[1,5-a]-pyridine (61); a search of the literature revealed that this compound had been prepared from pyridine-2-carboxaldehyde[49], and that the melting point and physical data agreed reasonably well with those of our reduction product. Subsequent studies by Tisler and Stanovnik[4] have also led to the synthesis of compound (61). Treatment of compound (60) with either hydrochloric acid or sodium hydrogen carbonate gave compound (61) in 35% yield.

On catalytic hydrogenation the nitro-compound (59) gave some imidazopyridine (61) and a compound identified by spectroscopy as the tetrahydroderivative (62); by analogy with indolizine the pyridine ring should be easily reduced[50].



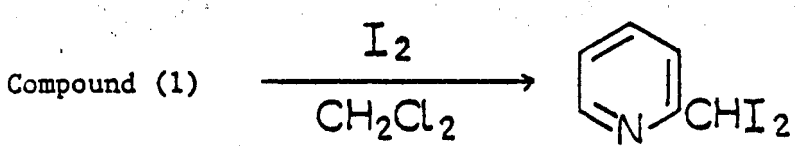
(60) (59) (61)

(62)

The mechanism of formation of the imidazopyridine will be discussed later.

Previous workers[51] at this university have shown that treatment of a solution of triazolopyridine (1) in carbon tetrachloride with either chlorine or bromine, at a temperature of 0-5°C was accompanied

by a vigorous evolution of gas. As previously mentioned, the products were respectively, 2-dichloromethylpyridine (54) and 2-dibromomethylpyridine (55). Reaction with mercuric acetate in glacial acetic acid gave the substituted mercuriacetate[51] (56). It was found that the diiodomethylpyridine (63) could be obtained if a dichloromethane solution of triazolopyridine (1) was treated with a similar solution of iodine, the sharp singlet at δ6.2 p.p.m. being indicative of the diiodomethyl proton resonance.



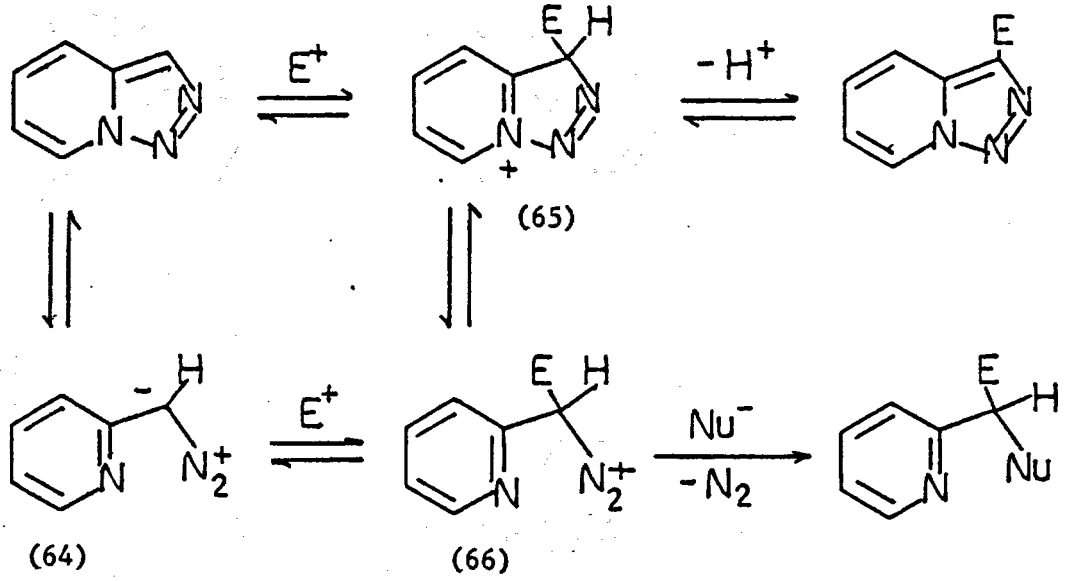
(63)

As can be seen triazolopyridine (1) reacts in two different ways towards electrophiles

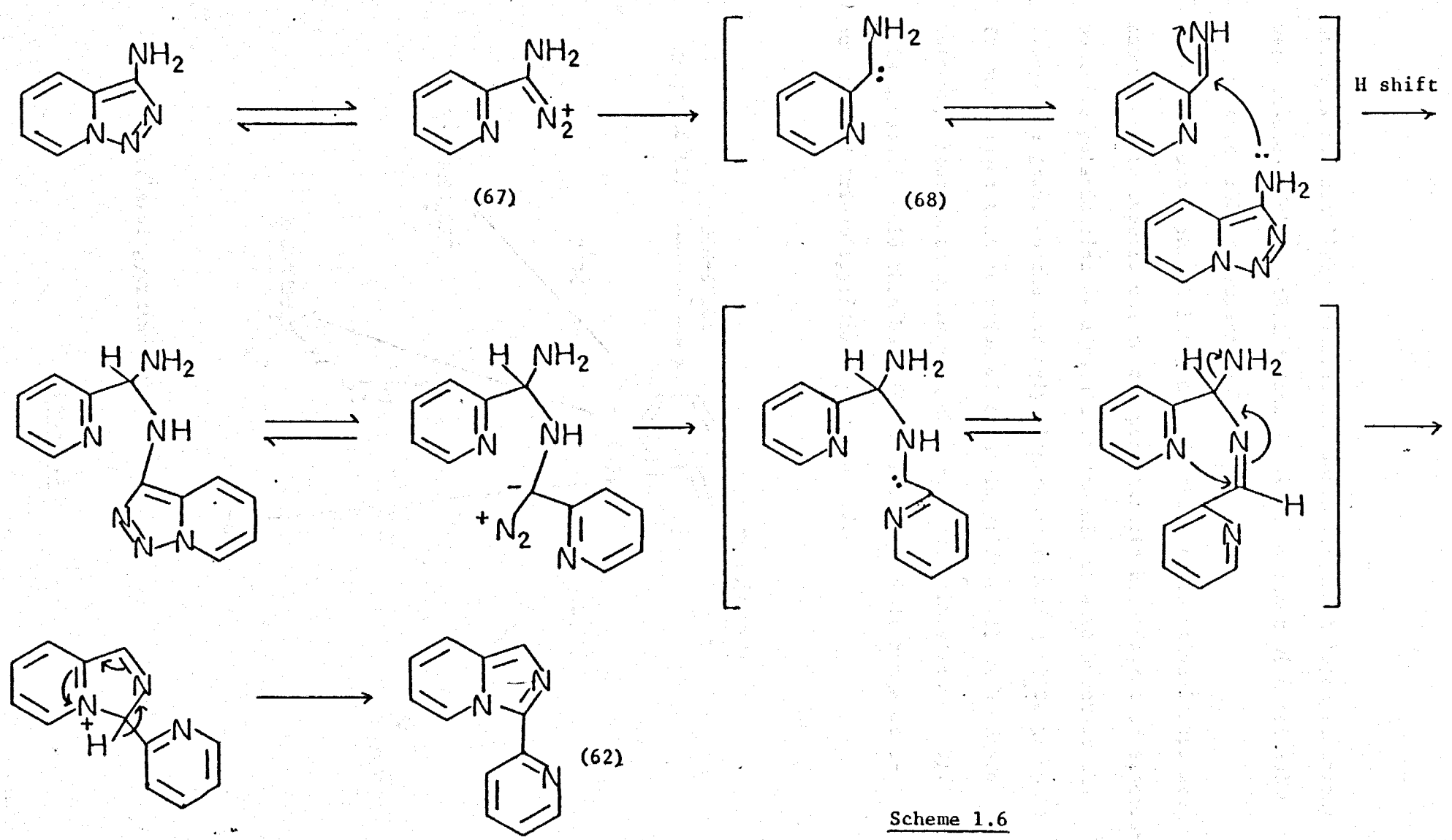
(i) simple substitution, as in formylation and nitration

(ii) reaction in which ring opening and nitrogen extrusion were characteristic.

The mode of formation of the pyridine derivatives (54), (55), (56) and (63), and of the imidazopyridine (61) are best discussed together.



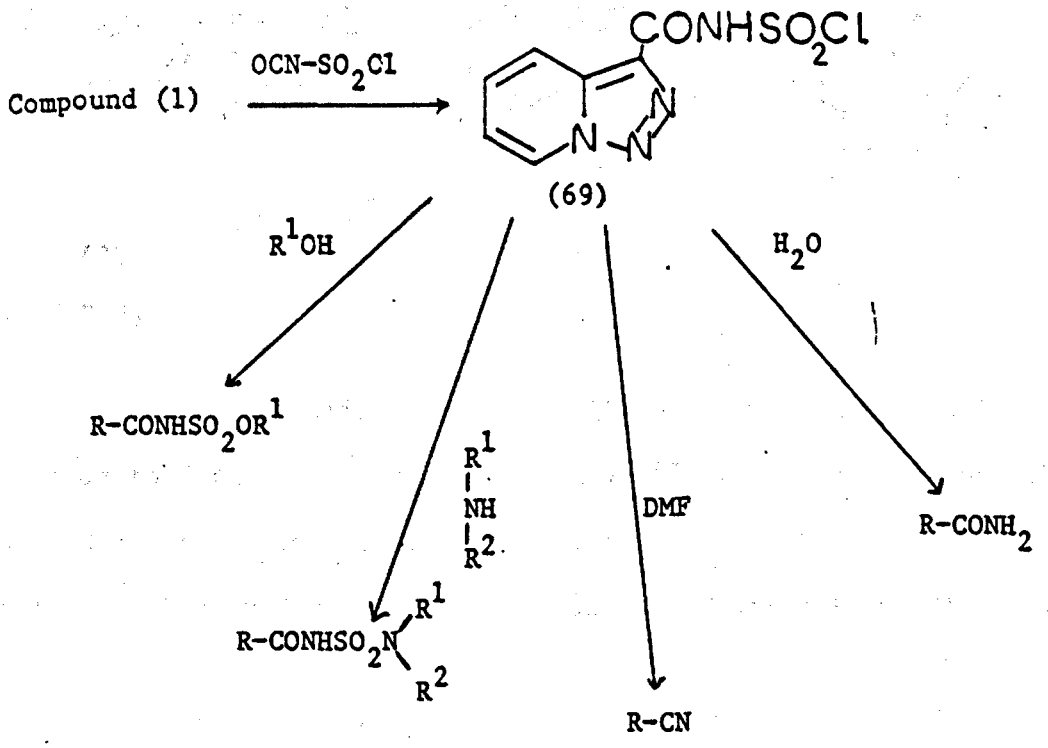
The formation of pyridine derivatives with loss of nitrogen must be attributed to the tautomerism (1) $\rightleftharpoons$(64), or, more likely, to the tautomerism (65) $\rightleftharpoons$(66) of the intermediate in electrophilic substitution. If the electrophile E is an electron-withdrawing group, the intermediate (66) will be longer-lived and deprotonation of the cyclic form competes successfully with loss of nitrogen. If the electrophile E is only weakly stabilising to the diazonium intermediate (66), nucleophilic attack with loss of nitrogen is the favoured process. This hypothesis has as a corollary the extreme instability of the tautomer (67) when the hydrogen atom is replaced by an electron donor such as the amino group. Loss of nitrogen from the tautomeric form (67) in 3-amino-triazolopyridine gives a reactive intermediate (68) similar to that proposed in the reaction between pyridine-2-carboxaldehyde and ammonium chloride. The intermediate (68) can attack unchanged 3-aminotriazolopyridine to produce 3-(2-pyridyl)imidazopyridine (61) as shown in Scheme 1.6.



Scheme 1.6

Attempts to establish a radical mechanism for the halogen reactions were unsuccessful; methyl radicals failed to react with triazolopyridine at ambient temperatues[58].

Chlorosulphonyl isocyanate is the most reactive isocyanate known. This appears due to the particularly high degree of electropositive polarisation as a result of the direct attachment of the isocyanate group to the strongly electron-attracting SO_2Cl group[53]. It was thought that reaction of triazolopyridine (1) with chlorosulphonyl isocyanate would give the N-chlorosulphonylamide (69). This compound could then be used to provide a whole range of 3-substituted triazolopyridines - Scheme 1.7.

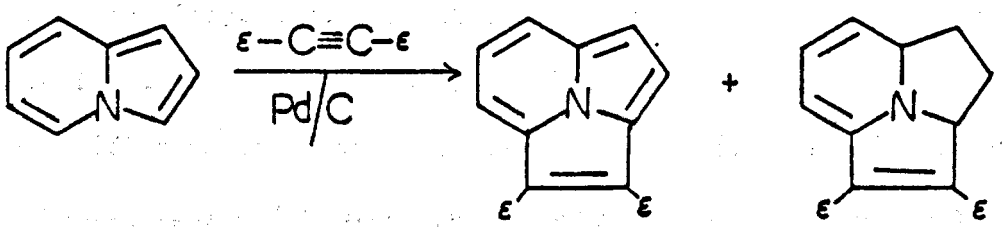


R = triazolopyridin-3-yl

Scheme 1.7

Upon addition of chlorosulphonylisocyanate to triazolopyridine in dry benzene a white precipitate formed immediately. The white precipitate was identified, by n.m.r. spectroscopy and microanalysis, to be probably a 1:1 complex of triazolopyridine and chlorosulphonyl-isocyanate.

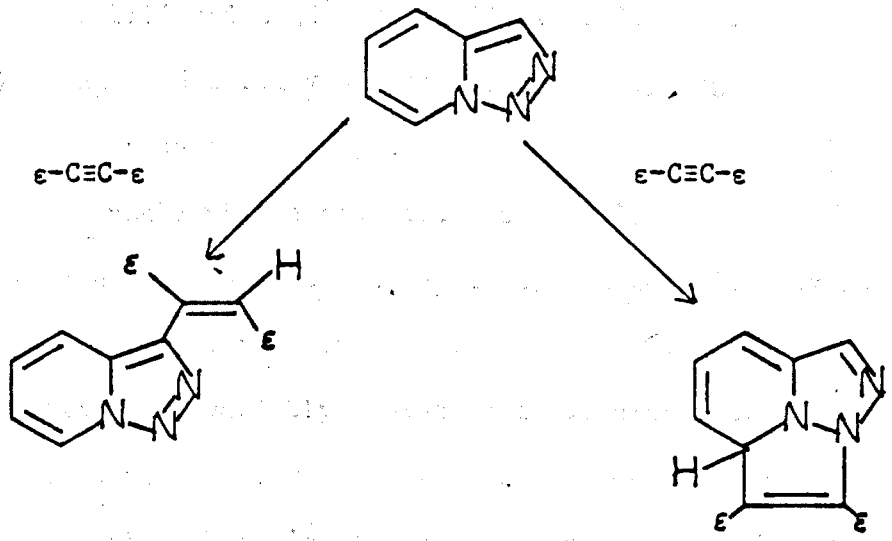
Indolizine (70) reacts with dimethylacetylenedicarboxylate (DMAD) in toluene solution in the presence of 5% palladium-on-charcoal to give 1,2-dicarbomethoxycycl[3.2.2]azine (71) in good yield.[54,55] In addition to (71), 1,2-dicarbomethoxy-3,4-dihydrocycl[3.2.2]azine (72), was isolated as a by-product in a 10-15% yield.



(70) (71) (72)

ε = $-CO_2CH_3$

It was thought that triazolopyridine (1) might undergo a similar reaction to form an azacyclazine such as (73). In another possible mode of reaction dimethylacetylenedicarboxylate acts as an electrophile and thus produces the vinyl substituted triazolopyridine (74).



(74) (73)

When triazolopyridine (1) was treated with DMAD in carbon tetrachloride solution at room temperature, a red colour developed immediately which intensified on standing. However, continuous monitoring by thin-layer chromatography and n.m.r. spectroscopy revealed nothing apart from the starting materials. Even after two years the intense red colour remained, but on work up only starting materials were isolated.

The reactions so far mentioned have all taken place at position 3, i.e. on the triazole ring. There have been no reactions reported on the pyridine portion of the triazolopyridine nucleus. In an attempt to increase the reactivity of the pyridine ring two possibilities were investigated:

(i) Formation of a chromium-arene complex

(ii) Formation of the N-oxide

In organometallic fields it has long been known that arene reactivity changes markedly when the arene is coordinated to the chromium tricarbonyl unit[56]. The changes are summarised below.

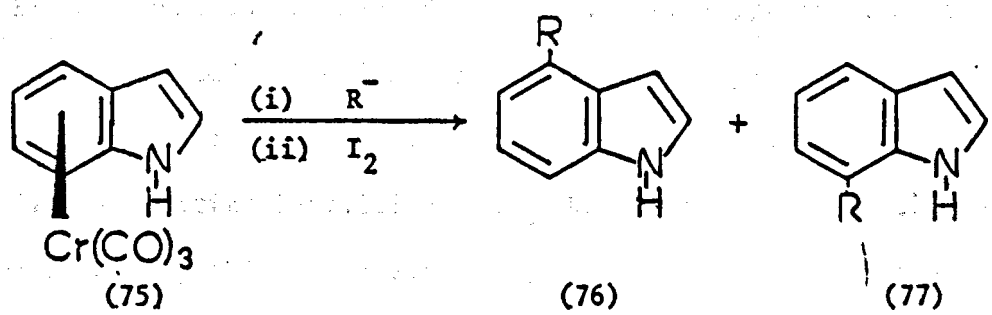
(i) steric effects of the metal-ligand system

(ii) stabilisation of side chain cationic sites

(iii) enhanced acidity of the arene ring hydrogens

(iv) addition of nucleophiles to the arene-π system leading to nucleophilic aromatic substitution.

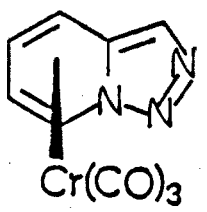
For example, indole does not react with nucleophiles by addition or substitution, it reacts only by deprotonation. Indoles with a free N-hydrogen are invariably deprotonated at nitrogen. The reaction of indole with chromium hexacarbonyl produces a single product (75). In this complex there is a strong preference for substitution at the 4-position (76). Minor amounts of substitution at C-7 (77) are also detected.



(75) (76) (77)

R = $^{-}CH_2CN$, $^{-}C(CH_3)_2CN$, $^{-}C(CH_3)_2CO_2^tBu$

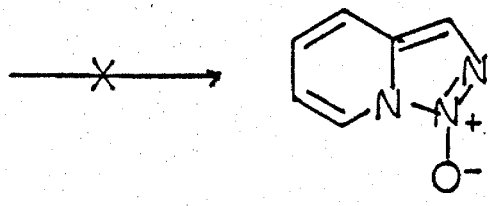
It was hoped that reaction of triazolopyridine with chromium hexacarbonyl would produce a complex such as (78), which could be then used as an electrophile and thus allow nucleophilic substitution on the pyridine ring.



(78)

However, refluxing triazolopyridine with chromium hexacarbonyl in dioxan for 4 days gave none of the expected product (78), but only a small amount of starting material with copious amounts of a pyrophoric powder. The powder was presumably finely divided chromium metal with the triazolopyridine present in complexation.

In a further attempt to increase the reactivity of the pyridine ring of triazolopyridine attention was turned to the possible formation of an N-oxide. The dipolar N-oxide group is both an electron donor and an electron acceptor. For pyridine, it has been reasoned that the N-oxide oxygen atom would release electrons to the 4 position thereby promoting electrophilic substitution at that position. However, electrons are pulled towards the positively charged nitrogen atom, consequently they can undergo nucleophilic attack in positions alpha and gamma to the N-oxide group[57]. Like pyridine, activation would be expected at position 5 of the triazolopyridine molecule. Attempts to mirror this reactivity by forming an N-oxide (79) failed. A mixture of triazolopyridine and m-chloroperoxybenzoic acid in ether was checked by thin-layer chromatography (T.L.C.) for 48 hours. There was, however, no reaction and a quantitative yield of starting material was recovered.

Compound (1) 

(79)

These preliminary experiments failed to achieve substitution on the pyridine ring. Chapter two discusses further efforts to effect such substitution.

Experimental

Preliminary notes

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared absorption spectra were recorded on a Pye-Unicam SP2000 instrument. Solids were recorded either as solutions (e.g. $CHCl_3$) or as nujol mulls, and liquids as thin films. Ultraviolet and visible absorption spectra were recorded on a Perkin Elmer 402 spectrophotometer. Nuclear magnetic resonance spectra were routinely measured on a Perkin-Elmer R.24 instrument at 60 mHz and/or a Hitachi Perkin-Elmer R.24B. Carbon^{13} n.m.r. and proton n.m.r. at 100 mHz were recorded on a Jeol FX100 Fourier Transform instrument. Chemical shift values are quoted in delta (δ) values in p.p.m. with respect to tetramethylsilane as internal standard. Micro-analyses were carried out on a Perkin-Elmer 240 carbon/hydrogen/nitrogen analyser at the University of Keele. Exact mass measurements were carried out by P.C.M.U. (Harwell). Mass spectra were recorded on a Hitachi-Perkin Elmer R.M.U.-6 instrument and a A.E.I. MS 12 instrument. Column chromatography was carried out using deactivated Woelm alumina, neutral grade. The activity values quoted refer to the Brockmann scale. Medium-pressure column chromatography was carried out with Merck grade 9385 silica gel (Kieselgel 60) at a pressure of ca. 50 p.s.i. Fractions were collected manually or using an Instrumentation Specialities Co. automatic Fraction Collector, (Model 328). Thin layer chromatography was carried out on 20 x 5 cm glass plates coated with Merck Kieselgel HF_{254}. Components were visualised under ultra-violet light or developed in iodine vapour. Preparative layer chromatography (P.L.C.) was performed on 40 x 20 cm glass plates coated with a 1.5 mm layer of Kieselgel HF_{254}. The separate components,

visualised under ultraviolet light, were scraped off the plates and extracted three times with methanol. The methanol solution was evaporated, taken up in dichloromethane, filtered and finally evaporated.

Abreviations used:

s	=	singlet
m	=	multiplet
d	=	doublet
dd	=	doublet of doublets
tr.	=	triplet
q	=	quartet
ex	=	exchangeable
br	=	broad
sh	=	shoulder

Preparation of [1,2,3]triazolo[1,5-a]pyridine (1)

Two methods were employed :

(i) Prepared by the method of Bower and Ramage[6] from pyridine-2--carboxaldehyde

mpt - 38-40°C

lit[6] mpt - 39-40°C

(ii) Prepared from the tosylhydrazone of pyridine-2-carboxaldehyde[14]

A solution of pyridine-2-carboxaldehyde (50g, 0.467 mol) in methanol (70 ml) was added to a stirred solution of p-toluenesulphonylhydrazide (87g, 0.467 mol) in methanol (300 ml). The solution was cooled in an ice-bath and pink crystals separated. The crystals were filtered and dried in a vacuum dessicator over calcium chloride. The weight of tosylhydrazone obtained was 92.4g (71%). The tosylhydrazone was dissolved in 400 ml morpholine and the mixture was heated on a water bath for thirty minutes. The excess morpholine was then removed under reduced pressure on a rotavapor. To the resulting orange solid was added 200 ml of dry ether, the orange solid (morpholine sulphinate) was filtered off. The filtrate was concentrated under reduced pressure and finally distilled (111°C, 0.45 mm) to yield 28g of triazolopyridine (1), (70%).

3-Deuterio-[1,2,3]triazolo[1,5-a]pyridine (58)

Prepared according to the method of Wentrup[28].

Preparation of hydrogen bromide salt of triazolopyridine

Through a cooled solution (0-5°C) of triazolopyridine (4g, 0.036 mol) in dichloromethane (100 ml) was passed dry hydrogen bromide gas ('freeze dried'). As the temperature rose to 25°C a pink solid

was deposited. After 1 hour the solid was filtered off under a stream of dry nitrogen. The HBr salt was dried in a vacuum dessicator (wt solid = 6g, % yield 89%). A sample of the salt was dissolved in water and basified with saturated sodium hydrogen carbonate solution. Extraction of the basified solution with dichloromethane, followed by drying over magnesium sulphate, filtering and evaporating gave triazolopyridine (1).

Attempts to prepare 3-Formyl-[1,2,3]triazolo[1,5-a]pyridine (53)

Three methods were employed

(i) According to Silverstein et al[48] - triazolopyridine (1) recovered.

(ii) According to Davies[26] - triazolopyridine (1) recovered.

(iii) Using a 'modified' Vilsmeier reagent[52] - triazolopyridine (1) recovered.

Preparation of N-formyl morpholine

To a solution of morpholine (87g, 1 mol) in 400 ml benzene was added formic acid (46g, 1 mol). The mixture was boiled under reflux, and using a 'Dean and Stark' apparatus, the water produced in the reaction was run off. When no more water was collected, heating was discontinued and the mixture was allowed to cool. The mixture was dried over magnesium sulphate. After filtration the mixture was distilled to yield 98.3g N-formylmorpholine (73%).

Bpt $92^{\circ}C/0.03$ mm

lit[52] Bpt $93^{\circ}C$

Attempt to prepare 3-Formyl-[1,2,3]triazolo[1,5-a]pyridine (53) using a 'modified' Vilsmeier reagent

N-formylmorpholine (5.3g, 0.039 mol) was cooled to $0^{\circ}C$ in an ice-bath. To this was added phosphorous oxychloride (7.1g, 0.046 mol) with stirring. At this temperature, the mixture froze. It was removed from the ice and some freshly distilled (P_2O_5) 1,2-dichloro-

ethane (50 ml) was added to dissolve the reagent. The mixture was then cooled to 0-5°C, and a solution of triazolopyridine (1) (5g, 0.042 mol) in 1,2-dichloroethane (50 ml) was added over a period of one hour with good stirring. The resulting brown solution was boiled under reflux for fifteen minutes and then allowed to cool. The mixture was then brought to pH 5-6 using saturated sodium carbonate. The hydrolysis was then completed by heating at 30-35°C for thirty-five minutes. The mixture was 'salted out' using sodium chloride, and thoroughly extracted with dichloromethane (4 x 100 ml). The organic extracts were then dried ($MgSO_4$), filtered and evaporated to yield a brown oil (11.2g). N.m.r. spectroscopy revealed the presence of N-formylmorpholine. The oil was redissolved in dichloromethane (100 ml) and shaken with water (2 x 100 ml). The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to yield 4.3g of a brown oil, later identified by n.m.r. spectroscopy as triazolopyridine (1).

3-Nitro-[1,2,3]triazolo[1,5-a]pyridine (59)

Triazolopyridine (1), (5g, 0.042 mol), was added in small portions to a cooled (0-5°C) stirred solution of fuming nitric acid (5 ml) in acetic anhydride (50 ml) and stirring was continued for one hour. The mixture was poured into ice-water giving a precipitate. Extraction of the precipitate with several quantities of boiling benzene, followed by concentration of the benzene solutions, gave the nitrotriazolopyridine (60). Further material was obtained from the benzene filtrate, and by preparative layer chromatography (P.L.C.) from the benzene-insoluble material.

Total yield	1.5-1.7g (20-25%)
M.pt.	167-169°C (benzene)
Analysis:	Found C, 43.8%; H, 2.4%; N, 34.4%
	$C_6H_4N_4O_2$ requires C, 43.9%; H, 2.45%; N, 34.15%

N.M.R. ($(CD_3)_2SO$) δ7.4 ppm, dd, 1H, H6, J6.5 and J7 Hz

7.9, dd, 1H, H5, J7 and 9 Hz

8.5, d, 1H, H4, J9 Hz

8.95, d, 1H, H7, J6.5 Hz

^{13} N.M.R. ($(CD_3)_2SO$). Multiplicities in off-resonance given in brackets.

δ118.0 (d), 118.8 (d), 127.8 (d), 129.4 (s), 134.3 (d), and 142.9 (s) ppm.

I.R. (Nujol) ν_{max} 1640, 1515, 1350, 1240, 1070, 830 and 772 cm^{-1}.

U.V. (95% EtOH) λ_{max} 280 nm, $\log_{10}\varepsilon$ = 3.34

287 nm, $\log_{10}\varepsilon$ = 3.39

335 nm, $\log_{10}\varepsilon$ = 3.88

Mass spectrum, m/e 164 (M^+), 118, 90, 78.

Reduction of 3-Nitro-[1,2,3]triazolo[1,5-a]pyridine (59)

(a) By transfer hydrogenation

A solution of 3-nitrotriazolopyridine (59) (1g, 0.006 mol) and cyclohexane (6 ml) in 95% ethanol (50 ml) was boiled with palladium--on-charcoal (1g, 10%) for four hours. The cooled mixture was filtered, the filtrate evaporated and the residue separated by P.L.C. (ethyl acetate - toluene, 1:4). The band of R_f 0.346 was extracted and identified as 3-(2-pyridyl)imidazo-[1,5-a]pyridine (61). M.pt 119-120°C (from cyclohexane) (120 mg, 20%). The ^{1}H n.m.r. data is given in the discussion.

(b) By catalytic hydrogenation

A solution of 3-nitrotriazolopyridine (59) (1.37g, 0.008 mol) in dimethoxyethane (50 ml) was hydrogenated at atmospheric temperature and pressure over palladium-on-charcoal catalyst (1g) until three equivalents of hydrogen were absorbed. Filtration and evaporation of the filtrate gave a mixture which was separated by P.L.C. (ethyl-acetate - toluene, 1:4). The band of the highest R_f (0.6) was found to be a small quantity of the imidazopyridine (61). The slowest band was extracted and identified as 3-amino-4,5,6,7,tetrahydro-[1,2,3]-triazolo[1,5-a]pyridine (62), (61 mg, 5%), a brown oil, which proved to be unstable to distillation and purification by chromatography.

N.M.R. ($CDCl_3$) δ1.8 - 2.1 ppm, m, 4H, H5 and H6
2.5 - 2.9, tr, 2H, H4
3.1, br.s, 2H, NH_2, Ex D_2O
4.1 - 4.4, tr, 2H, H7

I.R. ($CDCl_3$) ν_{max} 3400 cm^{-1}

Reaction of triazolopyridine (1) with halogens

(i) With chlorine

See work of Jones et al[51]

(ii) With bromine

See work of Jones et al[51]

(iii) With iodine

A solution of triazolopyridine (1) (4g, 0.033 mol) in dichloromethane (80 ml) was cooled to 0-5°C. To this was added dropwise a solution of iodine (resublimed) (8.5g, 0.033 mol) in dichloromethane (100 ml). The reaction was stirred at this temperature for one hour and then allowed to warm to room temperature. The mixture was then

washed with saturated sodium bicarbonate and sodium thiosulphate solution. The organic extract was dried ($MgSO_4$), filtered and finally evaporated to yield a black oil (8.0g, 69%) identified by n.m.r. to be almost pure 2-iodomethylpyridine (63). The oil later solidified but attempts at further purification (by recrystallisation, distillation and chromatography) all failed.

Mpt. 48 - 50°C (ether/ 40/60 Petether)

Analysis: Found: C, 20.89%; H, 1.46%; N, 4.06%

$C_6H_5I_2N$ requires C, 18.49%; H, 1.31%; N, 3.76%

N.M.R.($CDCl_3$) δ8.4 ppm, d, 1H. pyridine α H's

7.5, m, 2H, pyridine β H's

7.1, m, 1H, pyridine γ H's

6.2, s, 1H, CH

I.R. ($CHCl_3$) ν_{max} 510 cm^{-1}

U.V. (95% EtOH) λ_{max} 220 nm (sh)

274 nm $\log_{10}\varepsilon$ 4.2

Mass spectrum, m/e, 344(75) M^+, 331(100), 319(95),
305(27), 293(80), 281(100), 269(100),
231(100), 219(100), 205(37), 193(55), 181(100),
169(100), 162(55), 131(100), 119(100), 113(50), 100(100).

Attempted radical methylation of [1,2,3]triazolo[1,5-a]pyridine (1)

To a solution of triazolopyridine (1) (1g, 0.0084 mol) in 30 ml 7% aqueous sulphuric acid, was added $FeSO_4.7H_2O$ (4.67g, 0.0168 mol) with good stirring. To this solution was added t-butylhydroperoxide (1.51g, 0.0168 mol). The mixture was stirred for twenty minutes at room temperature. The mixture was then extracted with chloroform, the aqueous layer was basified and extracted with chloroform. Each

organic layer was dried ($MgSO_4$), filtered and evaporated. Both extracts yielded only triazolopyridine (1) (0.9g).

Reaction of triazolopyridine (1) with chlorosulphonylisocyanate

To a stirred solution of triazolopyridine (1) (5g, 0.042 mol) in anhydrous benzene (150 ml) was added, in one portion, chlorosulphonylisocyanate (3.65 ml, 0.042 mol), under a dry nitrogen atmosphere. Upon addition a white precipitate formed immediately. On warming the mixture to 30°C this white precipitate turned orange in colour. The mixture was heated for a further one hour at 50°C. The mixture was then allowed to cool, and the orange precipitate was filtered. N.m.r. spectroscopy on the orange solid revealed only the presence of peaks due to triazolopyridine (1).

Analysis of the solid gave the following results:

Found: C, 31.85%; H, 3.02%; N, 18.21%

Mpt. 40 - 50°C

Analysis figures expected for a 1:1 complex of triazolopyridine (1) and chlorosulphonylisocyanate would be

C, 32.25%; H, 1.93%; N, 21.50%

Further purification of the solid failed. On attempted recrystallisation, the solid turned to an oil, which by n.m.r. spectroscopy was shown to be triazolopyridine (1). On t.l.c. plates, the solid gave a spot with an identical R_f value to that of triazolopyridine (1).

Reaction of triazolopyridine (1) with dimethylacetylenedicarboxylate

To a solution of triazolopyridine (1) (2g, 0.0168 mol) in carbon tetrachloride (50 ml) was added dimethylacetylenedicarboxylate (2.39g, 0.0168 mol). The resulting mixture turned pink in colour, over a period of days this colour intensified to a deep red.

Repeated T.L.C. (1:1 ethylacetate - toluene) revealed the presence of nothing but starting materials. After several months the reaction mixture was evaporated to yield a red oil (4.5g). N.m.r. spectroscopy revealed it to be a mixture of triazolopyridine (1) and dimethylacetylenedicarboxylate.

Reaction of triazolopyridine (1) with chromium hexacarbonyl

To a solution of triazolopyridine (1) (5g, 0.042 mol) in dioxan (200 ml) was added chromium hexacarbonyl (10.26g, 0.046 mol) under a dry nitrogen 'blanket' atmosphere. The mixture was boiled under reflux for 5 days. Repeated T.L.C. (1:1 ethyl acetate - toluene) showed nothing but the presence of starting material. The mixture was allowed to cool after 5 days refluxing and filtered to remove unreacted chromium hexacarbonyl. The filtrate was evaporated to yield $\sim$ 0.1g of a brown oil, which was identified by n.m.r. spectroscopy as triazolopyridine (1). The filtered material ignited spontaneously in the air (probably due to finely divided chromium metal). The remainder of the starting material must be presumed to be amongst the filtered material.

Reaction of triazolopyridine (1) with m-chloroperoxybenzoic acid. An attempt to synthesise the N-oxide of triazolopyridine (79).

To a solution of triazolopyridine (2g, 0.0168 mol) in anhydrous ether (20 ml) was added one equivalent of m-chloroperoxybenzoic acid (2.9g, 0.0168 mol). The resulting yellow solution was stirred at 0-2°C. The reaction was followed by T.L.C. (1:1 ethyl acetate - toluene). After 48 hours only starting materials could be detected. The solvent was removed under reduced pressure to yield

a yellow oil (5g). N.m.r. spectroscopy revealed only the presence of starting materials.

CHAPTER TWO

DIRECTED LITHIATIONS

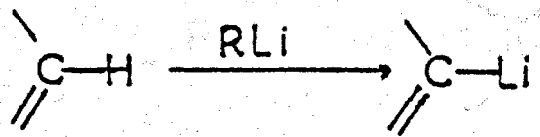
(2.1) Introduction

This chapter continues the efforts to substitute the pyridine ring of triazolopyridine. Directed lithiation reactions were used; there now follows a review on the concept of directed lithiations. Examples of directed lithiation reactions on some analogous heterocyclic systems are included. As will be seen later the synthesis of 2,6-disubstituted pyridines was possible, along with a possible synthesis of bipyridyls. Previous methods of synthesis of these two classes of compounds are also reviewed.

(2.2) Review of directed lithiations

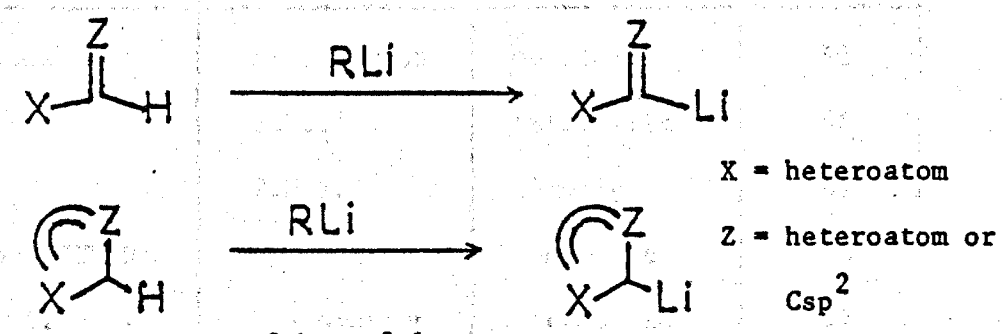
Since Gilman and Morton[59] first reviewed the topic of metalation reactions, there has been intensive explorations in this area. Research efforts have been characterised by the discovery of new functional groups that promote metalation, elaboration of novel heterocyclic and olefinic substrates which may be metalated, recognition of new types of lithiating agents, and the continuation of efforts to define accurately the mechanism of metalation. Accordingly, heteroatom-facilitated lithiation has become recognised as an increasingly important tool. There has been one excellent review[60] on the topic of heteroatom-facilitated metalations and several others covering the topic in a more limited[61,62] or less specific sense[63,64,65].

In this review, lithiation is defined as the exchange of a hydrogen atom attached to an sp^2-hybridised carbon atom by lithium to form a covalent lithium-carbon bond.



More specifically, discussion is limited to those metalations which, through the influence of a heteroatom, are characterised by rate enhancement and regioselectivity. In fact lithiations of this type are noted for a high degree of regioselectivity, metalation generally occurring on the sp^2-carbon atom closest to the heteroatom. Based on the relative position of the heteroatom such lithiations are conveniently classified into two principal categories : alpha and beta (ortho) lithiations.

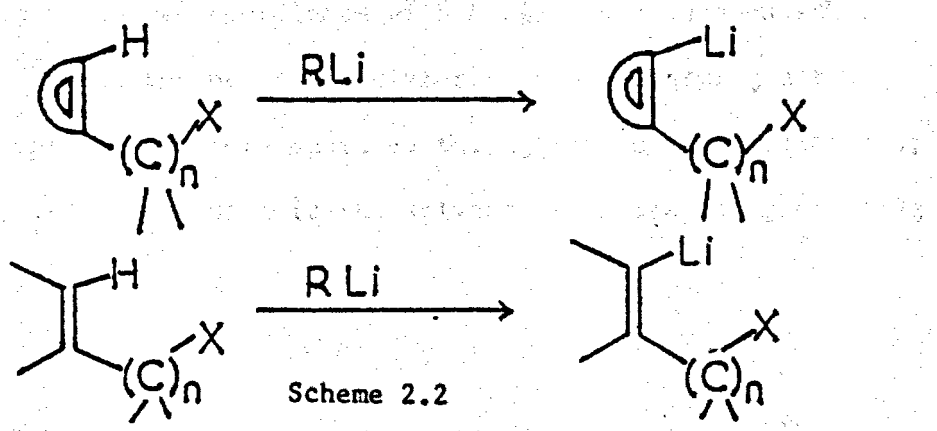
In alpha lithiations the metalating agent deprotonates the sp^2-carbon atom alpha to the heteroatom to form a carbon-lithium bond. See scheme 2.1.



Scheme 2.1

This sp^2-carbon atom may be part of an olefinic or heteroaromatic π system.

In beta lithiations the metalating agent is directed to deprotonate the sp^2-carbon atom beta to the heteroatom-containing substituent. See scheme 2.2.



Scheme 2.2

The designation "ortho metalation" is used specifically for the beta metalation of carbocyclic aromatic systems. An understanding of the mechanism can be facilitated by the recognition of the existence of two distinct types of metalating agents.

(i) Lithium alkyls and aryls

These are oligomers of varying complexity in solution. See table 2.1.

Table 2.1

Lithiating Agent	Solvent	State of aggregation	Reference
n-BuLi	hydrocarbon	hexameric	66
	ether	tetrameric	66
	T.H.F.	dimeric	67
n-BuLi/TMEDA	hydrocarbon	monomeric	68
t-BuLi	hydrocarbon	tetrameric	69
	T.H.F.	dimeric	67
C_6H_5Li	ether	dimeric	63
	T.H.F.	dimeric	70

In addition they are electron-deficient species[71] and therefore Lewis acids which can coordinate with Lewis bases such as ethers and amines[65] with consequent depolymerisation to varying extents. These reagents become more basic as the aggregate size diminishes; therefore, tetrahydrofuran is the solvent of choice for generating reactive species.

(ii) Lithium dialkylamides and n-butyllithium/amine complexes.

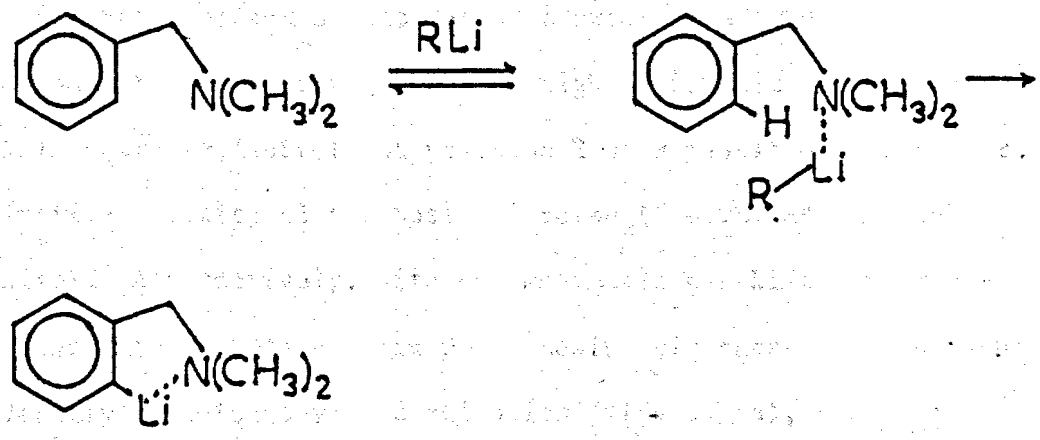
The distinguishing characteristic of these reagents is the negligible extent of Lewis-acid character relative to uncomplexed lithium alkyls and lithium aryls. Another distinctive property of the lithium dialkylamides is their decreased thermodynamic basicity relative to lithium alkyls. Although an apparent contradiction in terms, it has often been noted[72,73] that lithium dialkylamides are generally more effective metalating agents than the thermodynamically more basic lithium alkyls. The phenomenon of increased kinetic basicity of lithium amides may be rationalised by the availability of a free pair of electrons, which permits the formation of a four-membered transition state. The intermediacy of a free carbanion is thus avoided[72]. It should be recognised that the deprotonation of an unsaturated carbon acid such as benzene or ethylene is thermodynamically feasible with lithium alkyls. Yet these metalations are exceedingly slow even in ethereal solvents; e.g., benzene shows negligible lithiation with n-butyllithium in hexane after 3 hours at room temperature[59]. Therefore, one phenomenon that must be explained by any mechanism concerning heteroatom-facilitated lithiation is the great rate enhancement; e.g., anisole metalates to the extent of 30% with n-butyllithium in ether in 2 hours[74]. In addition the high degree of regioselectivity must be accounted for.

It has been assumed for many years that the initial step in the heteroatom-facilitated lithiation reactions is the coordination of the electron-deficient metalating agent with the non-bonding electrons in the substrate heteroatom (with attendant depolymerisation). This coordination is then followed by a protophilic

attack of the carbanionic portion of the lithiating agent on the adjacent hydrogen atom, leading to the metalated product[75]. Other factors, particularly the inductive effects of heteroatoms or substituents can play important roles in these reactions. Hydrocarbon acidity can become the sole determinant[60]. It is postulated that there are, in fact, two limiting mechanisms:

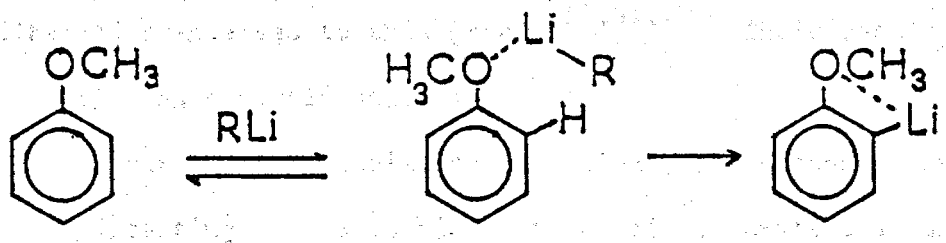
1. "coordination only" mechanism
2. "acid-base" mechanism.

A full explanation of these concepts (with particular reference to beta lithiations) is best presented through illustration. The best example of a "coordination only" mechanism is the ortho lithiation of N,N-dialkylbenzylamines[76]. Despite the fact that the benzylic methylene group has an inductive effect on the ortho position which actually decreases its acidity, lithiation occurs exclusively at position 2. Thus it has been assumed that the initial step in this reaction is the coordination of the metalating agent with the lone pair of the basic nitrogen atom. The nearest available proton, in the ortho position, then suffers a protophilic attack, leading to the internally chelated and isolable organo lithium species. See scheme 2.3.



Scheme 2.3

Most mechanistic studies of the ortho lithiation have been carried out with alkylaryl ethers, where a combination of the two mechanistic determinants, i.e., coordinative and inductive effects, is operative. For anisole the whole process is generally and simplistically pictured as in scheme 2.4[77].



Scheme 2.4

In the intermediate coordinated species the carbon-lithium bond of the metalating agent and the carbon-hydrogen bond of the substrate are polarised to a greater extent, thus allowing the proton easily to be removed by induction. The second step, namely the actual deprotonation is rate determining.

An important example is the lithiation of p-methoxy-N,N--dimethylbenzylamine[70]. The acidity of the hydrogen atom at position 3 should be distinctly higher than at position 2 because of the inductive effect of the methoxyl group. Nevertheless, metalation with a lithiating agent of high Lewis-acid character (n-BuLi) occurs exclusively at position 2 as a result of the higher coordinative capacity of the basic nitrogen ("coordination only" mechanism). Alternatively, with the monomeric n-BuLi/tetramethyl--ethylenediamine(TMEDA) complex whose Lewis-acid character has been considerably diminished via coordination (vide supra), the most

acidic proton at position 3 is removed selectively ("acid-base" mechanism).

Each individual group (containing one or more heteroatoms) has its own distinct beta-directing ability. The establishment of a ranking system is of considerable practical interest for π-systems bearing more than one directing group. Various research groups have addressed themselves to this problem[59,61,70]. Their results permit the following generalisations:

(1) Under kinetic lithiating conditions, the strongest beta directing groups combine both an electron-withdrawing effect and the properties of a good ligand.

(2) Among the groups in which the directing heteroatom is separated from the π-system by a saturated carbon atom, thus providing no electron-withdrawing effect, a basic nitrogen atom is the most powerful director.

(3) In the presence of non-Lewis-acid metalating agents, the rank order of the directing groups is determined largely by their inductive or acidifying effect.

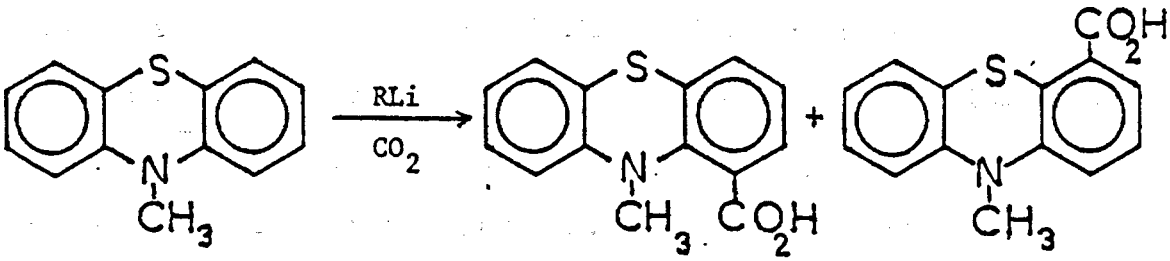
Thus the following order of beta-directing potential can be established:

$SO_2NR_1R_2$, SO_2-aryl>2-oxazolines>CONHR, CSNHR>$CH_2N(CH_3)_2$> $CR(O^-)CH_2N(CH_3)_2$>OCH_3>O-aryl>NH-aryl>S-aryl>NR-aryl> $N(CH_3)_2$>CR_1R_2O.

Examples of heteroatom-facilitated lithiations amongst heterocycles.

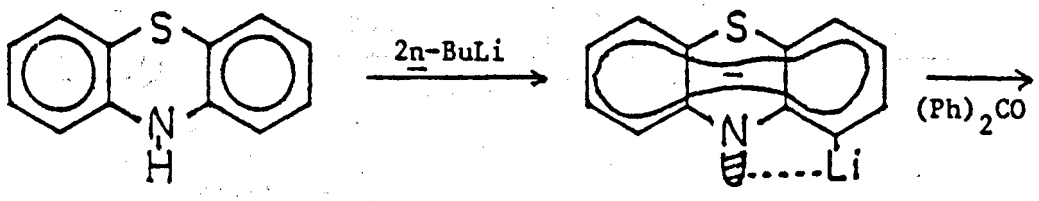
An interesting observation with the phenothiazines is that N-unsubstituted derivatives are lithiated more readily and regioselectively than are the N-alkylated homologues. Lithiation of

N-methylphenothiazine (80) leads to a mixture of products (81) and (82)[78,79]

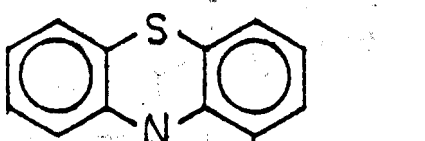


(80) (81) (14%) (82) (16%)

indicating the approximate equivalence of sulphur and nitrogen as ortho-directing groups. However, phenothiazine itself is lithiated exclusively ortho to nitrogen to give compound (84).



(83)



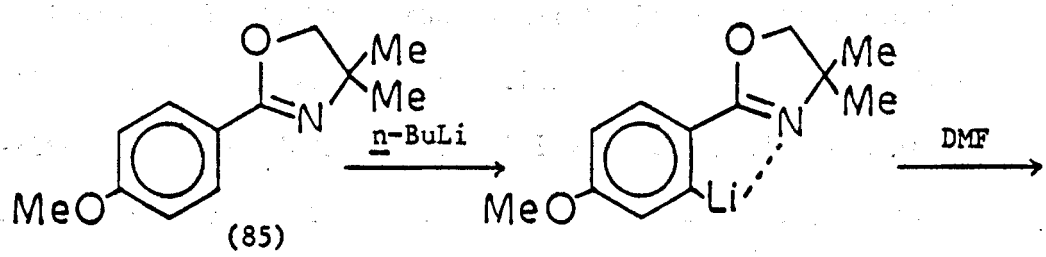
(84) (70%)

If it is indeed the relative unavailability of the nitrogen lone pair for chelation with the lithiating agent that makes the tertiary nitrogen of N-methylphenothiazine a poorer ortho-direction, one rationale is the following:

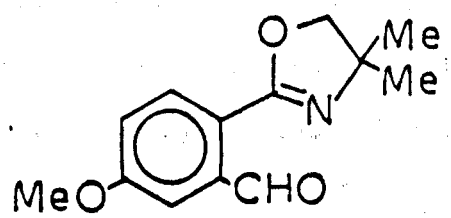
As the formal negative charge of the monoanion generated by N-deprotonation of phenothiazine is delocalised over the entire π-system (83), the non-bonding pair of electrons of the nitrogen atom, now coplanar with the tricyclic system, become available for chelation with the lithiating agent.

The azomethine linkage has long been recognised as an

excellent ligand[80]. This property, combined with a strong electron-withdrawing effect, makes this functionality one of the most powerful beta directors known to date. 4,4-dimethyl-2-oxazolines and 1,3-oxazines constitute synthetically useful directing groups that contain this common structural element. The ortho lithiation of 2-aryloxazolines proceed readily even at low temperatures. The ortho metalated species react with numerous electrophiles[81-83]. For the para-methoxylderivative (85) lithiation occurs regio-selectively in the position ortho to the oxazoline ring, as the aldehyde (86) is the only product isolated[84].



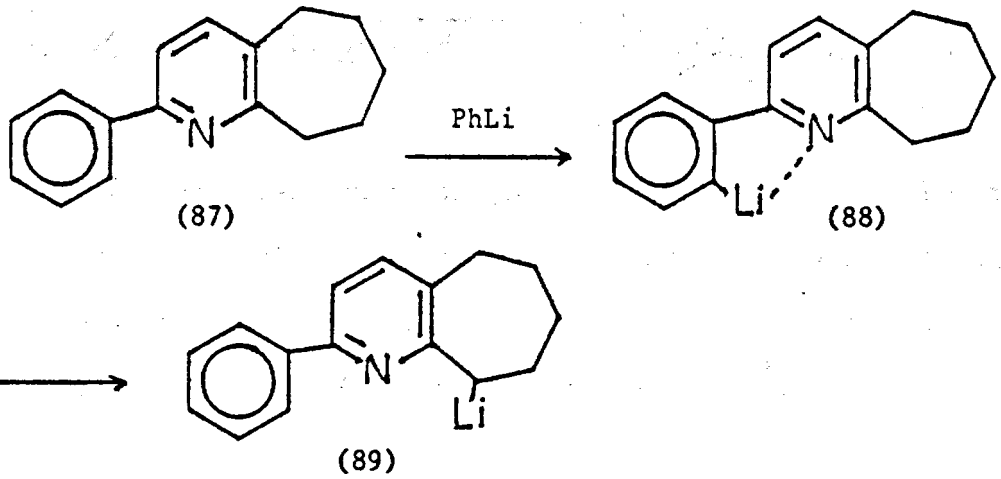
(85)



(86)

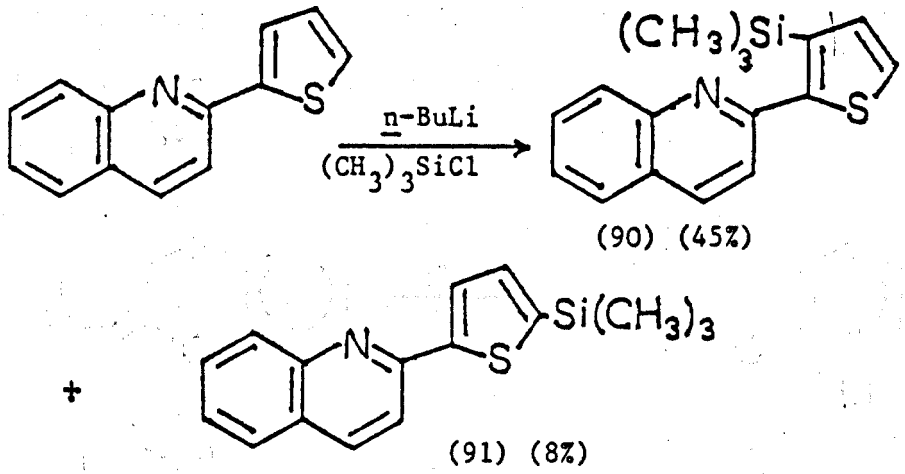
In fact, the directing capacity of the oxazoline ring is so high that it can compete successfully with the alpha metalation of the thiophen nucleus, one of the more readily lithiated substrates known[85].

Although pyridines generally are susceptible to nucleophilic attack by the metalating agent on the azomethine linkage, some can serve as powerful ortho-directing groups. Metalation of the aryl pyridine (87) followed by deuteration indicates that the kinetic product (88) arises from an ortho lithiation and slowly equilibrates to the thermodynamic product (89)[86,87].



(87) (88) (89)

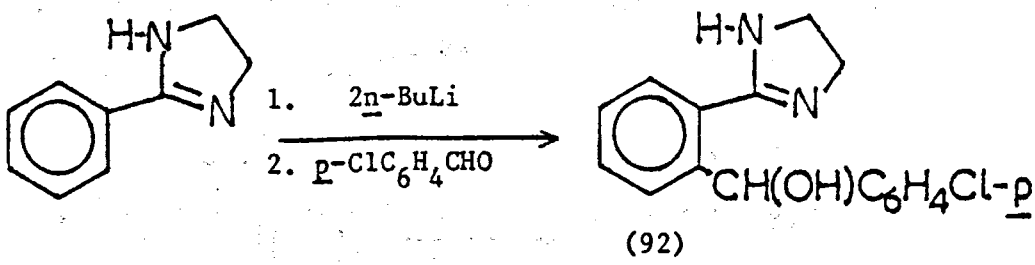
When viewed in the light of the rather facile deprotonation of picolines[88], the successful ortho lithiation of compound (88) clearly underlines the marked directing ability of the pyridine nucleus. In 2-(2'-thienyl)quinoline the ortho-directing ability of the quinoline nitrogen leads to predominant metalation in the 3-position of the thiophen nucleus and only a small amount of alpha lithiation, as reflected by the isolation of the silanes (90) and (91)[89].



(90) (45%)

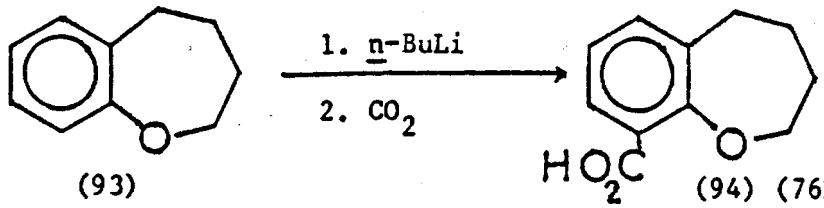
(91) (8%)

2-Arylimidazolines are metalated in their ortho position in a manner reminiscent of the 2-aryloxazolines. Thus lithiation of 2-phenylimidazoline followed by reaction with p-chlorobenzaldehyde produces the alcohol (92)[90].



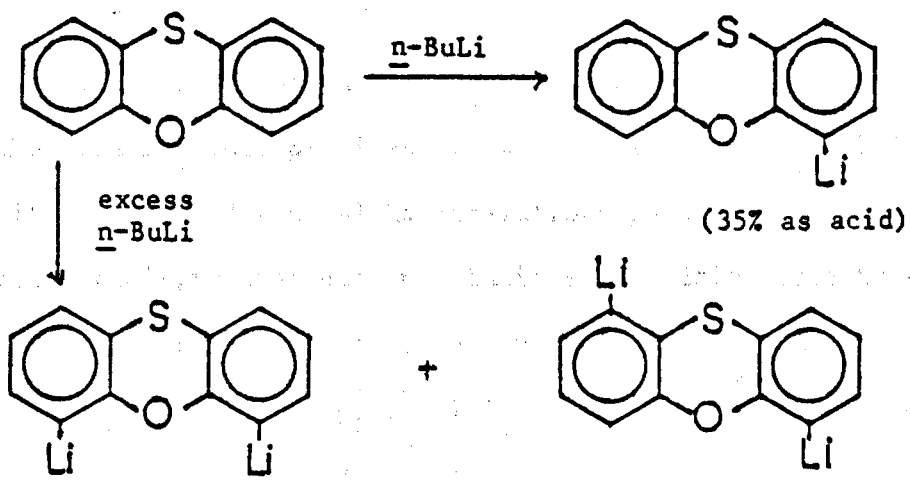
(92)

Turning our attention to oxygen as the ortho directing heteroatom, cyclic alkyl aryl ethers such as compound (93) can be metalated as expected in the position ortho to the oxygen function to give upon carbonation the acid (94) in respectable yield[91].



(93) (94) (76%)

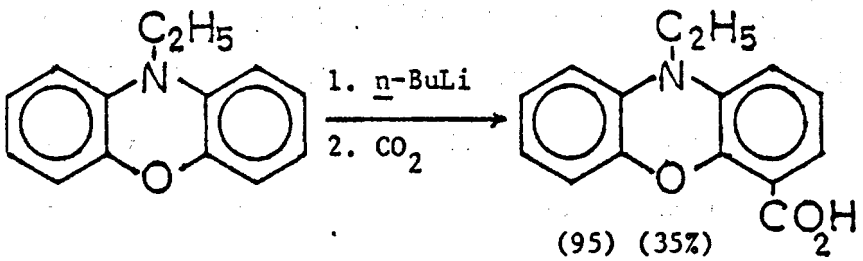
Competitive experiments show that the ethers have a greater ortho-directing effect than either sulphides or amines[59]. This differential directing ability is best documented by the lithiation of phenoxathiine, in which monometalation occurs exclusively adjacent to oxygen. Even dimetalation, using excess n-butyllithium, takes place predominantly in the two positions ortho to oxygen and only to a smaller extent at position 1 [92,93].



(35% as acid)

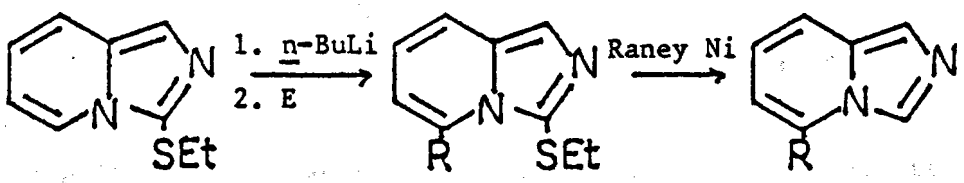
(35% as diacid) (8% as diacid)

Likewise, N-ethylphenoxazine is metalated adjacent to oxygen exclusively to give the acid (95)[94].



(95) (35%)

The ability of the thioether to facilitate ortho lithiation is intermediate between that of ethers and anilines. Blatcher and Middlemiss[95] have used the thioether group to direct lithiation to position 5 on the imidazo[1,5-a]pyridine ring system, thus allowing substitution on the pyridine ring.

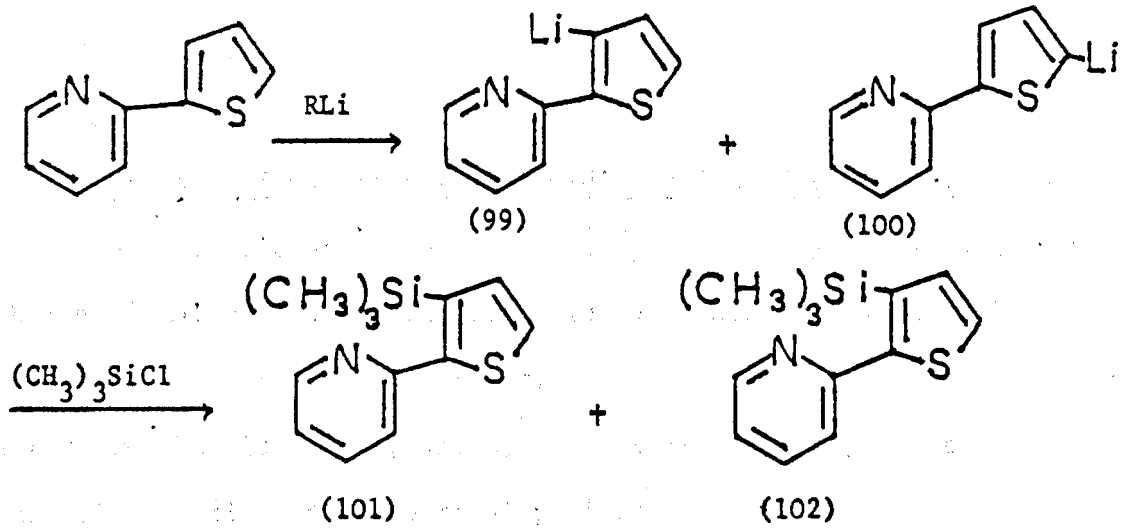


(96) (97) (98)

The thioether (96) reacts with butyl lithium and an electrophile to produce the 5-substituted imidazo[1,5-a]pyridine (97). Treatment with Raney Nickel removes the thioether function, leaving the 5-substituted compound (98).

The presence of both a beta- and an alpha- directing group within the same molecule provides for some interesting possibilities. Whereas it is accepted that alpha metalations generally proceed with greater facility than beta metalations, specific cases have been studied in which both reactions can successfully compete. In fact, a judicious choice of conditions can allow either one of the two processes to become dominant.

There are two potential sites for lithiation in 2-(2'-thienyl)-pyridine: the 3 position (invoking the beta-directing effect of the pyridine nitrogen) and the 5 position (alpha lithiation). By the appropriate combination of solvent, temperature, and metalating agent, either of these two positions can be lithiated predominantly, as documented by the formation of the silanes (101) and (102) [89].



It appears that the beta metalation is kinetically controlled because the species (99) slowly equilibrates to the thermodynamically more stable compound (100) under the reaction conditions. Evidently under kinetic conditions, n-butyllithium (tetrameric in ether) preferentially coordinates with the pyridine nitrogen: abstraction of the nearest proton then leads to (99). By contrast, in tetrahydrofuran, n-butyllithium (a solvated dimeric species) acts more as a base than as a Lewis acid, thus abstracting the most acidic proton in the alpha position of the thiophen nucleus. The fact that lithium diisopropylamide in ether produces essentially the same result is consistent with this rationale, as it displays, unlike tetrameric n-butyllithium, only negligible Lewis-acid character. See table 2.2.

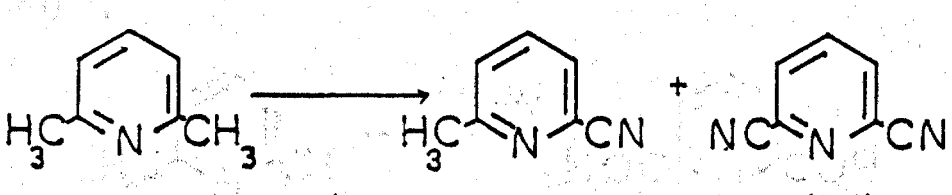
RLi	Solvent	Temperature °C	Yields	
			(101)	(102)
n-BuLi	THF	0	4	93
LDA	ether	0	1	74
n-BuLi	ether	0	62	13

Table 2.2.

(2.3) Synthesis of unsymmetrical 2,6-disubstituted pyridines.

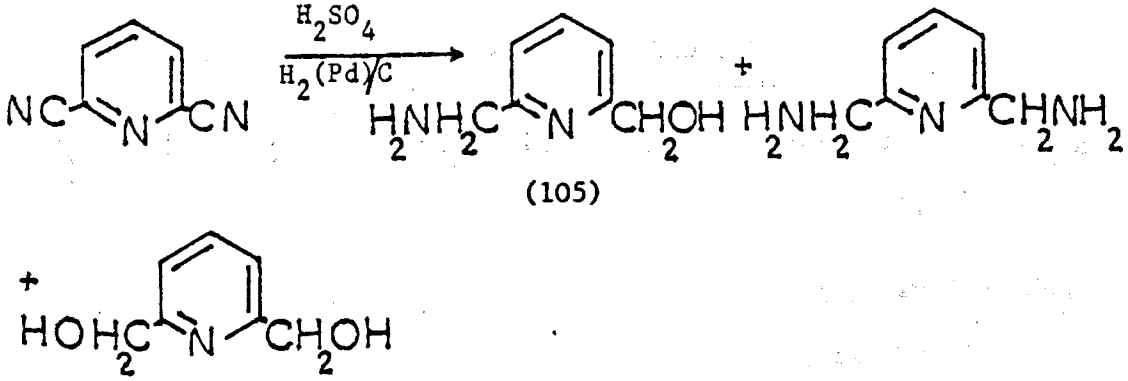
The synthesis of these compounds, particularly those containing such functional groups as alcohols, aldehydes and carboxylic acid derivatives, is extremely difficult. Examples of such syntheses are rare in the literature, while, those that do exist, start from a suitably substituted symmetrical pyridine.

Oxidative ammonolysis, using a vanadium-silver catalyst, of 2,6-dimethylpyridine gives 2-cyano-6-methylpyridine (103). 2,6-dicyanopyridine (104) is also formed[96].



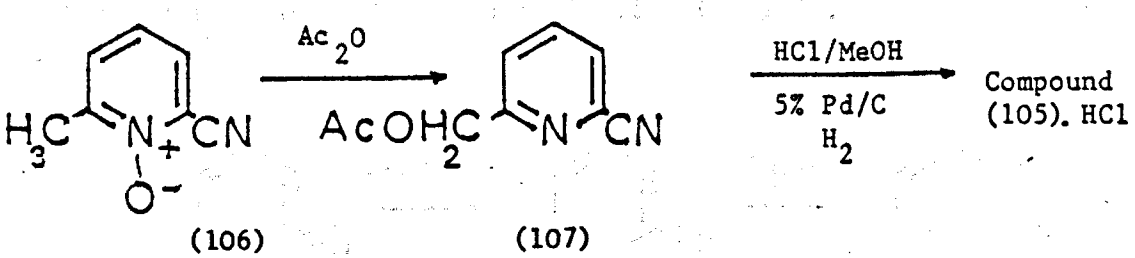
(103) (104)

Treatment of 2,6-dicyanopyridine with sulphuric acid followed by hydrogenation over a palladium-charcoal catalyst gives 6-aminomethyl-2-pyridine methanol (105) amongst other products[97].



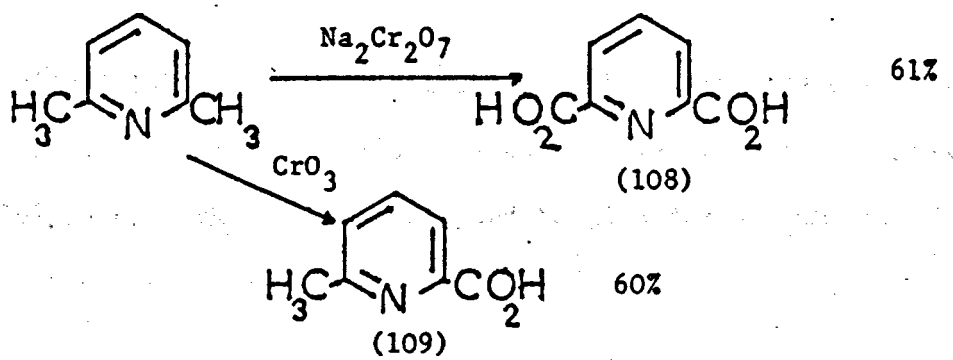
(105)

The same compound (105) can be obtained by treatment of the N-oxide (106) with acetic anhydride, this gives the acetate (107) which upon treatment with 5% HCl in methanol followed by hydrogenation gives compound (105) as the hydrochloride salt[98].



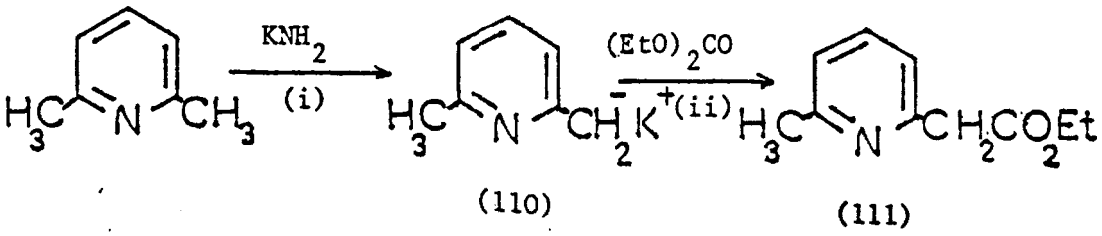
(106) (107)

Oxidation of 2,6-dimethylpyridine with sodium dichromate gives the dicarboxylic acid (108); chromium trioxide selectively oxidises only one methyl group to give the monocarboxylic acid (109)[99].



(108) (109)

Metalation of 2,6-dimethylpyridine with potassium amide in liquid ammonia gives the potassium salt (110); on treatment with diethyl-carbonate the acetate (111) is obtained[100].

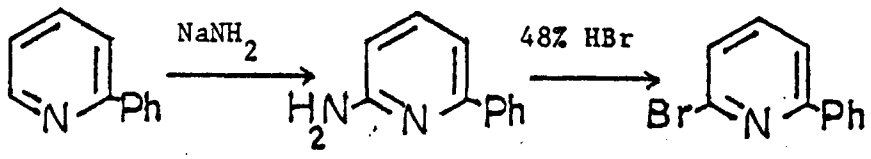


(110) (111)

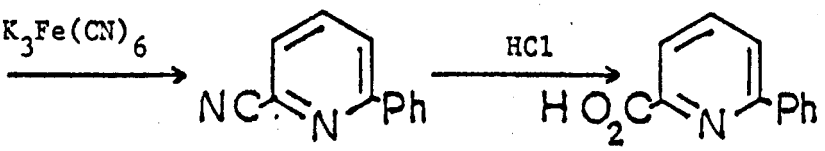
(i) in liq. NH_3

(ii) NH_4Cl

In a classic Chichibabin reaction, 2-phenylpyridine reacts with sodamide to yield 2-amino-6-phenylpyridine (112) in 87% yield. Treatment of compound (112) with aqueous HBr gives the bromopyridine (113) which on treatment with potassium ferricyanide followed by HCl gives the carboxylic acid derivative (114)[101].

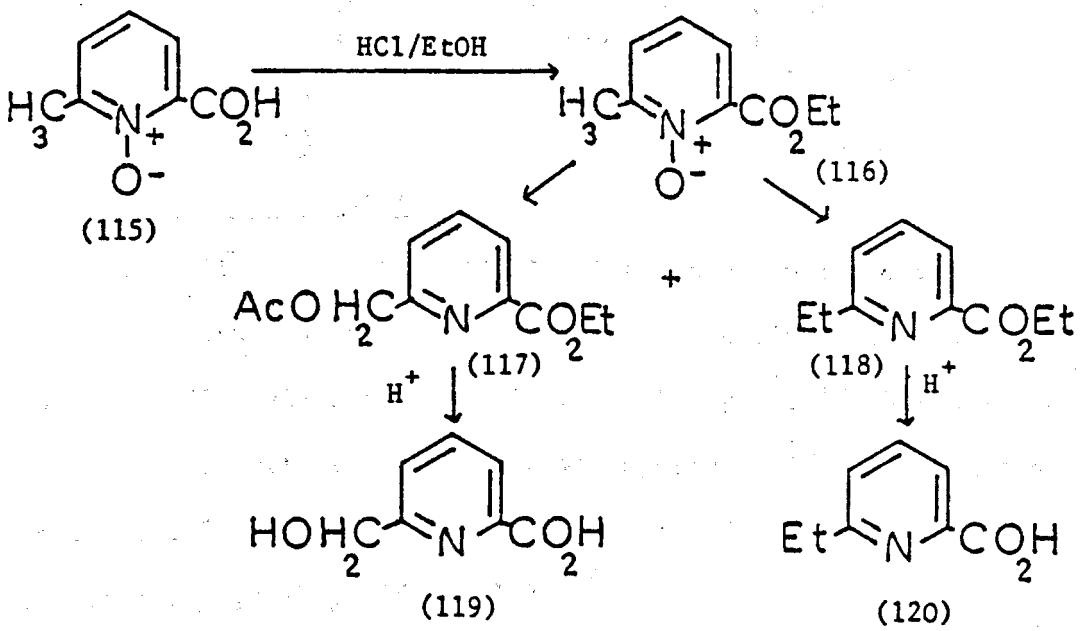


(112) (113)



(114)

The N-oxide (115) reacts with HCl in ethanol to give the ester (116). On heating with acetic anhydride the ester gives two products, (117) and (118), which both can be hydrolysed to give the unsymmetrically disubstituted pyridines (119) and (120)[102].

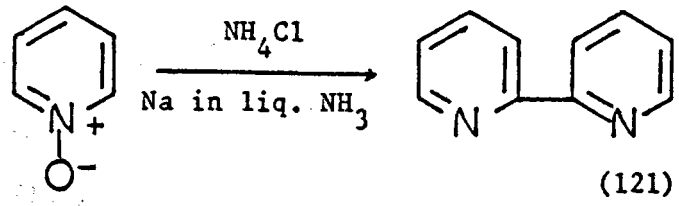


(2.4) Synthesis of 2,2'-bipyridyls.

Bipyridyls, like the alkylpyridines have been obtained by pyrolytic reactions, but these are of little practical value. There are four main methods employed for the synthesis of bipyridyls.

(a) From alkali metals or amides and pyridines.

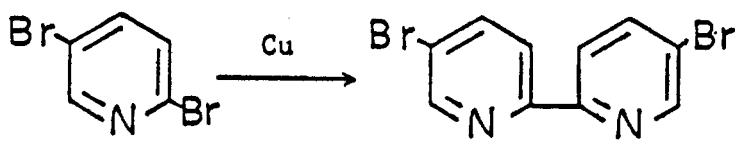
The reaction of pyridine with sodium amide or sodium in liquid ammonia results in the formation of 2,2'- and 4,4'-bipyridines as well as the expected 2-aminopyridine. The relative amounts of the bipyridines which are formed vary according to conditions: their formation is favoured by hydrocarbon solvents when sodium amide is used[103]. The reaction of sodium, air and an excess of pyridine gave a mixture of 2,2'-, 2,3'-, and 4,4'-bipyridines. 2,2'-bipyridine (121) has been obtained in 43% yield from pyridine--1-oxide by treatment with ammonium chloride and sodium in liquid ammonia. A small amount of pyridine was obtained as a by-product[104].



(121)

(b) The Ullmann Reaction

The Ullmann reaction of halo derivatives with copper powder is useful for the preparation of symmetrical bipyridines. 2-bromopyridine gives compound (121) in 60% yield,[105] but the yields are much lower with substituted 2-bromopyridines[106]. As might be expected, 2,5-dibromopyridine reacts at the 2 postition to give 5,5'-dibromo-2,2'-bipyridine (122)[106].



(122)

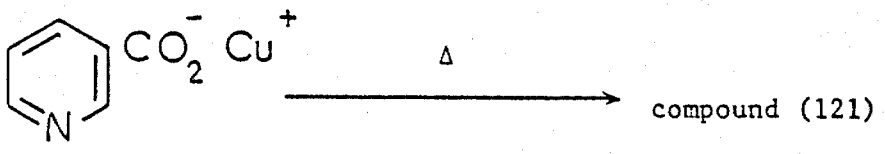
Ferric bromide and bromine have also been used to form bipyridines from 2-bromopyridines in the presence of sunlight[107].

(c) Thermal and catalytic dehydrogenation

Pyridine when heated undergoes dehydrogenation to form bipyridines; the 2,2'-isomer was obtained in a quartz tube with a host of impurities[108]. Heating pyridine with ferric chloride[109], iodine[110], or a nickel alumina catalyst[111] gave 2,2'-bipyridine.

(d) Decarboxylation reactions

Phenanthrolines on oxidation yield bipyridine carboxylic acids which can be decarboxylated to give bipyridines. Salts of pyridine carboxylic acids decompose on heating to yield bipyridines; for example, 2,2'-bipyridine (121) was obtained from copper nicotinate (123)[113].



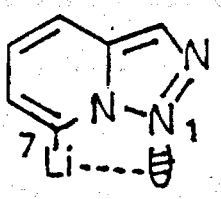
(123)

PART A

SYNTHESIS OF 7-SUBSTITUTED[1,2,3]TRIAZOLO [1,5-a]PYRIDINES.

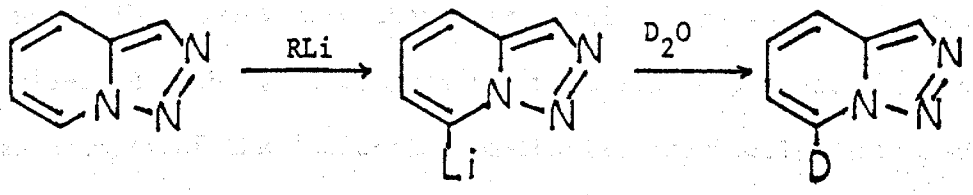
Discussion

Our goal in the research described in this chapter was the use of directed lithiation to functionalise the pyridine ring of the triazolopyridine (1) ring system. If we examine compound (1) we see that on each non-bridged nitrogen atom there is a lone pair of electrons. It was thought that the directing ability of the lone pair of electrons on the peri-nitrogen atom (N1) could be used to direct lithiation to position 7 on the triazolopyridine (1) ring.



It was thought that a lithiating agent would first coordinate with the lone pair and then, the nearest proton, H7, in the peri position, would suffer deprotonation (protophilic attack), leading to an organolithium species. This organolithium species could then react with a variety of electrophiles to produce 7-substituted triazolopyridines.

Our first task was to find the best lithiating agent, temperature and reaction time to give an optimum yield of the organolithium species. Triazolopyridine (1) was treated with a variety of lithiating agents, varying both temperature and reaction time. The organolithium species (124) obtained was then quenched with D_2O to give 7-deuteriotriazolopyridine (125).



(1) (124) (125)

The extent of lithiation was measured by n.m.r. spectroscopy. This technique was also used to verify the position of lithiation. On quenching with D_2O the signal due to H7 (at δ8.7 ppm) was much less intense, so indicating that deuterium had replaced the hydrogen atom at position 7. It is believed that the lithiation is directed by the peri-nitrogen atom (N1), because deuterium exchange normally occurs first at position 3, under base catalysis[28]. Our results are summarised in table 2.3

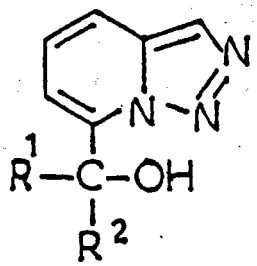
Lithiating agent	Solvent	Temperature °C	Reaction time hrs	% Lithiation
n-BuLi	Ether	-10	3	50
"	"	-40	6	70
"	"	-50	2	66
"	"	-70	0.5	50
n-BuLi	THF	-40	6	50
"	"	-40	24	50
n-BuLi/TMEDA	THF	-40	6	10
"	"	-40	24	20
L.D.A.	Ether	-40	5-6	85
"	THF	-60	6	60

Table 2.3

Table 2.3 shows that the best results were obtained using the lithium diisopropylamide/ether lithiating system. This system has negligible Lewis-acid character, acting more as a base than as a Lewis-acid. Thus, it removes the most acidic proton, H7. This is an example of the 'acid-base' mechanism previously mentioned.

The n-BuLi/ether system, however, has high Lewis-acid character. It is expected to coordinate preferentially with the nitrogen atom (N1) lone pair and then abstract the nearest proton H7, thus exemplifying the 'coordination only' mechanism. The fact that the LDA/ether systems give the highest percentage of lithiation suggests that the acidity of the proton at position 7 is the determining factor in this lithiation. An apparent contradiction of this hypothesis is the fact that both the n-BuLi/TMEDA and n-BuLi/THF systems, which both have negligible Lewis-acid character, give lower percentage lithiation than the n-BuLi/ether system.

Throughout the research described in this thesis, most of the lithiation was done with the lithium diisopropylamide/ether system, the reaction temperature and time being -40°C and 6 hours respectively. Under these conditions, the 7-lithiotriazolopyridine (124) was treated with various aldehydes and ketones chosen to provide a full range of reactivities.

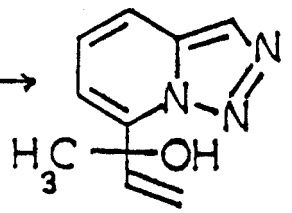
Compound (124) $\xrightarrow{R^1COR^2}$  (126) a-h

The results are summarised in table 2.4. The spectral feactures of these compounds will be discussed in chapter 4.

Compound (126)	R^1	R^2	% Yield	M.pt. °C
a	H	$n\text{-}C_7H_{13}$	30	unstable brown oil
b	H	Ph	30	123.5 - 124.5
c	H	$4\text{-}MeOC_6H_4$	69	171 - 172
d	H	$4\text{-}NO_2C_6H_4$	20	180 - 182
e	Me	4-pyridyl	40	125 - 126
f	$CH_2CH_2CH_2CH_2CH_2$		25	100
g	Ph	Ph	52	186.5 - 187.5
h	Me	$CH = CH_2$	38	unstable oil

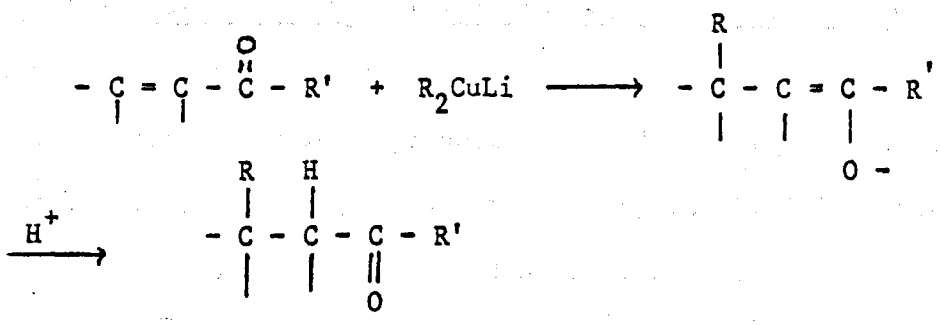
Table 2.4

The reaction of 7-lithiotriazolopyridine (124) with methyl vinyl ketone (an α,β-unsaturated ketone) produces the expected 1,2 addition product (126 h)[114]

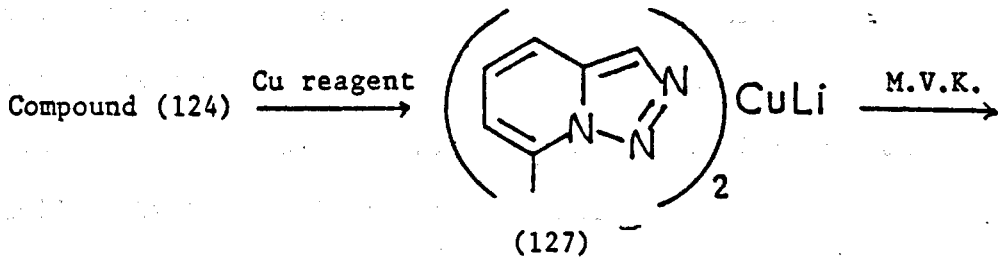
Compound (124) $\xrightarrow{\text{M.V.K.}}$ 

(126h)

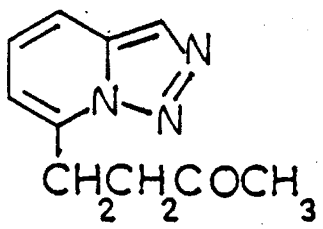
It is known that lithium dialkyl copper reagents add to α,β--unsaturated aldehydes and ketones to give conjugate addition products (1,4 addition)[115,116].



It was thought that the 1,4 addition product (128) could be obtained by converting the lithio species (124) into the bis(triazolopyridin-7-yl) copper reagent (127) and then by subsequent reaction with M.V.K.



(127)



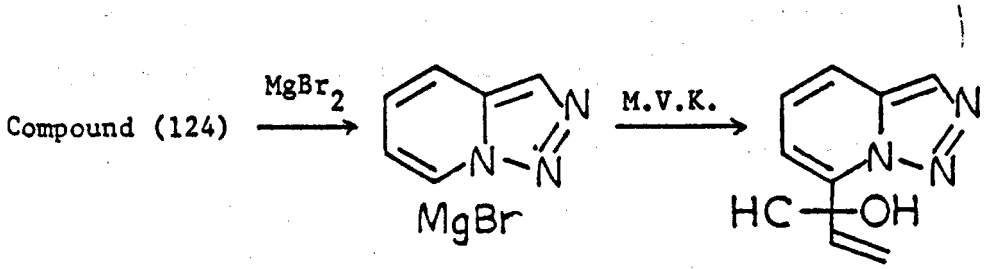
(128)

Two copper reagents were employed to effect this conversion.

(i) Use of cuprous halides. $R_2'CuLi$ reagents can be prepared by mixing 2 moles of the alkyl lithium reagent with 1 mole of cuprous halide. The cuprous halide has to be very pure[117], or better still, freshly prepared[118]. However, upon addition of M.V.K. and after work-up, only the 1,2 addition product was isolated in 37% yield.

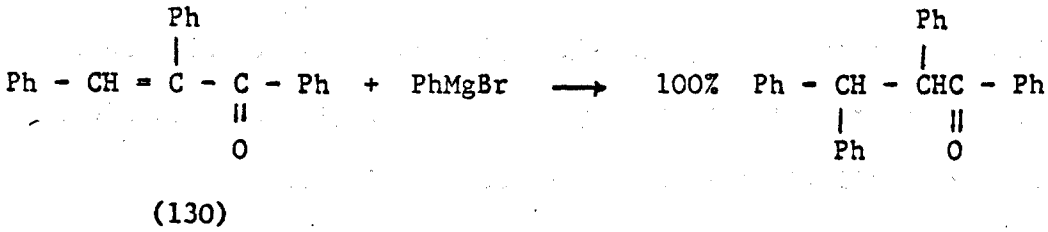
(ii) Use of a dimethyl sulphide - cuprous bromide complex to prepare the lithium diarylcuprate[119]. The complex is easily synthesised using equimolar proportions of dimethyl sulphide and cuprous bromide. The complex was then recrystallised from hexane. However, when this complex was used no reaction at all was observed with M.V.K. and triazolopyridine (1) was recovered.

From table 2.4 it can be seen that the yields for some of the triazolopyridin-7-yl methanols (126) are low. It was thought that conversion of the lithium species (124) into a Grignard reagent (129) would improve the yields. The reaction with M.V.K. was used in this investigation. The lithium species (124) was therefore treated with anhydrous magnesium bromide to give the Grignard reagent (129). Reaction with methyl vinyl ketone then gave the expected 1,2 addition product (126 h), but in a yield (35%) little different from that obtained from the lithium derivative.

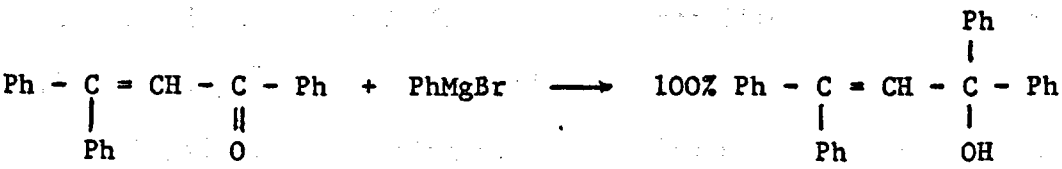


(129) (126h)

Grignard reagents may react with α,β-unsaturated ketones to give both 1,4 and 1,2 addition products: the product is often controlled by steric factors. Thus, compound (130) with phenylmagnesium bromide gives 100% 1,4 addition, while compound (131) gives 100% 1,2 addition[120].



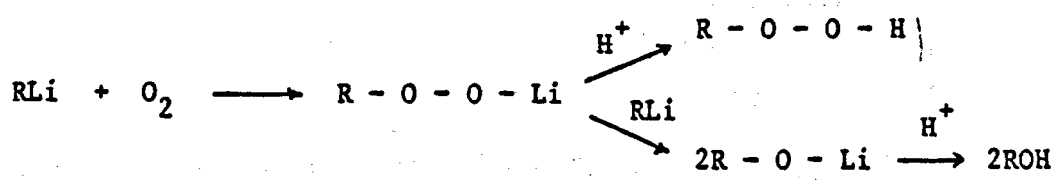
(130)



(131)

In general, substitution at the carbonyl group increases 1,4 addition, while substitution at the double bond increases 1,2 addition.

In the preparation of the 7-lithio derivative (124), the blanket gas used was nitrogen (dried by passing through sulphuric acid). However, even commercially available 'oxygen free' nitrogen contains 10 ppm of oxygen. Most organometallic compounds react with oxygen to give either hydroperoxides or alcohols[121].

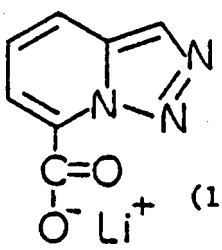


It is because of the possibility of these reactions that oxygen must be excluded when organolithium reagents are desired for other purposes. So it was decided to use 'oxygen-free' nitrogen or an argon atmosphere in the lithiation reactions.

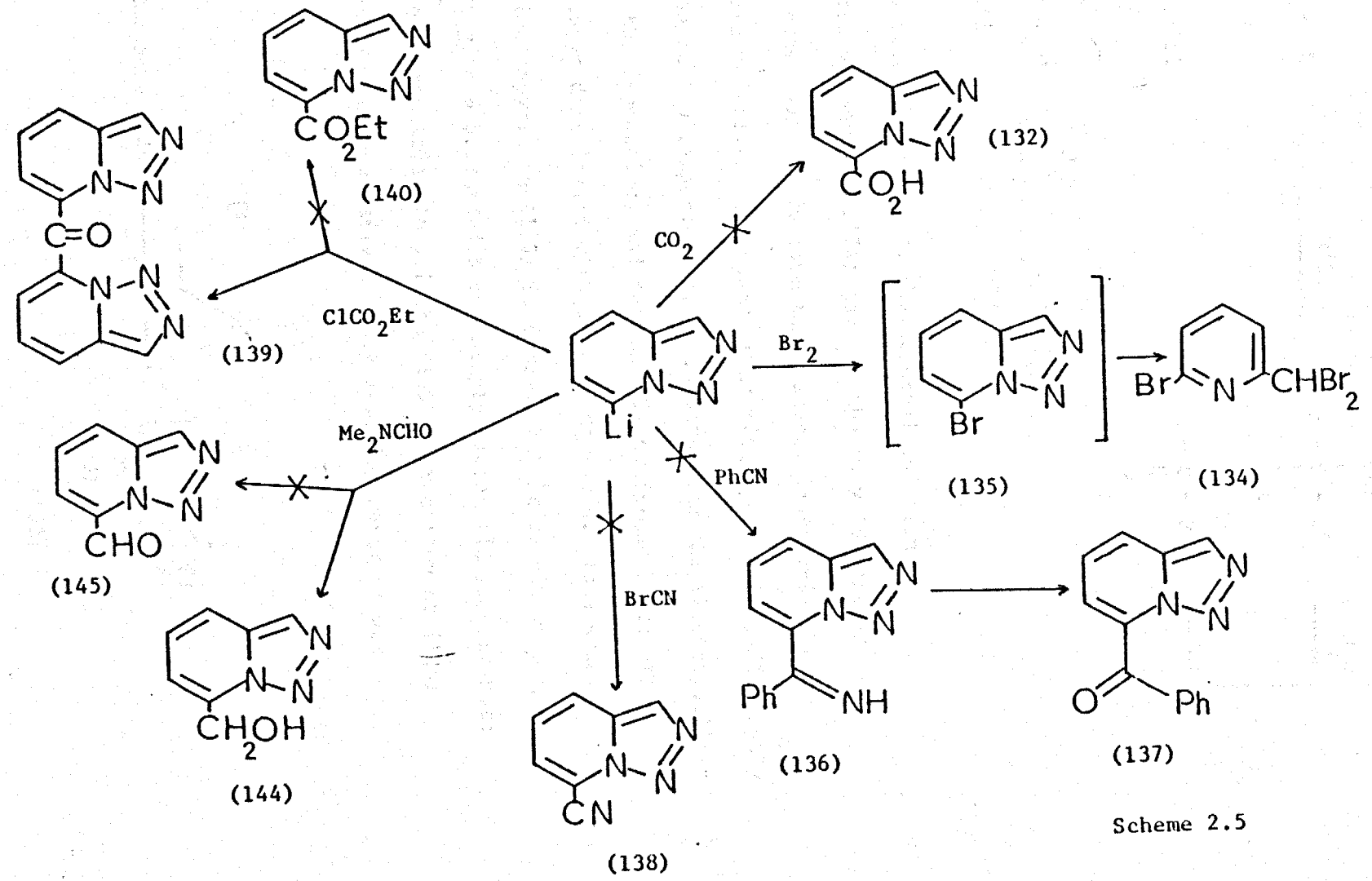
The synthesis of the triazolopyridin-7-yl methanols (126 a) and (126 b) was repeated using 'oxygen free' nitrogen. The

previous yields were each 30%, while the yields increased to 55 and 53% respectively when the 'oxygen-free' nitrogen was used.

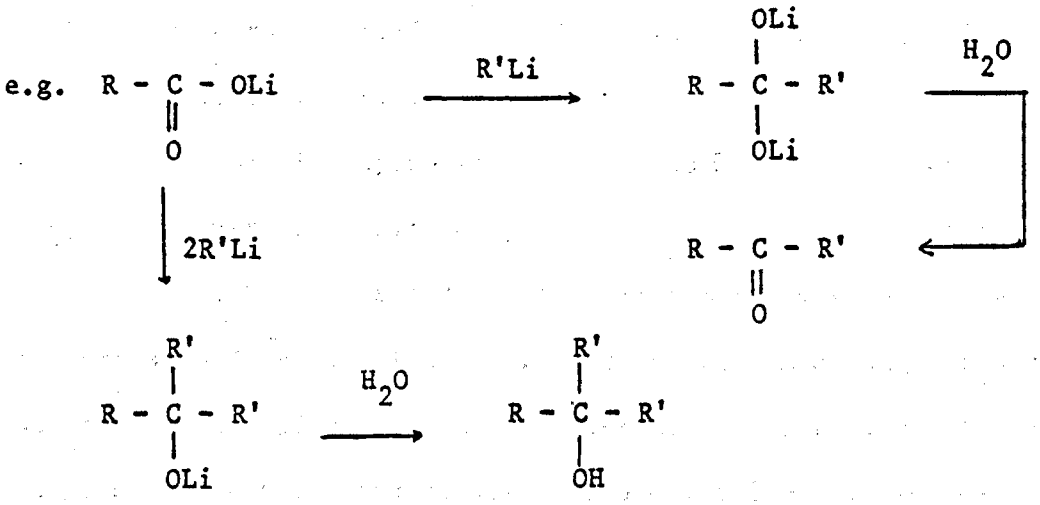
Attempts to bring about reactions of the 7-lithiotriazaolo--pyridine (124) with electrophiles other than aldehydes or ketones met with mixed success. The reactions are illustrated in scheme 2.5. No alkylation was achieved with either methyl iodide or benzyl bromide. Surprisingly, no reaction was observed between acetaldehyde and 7-lithiotriazolopyridine (124). However, this reaction was performed using n-BuLi as the metalating agent and not lithium diisopropylamide. Attempts to produce the 7-triazolopyridine carboxylic acid (132) failed. The reaction was performed by adding the organolithium reagent to solid CO_2. The product expected was the salt of the carboxylic acid (133).

Compound (124) $\xrightarrow{CO_2}$  (133)

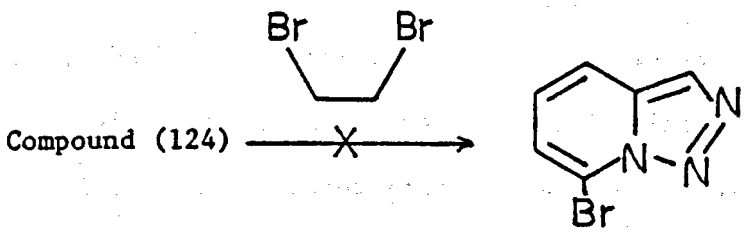
It is also possible to bubble carbon dioxide through the solution of the organolithium reagent. However, the latter procedure usually gives lower yields, since the salt can react with additional molecules of the organolithium species to give a ketone and a tertiary alcohol[120].


CO2Et
(140)
C=O
(139)
ClCO2Et
CO2
CO2H
(132)
Li
Br2
Br
(135)
Br
CHBr2
(134)
Me2NCHO
CHO
(145)
CH2OH
(144)
PhCN
BrCN
CN
(138)
Ph
NH
(136)
O
Ph
(137)

Scheme 2.5



Addition of bromine to the ethereal solution of 7-lithiotriazolopyridine (124) gave as the only identified material, after warming to room temperature, 6-bromo-2-dibromo--methylpyridine (134). It appears that ring opening is sufficiently rapid, even at low temperatures, to compete with the electrophilic attack on the 7-position, and this can be confirmed by treatment of triazolopyridine itself with bromine at -40°C. Thus some 7-bromotriazolopyridine (135) is formed, but it reacts with more bromine to give 6-bromo-2-dibromomethylpyridine (134). Attempts to prepare 7-bromotriazolopyridine (135) by reaction of (124) with 1,2-dibromoethane failed. Only starting material was recovered.



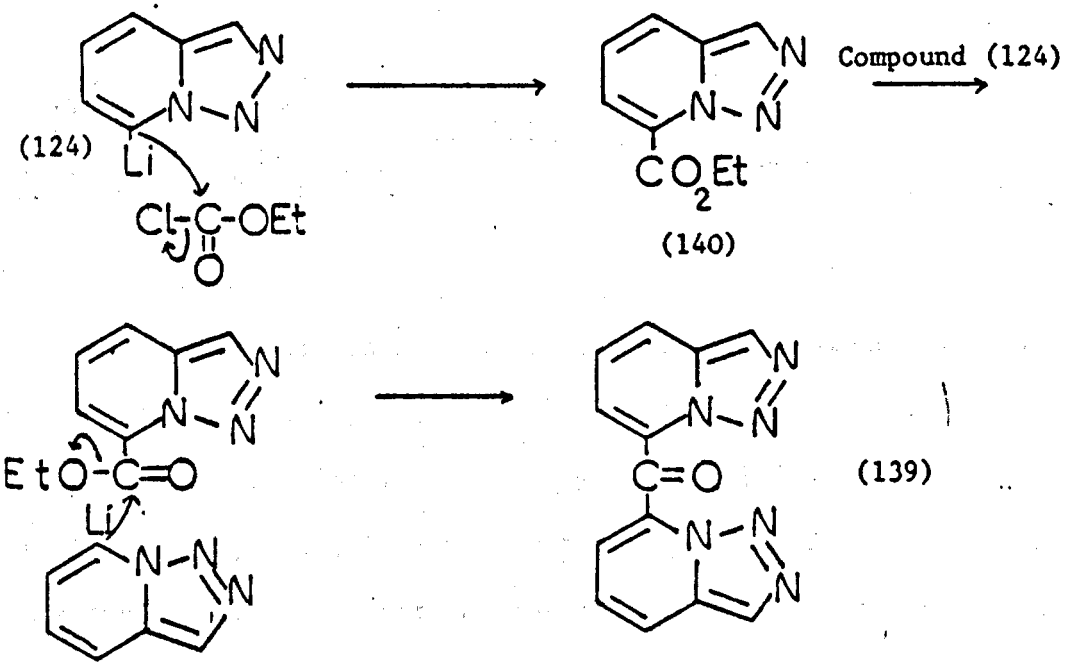
(135)

Reaction of the organolithium compound (124) with benzonitrile was expected to give the ketimine (136) which would

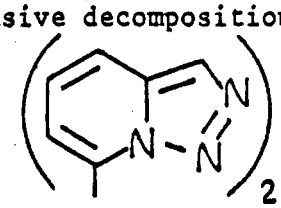
be hydrolysed to ketone (137) during work up. However, only starting materials were recovered.

Reaction with cyanogen bromide also failed to produce the 7-cyano derivative (138); only starting materials were recovered.

With ethyl chloroformate the lithium derivative gave a colourless powder of molecular weight 264 with a strong carbonyl absorption at 1635 cm^{-1} in the infra-red. The structure of the compound was established as bis-triazolopyridin-7-yl ketone (139). No ester (140) was isolated. The mechanism is probably as follows.

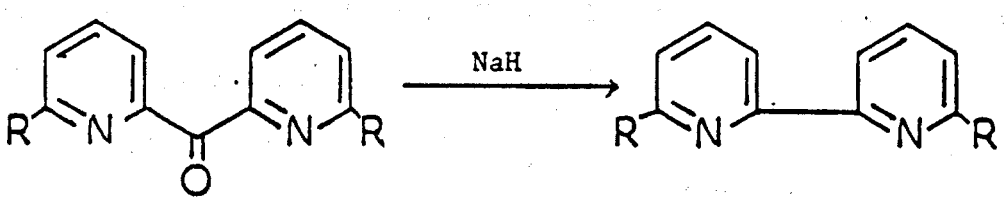


The yield of the ketone obtained was 19%. In an attempt to improve this yield the reaction was repeated using one half of an equivalent of ethyl chloroformate. However, no significant increase in yield was observed. Attempts to decarbonylate the ketone (139) in the hope of obtaining bis-triazolopyridin-7-yl (141) led to extensive decomposition. This was not unexpected.



(141)

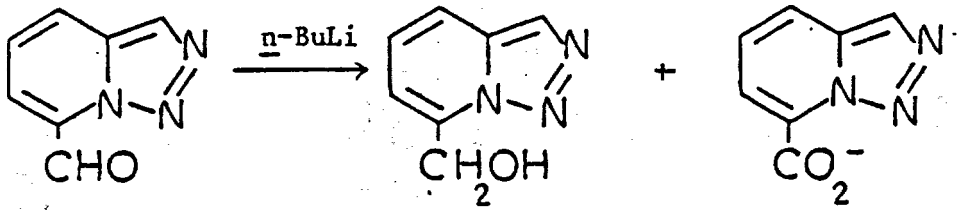
Although aldehydes undergo relatively easy decarbonylation under a variety of reaction conditions[125], decarbonylation of ketones has been achieved primarily via photolytic[126] or drastic pyrolytic (>500°C)[126,127] conditions. Newkome[128] has developed a method for decarbonylating ketones under mild conditions. Substituted di(2-pyridyl)ketones (142) undergo decarbonylation upon mild treatment with base to give the corresponding bipyridyls (143)



(142) (143)

Another surprising result was obtained from the reaction of 7-lithiotriazolopyridine (124) with dimethylformamide. The product was the triazolopyridin-7-yl methanol (144) (ν_{max} 3420 cm^{-1} (OH), δ5.19 ppm, 2H, CH_2) rather than the aldehyde (145). There are two possible explanations for the formation of the methanol (144)

(i) The Cannizzaro reaction[129]. If any aldehyde (145) was formed it could possibly undergo the Cannizzaro reaction in the presence of the base, n-butyllithium. It is thought that one molecule of aldehyde oxidises another to the acid and is itself reduced to the primary alcohol (144).



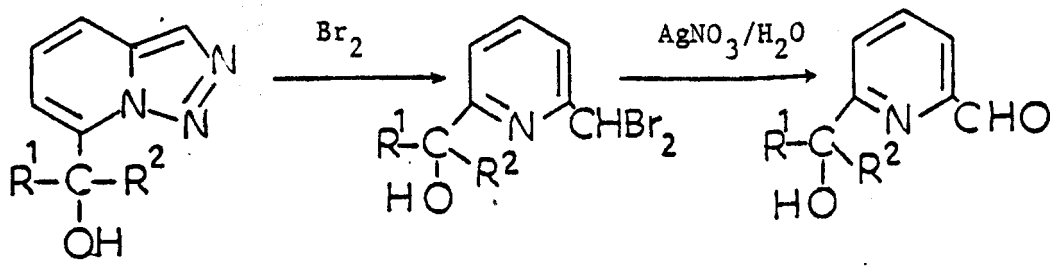
(145) (144) (146)

The other product of the reaction would be the carboxylic acid (146). However, no acid was isolated possibly because of the work up and purification procedure. The reaction mixture was subjected to medium pressure chromatography using a 50:50 mixture of ethyl acetate / toluene as eluant. This solvent system would not elute the carboxylic acid (146) from the silica.

(ii) Another possibility is the common side reaction which occurs during Grignard addition, reduction[120,130]. In the reduction, the carbonyl compound is reduced to an alcohol by the Grignard reagent, which itself undergoes elimination to give an olefin. However, this type of side reaction occurs mostly with hindered ketones and bulky Grignard reagents. Since we have neither a hindered aldehyde or bulky Grignard (organolithium) agent it seems probable that the first explanation is the more likely.

The route to the triazolopyridin-7-yl-methanols (126) could be used to prepare unsymmetrically substituted pyridine-2--carboxaldehydes. For example, compounds (126c and g) were treated with bromine in dichloromethane at 0-10°C and the dibromomethyl--pyridines (147c and g), thus obtained in excellent yields, were treated with aqueous silver nitrate in alcohol to give the

6-substituted-pyridine-2-carboxaldehydes (148c and g).



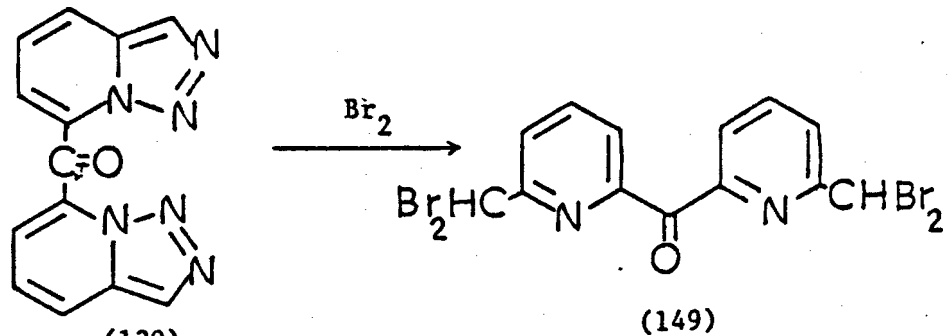
(126) (147) (148)

C; R^1 = H, R^2 = 4 - $MeOC_6H_4$

g; R^1 = R^2 = Ph

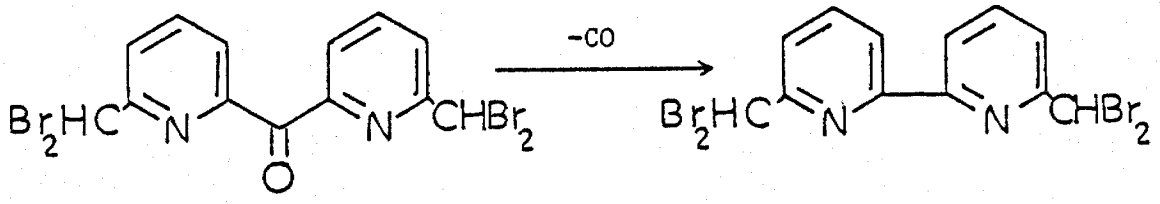
There is no reason why the excellent yields obtained for the alcohols (126c and g) cannot be repeated for the other alcohols previously obtained. This method is an excellent route to unsymmetrical 2,6-disubstituted pyridines. No easy method exists for the synthesis of such compounds (see review on synthesis of 2,6-disubstituted pyridines).

The ketone (139) also reacts with bromine to give the previously prepared[131] symmetrical dibromide (149).



(139) (149)

This method greatly simplifies the previous lengthy synthesis[131]. Decarbonylation of the dibromide (149) could give the bipyridyl (150).

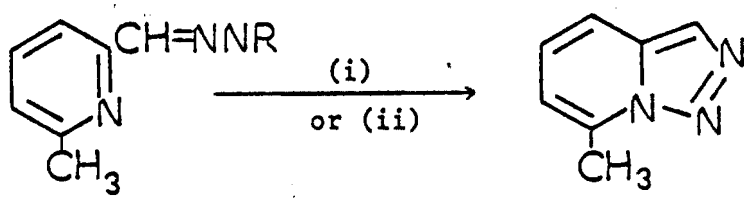


(149) (150)

PART B

SYNTHESIS AND LITHIATION OF 7-METHYL-[1,2,3] TRIAZOLO[1,5-a]PYRIDINE.

7-methyltriazolo(1,5-a)pyridine (153) was synthesised by oxidation of the hydrazone (151) of 6-methyl pyridine-2-carboxaldehyde, or by treatment of the tosylhydrazone (152) with morpholine.

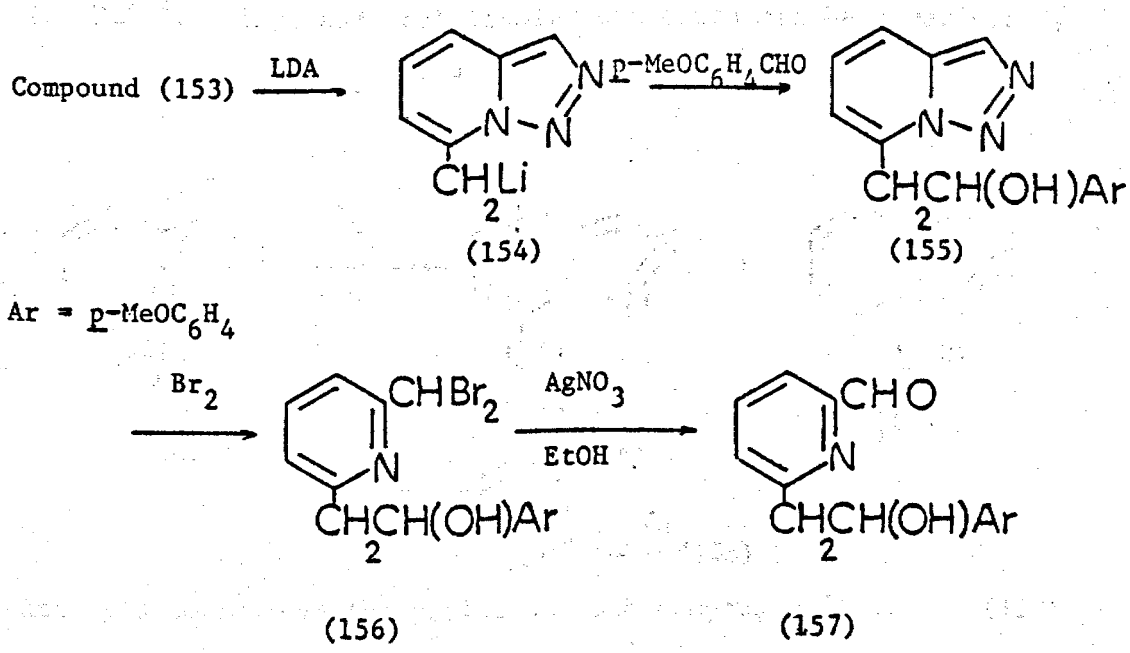


(151), R = H

(152), R = $SO_2C_6H_4Me$-p

(153) (i) $Fe(CN)_6^{3-}$,OH^- (ii) or morpholine

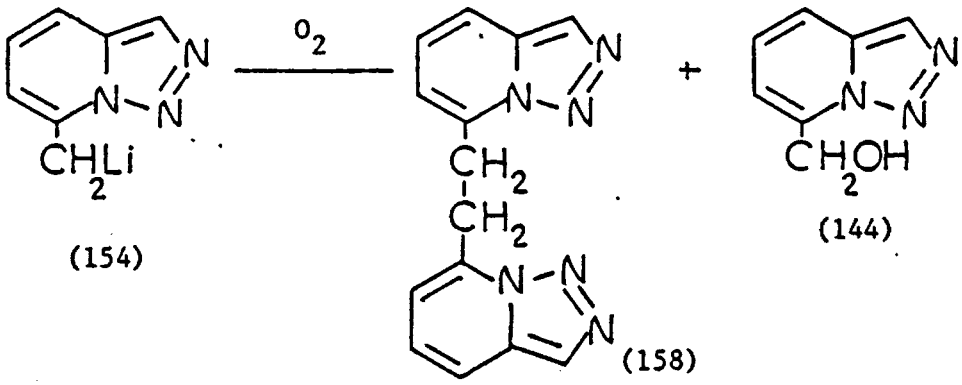
Experiments with lithium deuteroxide resulted in no deuterium exchange. The reaction was followed by n.m.r. spectroscopy. No change was observed in the spectrum of (153), the singlet at δ2.88 p.p.m. due to the methyl group showing no change after 20, 40 and 80 minutes. On treatment with sodamide followed by addition of benzylbromide, no alkylation was observed. Both these experiments showed that the methyl group in compound (153) had little if any activity of the type exhibited by 2-methylpyridine[120]. However, lithiation (again presumably directed by the peri-nitrogen atom, N1) with lithium diisopropylamide at -40°C for six hours, and treatment of the 7-lithiomethyl intermediate (154) with anisaldehyde gave the secondary alcohol (155) (M^+ 269, ν_{max} 3400 cm^{-1} (OH), δ3.51 ppm, 2H, CH_2) in 57% yield. The alcohol (155) reacted with bromine to give the dibromomethylpyridine (156) (87%), and this in turn, treated with alcoholic silver nitrate, gave the pyridine-2-carboxaldehyde (157) (68%).



Anisaldehyde was the only co-reactant tried but there is no reason why the 7-lithiomethyl derivative (154) should not react with other aldehydes and ketones in a manner similar to 7-lithiotriazolo--pyridine (124).

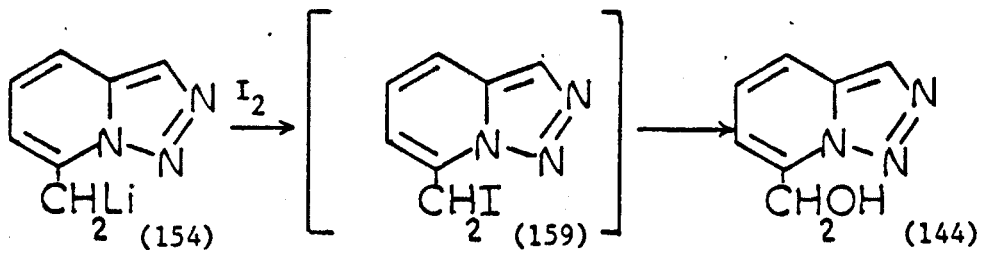
The above reaction was carried out using 'oxygen-free' nitrogen. In earlier attempts 'oxygen-free' cylinder nitrogen was used. None of the expected alcohol (155) was obtained, instead triazolopyridin-7-yl methanol (144) (35%) was isolated, together with very small ammounts of 1,2-bis(triazolopyridin-7-yl)ethane (158) (δ3.9 ppm, s, 4H, CH_2CH_2). Both these products are characteristic of the reaction of the 7-lithiomethyl derivative (154) with oxygen. The production of triazolopyridin-7-yl methanol (144) is from a direct reaction between oxygen and the 7-lithio--methyl derivative (154). The formation of the ethane bridged compound (158) is via a coupling reaction using oxygen as the

oxidising agent. It has been reported that lithium dialkyl copper reagents can be oxidised to symmetrical dimers by O_2 at -78°C in T.H.F.[132]. Alkyl and aryl lithium compounds can be dimerised by transition metal halides[133].



(154) (158) (144)

Attempts to improve the yields of both compounds (144) and (158) met with mixed success. There was little improvement in yield (35%) of compound (156) when dry air was bubbled into the reaction mixture containing the lithium derivative (154). Iodine has previously been used to couple aryllithium compounds[134]. However, upon adding half an equivalent of iodine, only compound (144) was produced. The initial product in this reaction was thought to be 7-iodomethyltriazolopyridine (159) which on work up was hydrolysed to compound (144)



(154) (159) (144)

None of the coupled product (158) was isolated. This proved to be a very good synthesis of the alcohol (144) (50%); even greater yields could probably be obtained by using one equivalent of iodine.

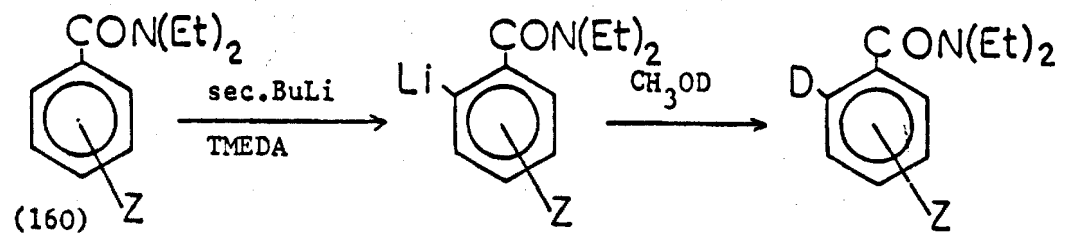
A common feature in all the reactions of (154) with anis-

-aldehyde was the isolation, after work up, of p-methoxybenzyl alcohol. If this was a result of a Cannizzaro reaction on p-methoxybenzaldehyde, the other product, p-methoxybenzoic acid was never isolated.

PART C

COMPETITIVE LITHIATION. INTRODUCTION OF THE ORTHO DIRECTING TERTIARY AMIDE MOIETY AT POSITION 3.

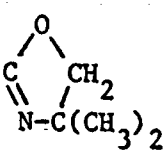
Recent work has suggested that the tertiary carboxamide group can function as an effective ortho director[135-141]. Beak[142] and Meyers and Lutomski[143] have communicated observations which suggest that with organolithium/tetramethylenediamine (TMEDA) bases the tertiary carboxamide is generally more effective as a director of ortho lithiation than any of the noncarboxamide directing groups previously studied. Beak[144] has carried out intramolecular competitions between the tertiary amide group and previously known directing groups by investigation of the position of lithiation of the substituted N,N-diethylbenzamides (160, a-m) with sec-BuLi/TMEDA. The extent and site of metalation was evaluated by treatment of solutions of lithiated amide with deuteriomethanol, followed by mass spectrometric and n.m.r. determination of the amount and location of deuterium in products (161, a-m).



(160) (161)

Z given below

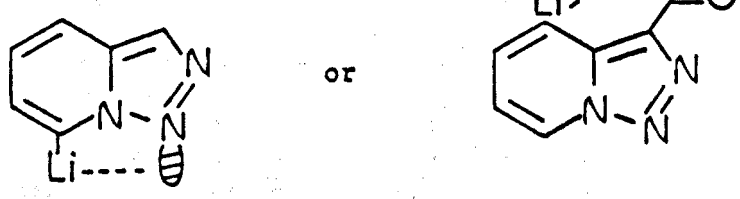
a, o-Cl; b, m-Cl; c, p-Cl; d, o-OCH_3; e, m-OCH_3; f, p-OCH_3; g, m-CH_3; h, p-CH_3; i, p-$SO_2N(Et)_2$; j, p-SO_2NHCH_3; k, p-$CH_2N(CH_3)_2$;

l, p-  ; m, p-CO_2H

The results show that the tertiary amide group is the most effective in directing ortho lithiation. It even competes

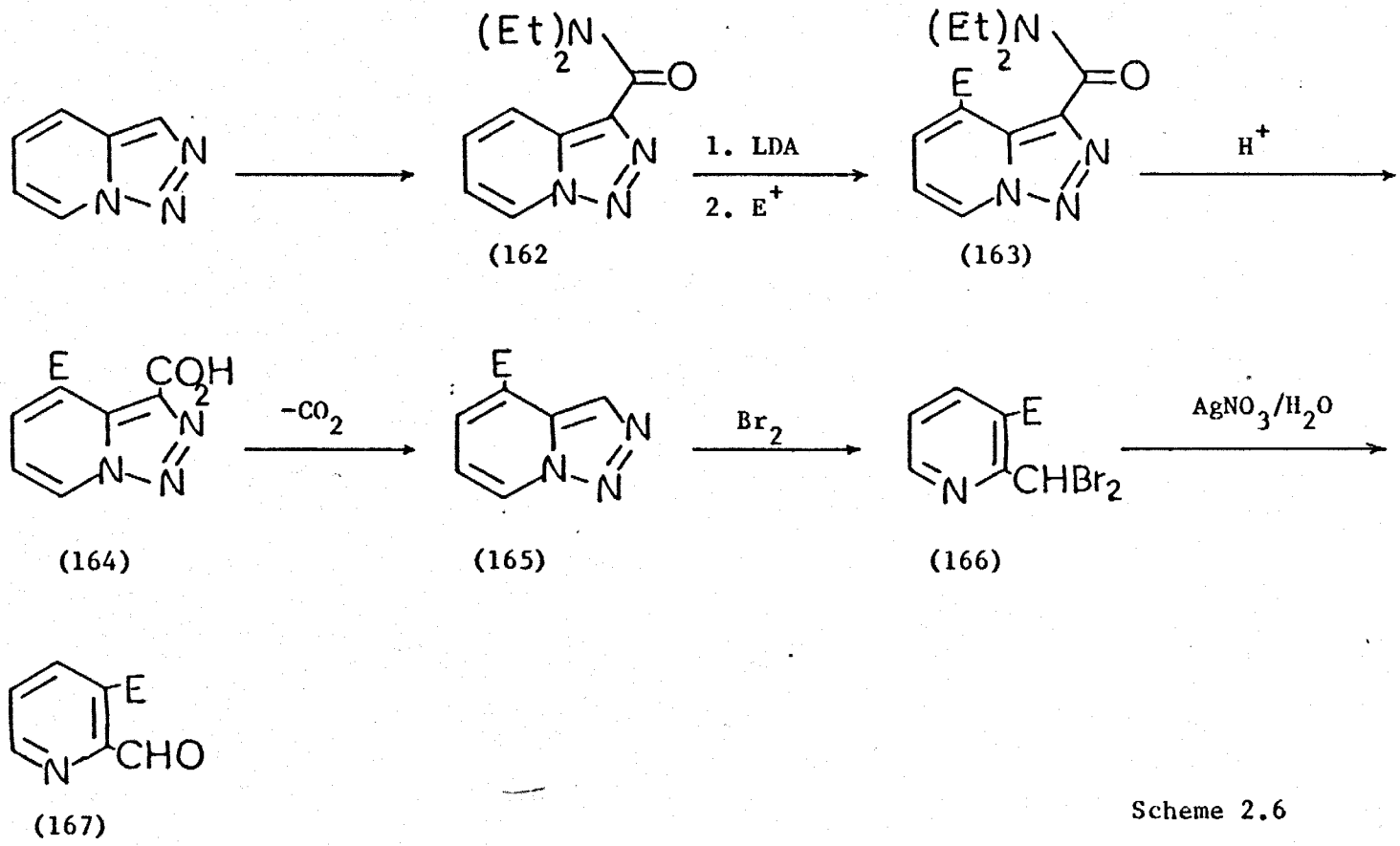
successfully with the diethylsulfonamide group which was previously thought to be the best of all ortho directors[60]. The only group which was found to be competitive with the tertiary amide in directing ortho lithiation, under the conditions specified, was the secondary amide.

Triazolopyridine provides the possibility of utilising the extraordinary directing ability of the tertiary amide group to synthesise 2,3-disubstituted pyridines. If the tertiary amide group could be introduced into position 3 of triazolopyridine and there the molecule then lithiated, there arises two directing groups in the molecule. The peri nitrogen atom N1 directs lithiation to position 7, whilst the tertiary amide group might possibly direct lithiation to position 4.



On the strength of previous work[135-144] the tertiary amide would be expected to compete successfully with the peri-nitrogen atom N1. In this case a 4-substituted triazolopyridine would be the product after lithiation and reaction with a co-reactant. Scheme 2.6 shows the possible route to 2,3-disubstituted pyridines.

Lithiation of the amide (162) followed by reaction with an electrophile would give the 3,4-disubstituted triazolopyridine (163). Hydrolysis of the amide function would give the acid (164) which could be decarboxylated to give the 4-substituted triazolo--pyridine (165). Bromination would give the 2,3 disubstituted

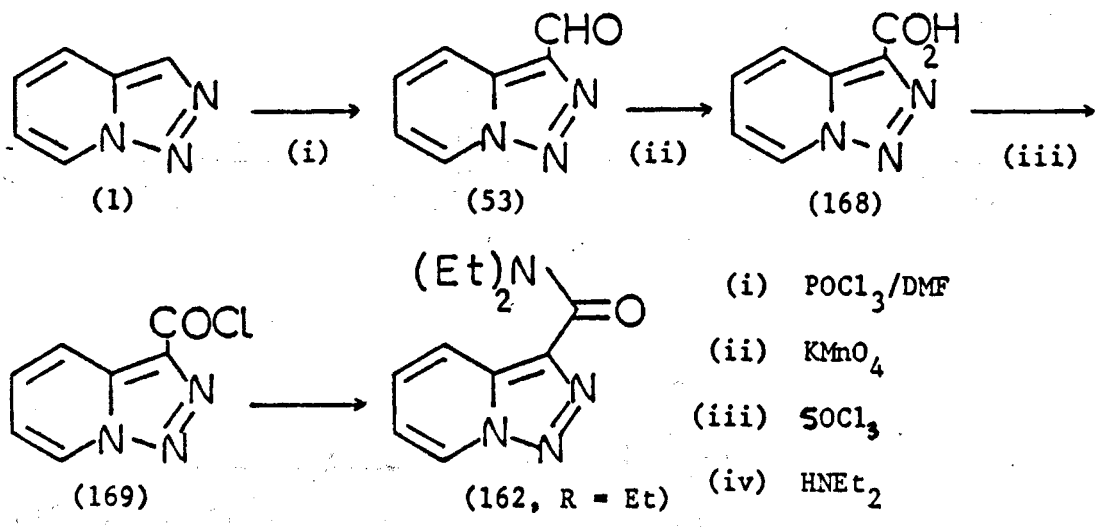

(Et)2N
O
1. LDA
2. E+
H+
(162
(163)
E
CO2H
-CO2
Br2
AgNO3/H2O
CHBr2
(164)
(165)
(166)
CHO
(167)

Scheme 2.6

pyridine (166) and reaction with aqueous silver nitrate in ethanol would convert the dibromomethyl function to the aldehyde function as in compound (167).

The first task was the synthesis of the amide (162). The routes tried were as follows:

(i) via 3-formyltriazolopyridine (53)

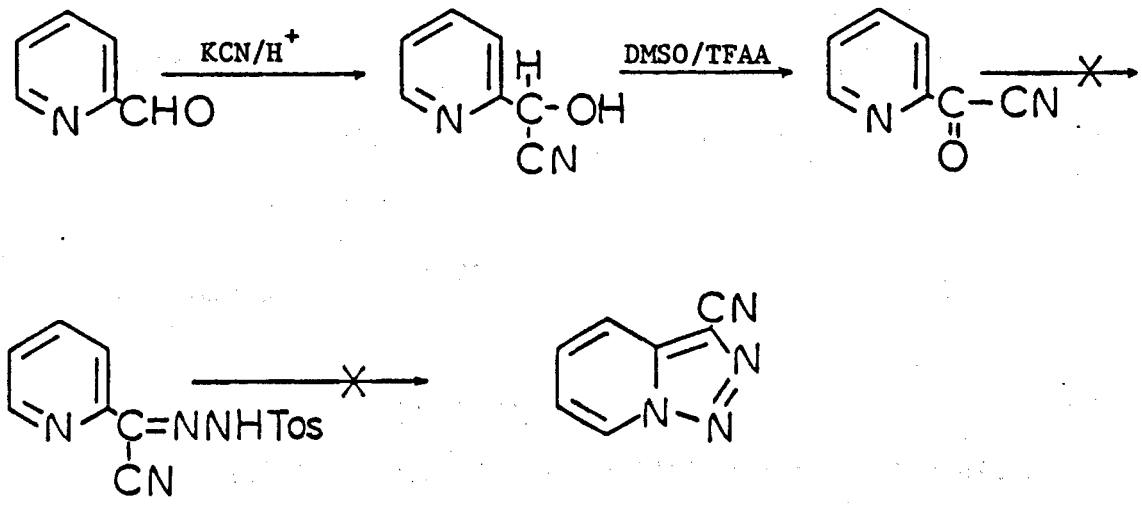


It was thought that the formyl compound (53) could be oxidised to the acid (168) using potassium permanganate[145]. Reaction of the acid with thionyl chloride followed by diethylamine would give the amide (162). However as has previously been mentioned, Vilsmeier-Haack formylation of triazolopyridine (1) failed to give any of the 3-formyl compound (53). This method was thus abandoned.

(ii) From suitably substituted pyridylglyoxylic acid derivatives.

If a suitably substituted pyridylglyoxylic acid derivative could be prepared which already contained a synthon for the

tertiary amide, the normal triazolopyridine synthesis, could be followed, i.e. hydrazone formation and then cyclisation, to yield the required 3-substituted triazolopyridine. It was decided to attempt the synthesis of 3-cyanotriazolopyridine (173) starting from pyridine-2-aldehyde. 3-Cyanotriazolopyridine has been synthesised before[20] using the rather inaccessible 2-cyanomethyl--pyridine[146]. The route attempted is shown in scheme 2.7.



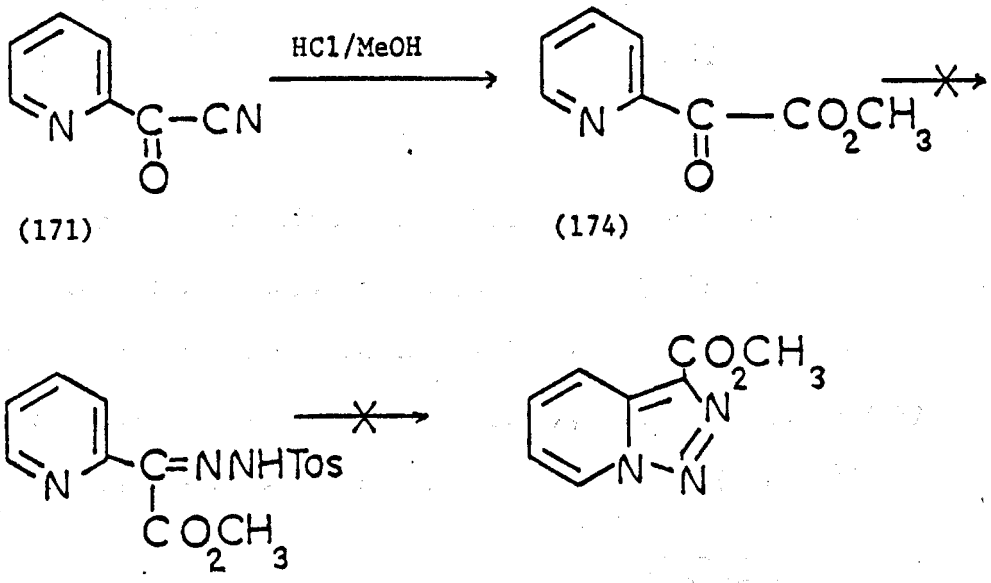
(172) (173)

Tos = Tosyl

Scheme 2.7

The cyanhydrin (170) was prepared from pyridine-2-carboxaldehyde[147]. Pyridoin was a by-product. Oxidation with dimethylsulphoxide/· trifluoroacetic anhydride[148] gave the cyanoketone (171). However attempts to prepare the tosylhydrazone (172), using a variety of conditions, failed. The reason for this lack of reaction was not immediately obvious. The cyano group was coverted to a methyl ester group (174) by bubbling hydrogen chloride into a methanolic solution of the cyanoketone[149]. However attempts to form the tosylhydrazone (175) under a variety

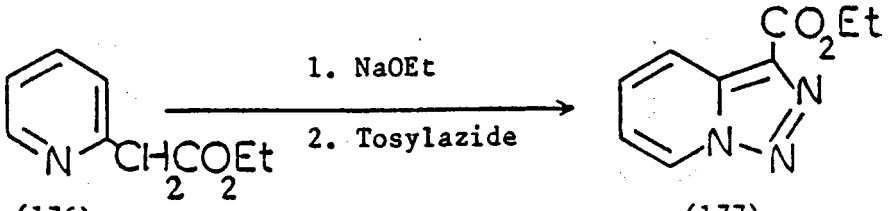
of conditions failed, this method was thus abandoned. See scheme 2.8.



Tos = Tosyl. Scheme 2.8

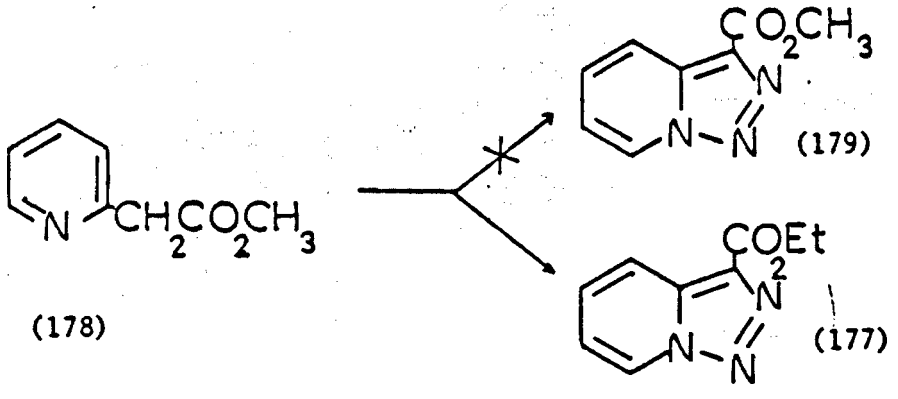
(iii) Direct diazo group transfer.

As previously mentioned, Regitz[18,19] has shown that diazo groups can be introduced to suitably active methylene compounds using a base and tosylazide. By using a suitably substituted methylene compound, the synthon for the amide group could be introduced directly into position 3. Ethyl 2-pyridyl acetate (176) was synthesised[150] and treated with tosylazide and sodium ethoxide in ethanol. This gave a compound of mass 191 m/e with a strong carbonyl absorption at 1650 cm^{-1} (characteristic of an ester carbonyl). In the n.m.r. spectrum, the typical pattern expected for a triazolopyridine was observed. All these spectral features lead to the conclusion that the compound was 3-ethoxy-carbonyltriazolopyridine (177).



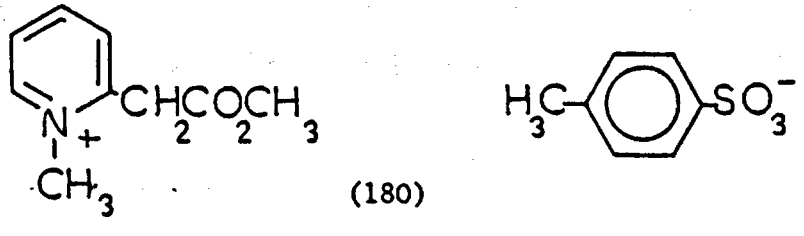
(176) (177)

Attempts to synthesise the methyl ester led to some interesting results. Methyl 2-pyridyl acetate (178) was synthesised[150] and treated with tosylazide and sodium ethoxide in ethanol. Instead of the methyl ester (179), the ethyl ester (177) was produced presumably by a process of transesterification[151].



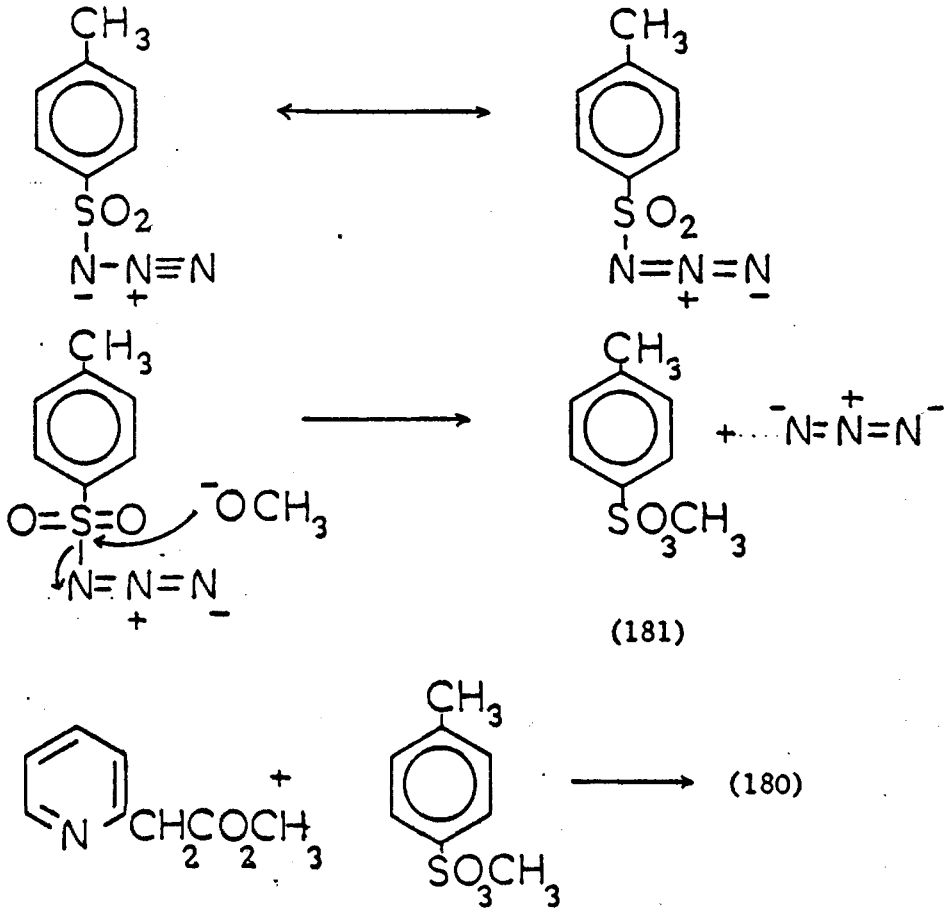
(178) (179) (177)

When potassium methoxide in methanol or sodium methoxide in methanol were used as the base, the salt (180) was isolated. The structure was confirmed by synthesis. The acetate (178) was treated with methyl toluene-4-sulphonate in benzene solution and boiled under reflux to give the same salt (180).



(180)

The formation of this salt can be explained as shown in scheme 2.9.

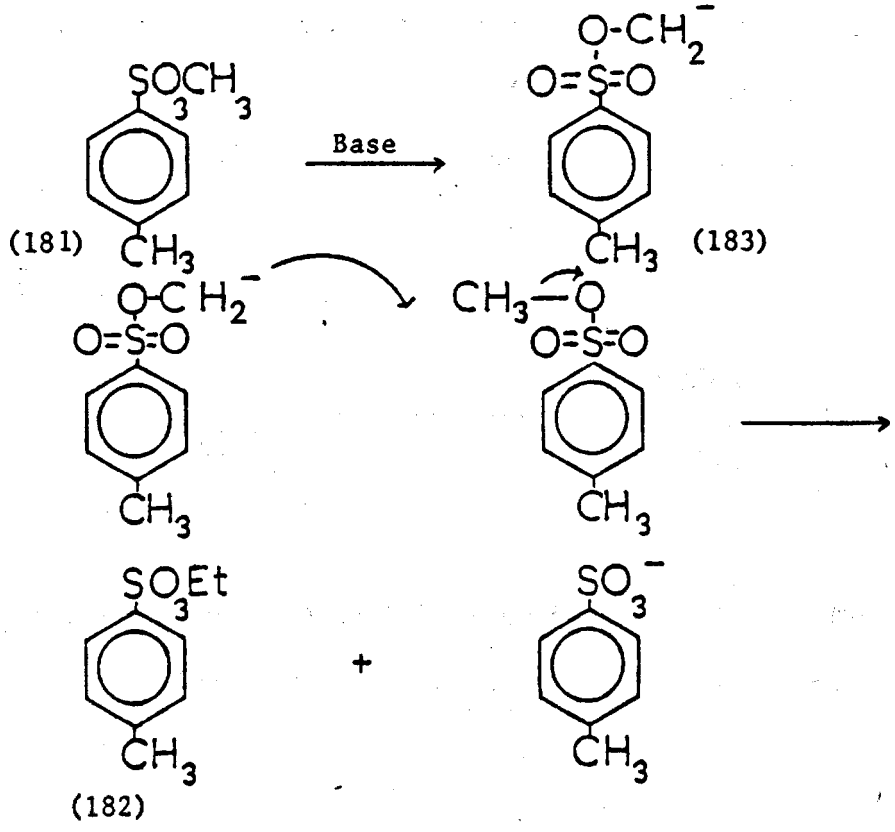


(181)

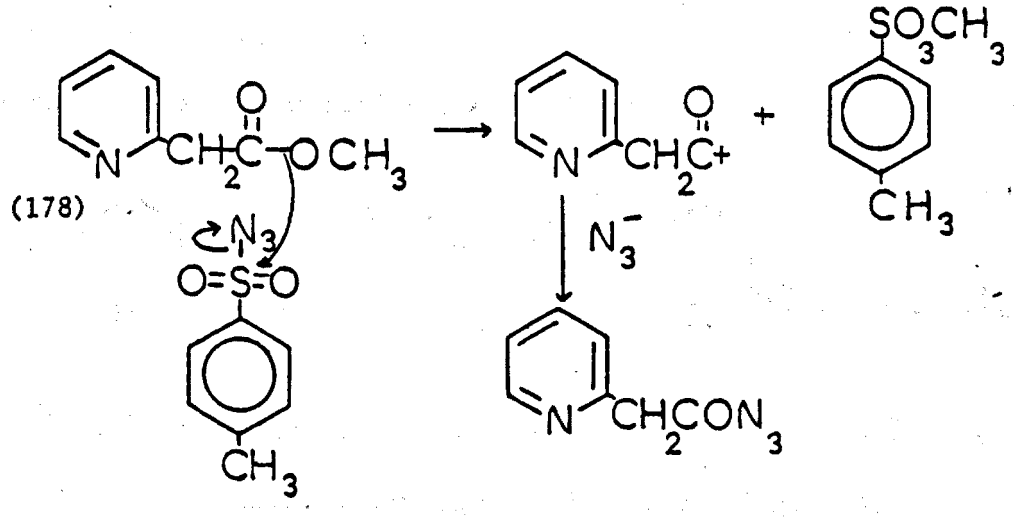
(178)

Scheme 2.9

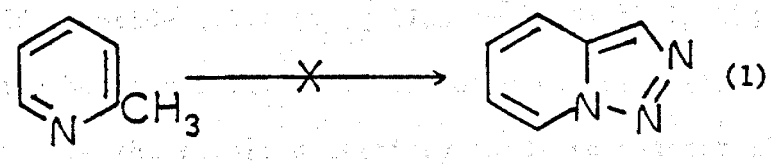
Methoxide ion acting as a nucleophile, displaces the azide ion from tosylazide giving methyl toluene-4-sulphonate (181). This is a methylating agent which readily methylates the acetate (178) to give the salt (180). The fact that ethoxide ion does not displace the azide ion could be due to steric factors. Another product isolated in varying amounts in these reactions was ethyl toluene--4-sulphonate (182). The formation of this compound can be postulated as shown.



Reaction of methyl toluene-4-sulphonate with base (methoxide ion) gives the anion (183). This attacks unchanged methyl toluene-4--sulphonate to give ethyl toluene-4-sulphonate (182). The same compound, along with some of the salt (180), was obtained when lithium diisopropylamide was used as the base. The source of the methoxide could be methyl-2-pyridyl acetate (178).

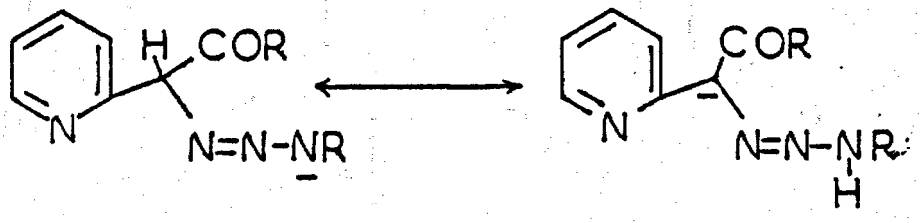


Attempts to use diazo group transfer as a possible synthetic route to the parent triazolopyridine (1) failed. Reaction of 2-methylpyridine (184) with either phenyllithium or lithium diisopropylamide, followed by tosylazide failed to give any triazolopyridine (1).

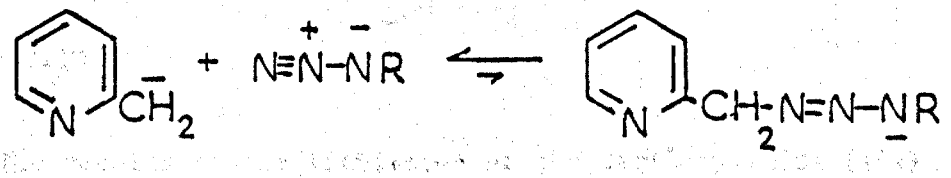


(184)

The immediate reason for this behaviour is not obvious. The key step in the reaction mechanism (see scheme 1.5) may be the transfer of the hydrogen atom to the leaving group i.e.

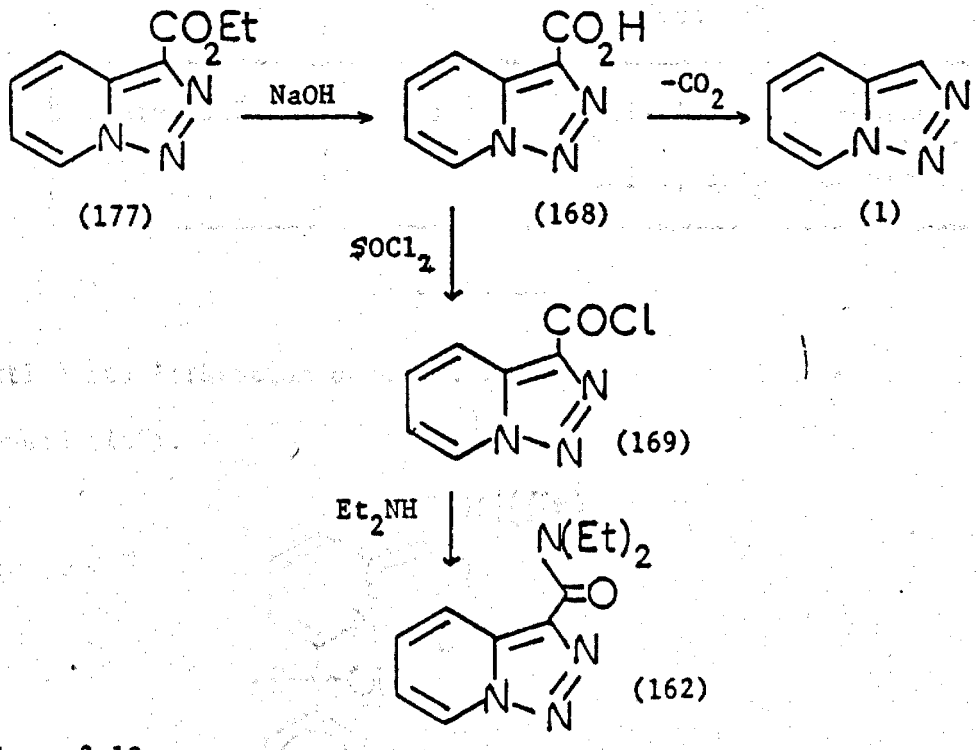


The electron withdrawing power of the ketone present may be necessary to enhance the acidity of the hydrogen atom. This enhancement is not present in the 2-methylpyridine case. Instead of driving the reaction to completion, the equilibrium is shifted back to the starting material i.e.



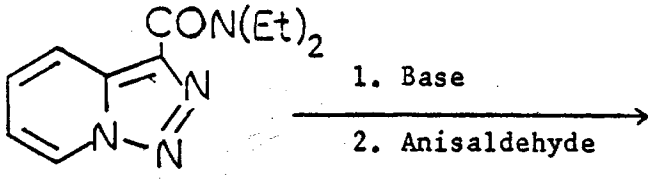
The ethyl ester (177) was easily hydrolysed to the carboxylic acid (168). The n.m.r. spectrum showed a broad singlet at δ8.4 ppm which was exchangeable with D_2O, the infra red spectrum

also had a strong carbonyl absorption at 1680 cm^{-1}. Attempts to form the amide (162) by heating the ester (177) with diethylamine in a sealed tube at 160°C for 7 hours failed. A small amount of starting material was recovered along with some black tar. However treatment of the acid with thionyl chloride in benzene gave the acid chloride (169) (ν_{max} 1735 cm^{-1} (C=O)) in 83% yield. Treatment of a benzene solution of the acid chloride (169) with diethylamine gave the required tertiary amide in quantitative yield. The carboxylic acid (168) was easily decarboxylated to give triazolopyridine as shown in scheme 2.10.



Scheme 2.10

The results of the lithiation of the tertiary amide (162) are summarised in table 2.5. Anisaldehyde was used as co-reactant in all cases.

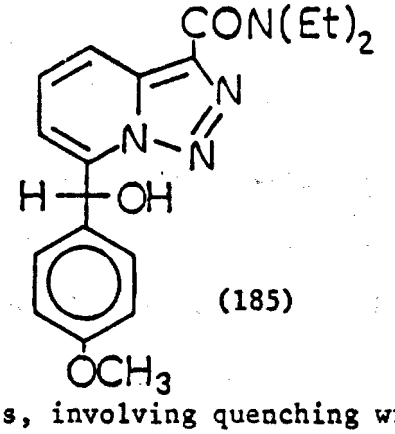


(162)

Base	Reaction time	Products
1 equiv. LDA	6 hrs	anisaldehyde, p-methoxy benzylalcohol, starting amide
2 equiv. LDA	6 hrs	p-methoxybenzylalcohol starting amide, lithiated product
2 equiv. BuLi	6 hrs	anisaldehyde, p-methoxy benzylalcohol, starting amide, lithiated product

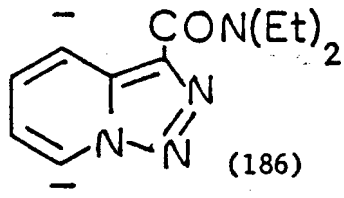
Table 2.5

In all cases lithiation occurred at position 7 thus forming the compound (185).



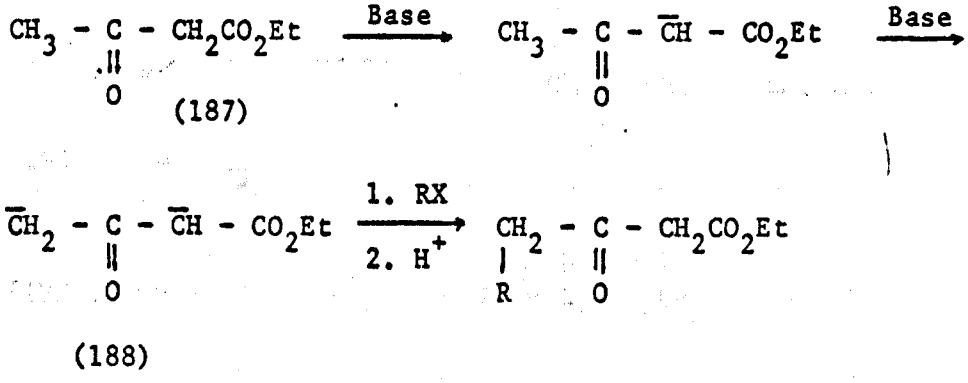
(185)

Initial experiments, involving quenching with D_2O, showed that on using 2 equivalents of base the dianion (186) was formed.



(186)

The rate of formation of the anion at position 7 was much greater than the rate of formation of the anion at position 4. It was thought that the more slowly formed anion (at position 4) would have the greater reactivity and thus react with anisaldehyde but the results show that reaction only occurred at position 7. Such a rationale has as an analogy the ambident nucleophilic behaviour of ethyl acetoacetate (187). When treated with 2 moles of base it forms a dicarbanion (188) which can be alkylated as shown.

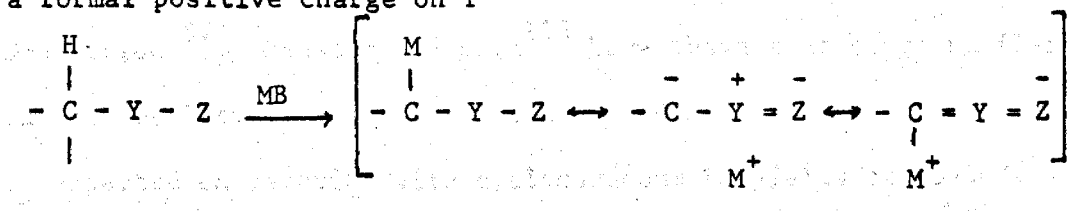


(187)

(188)

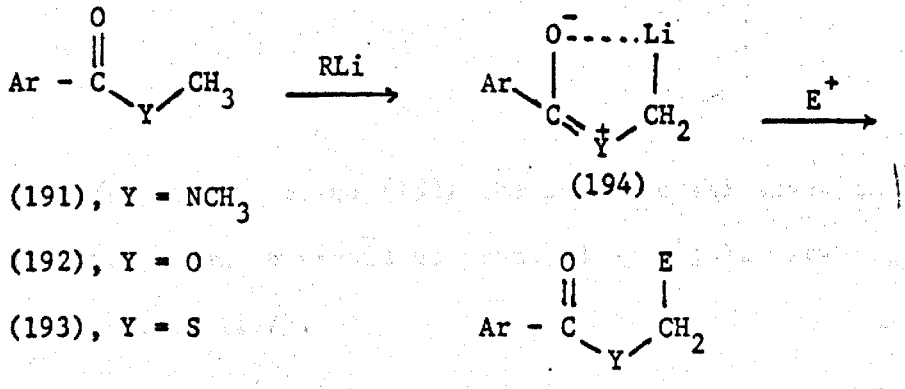
As can be seen the most acidic hydrogen is removed first, however reaction with RX occurs with the more slowly formed anion. Attack is always by the more basic carbon[152]. However the reason why no lithiation is observed at position 4 is probably due to a certain amount of steric hindrance and the concept of dipole stabilised carbanions[153]. A general representation of a dipole stabilised carbanion is provided by (189) in scheme 2.11 where Y represents nitrogen, oxygen or sulphur and Z is a group capable of inducing

a formal positive charge on Y



Scheme 2.11 (189) (190) +BH

If (190) is a significant contributor to the hybrid, dipole stabilisation is an important factor in the stability of (189) and, presumably, in the transition state leading to (189). Specific examples of such reactions for nitrogen, oxygen and sulphur are provided by the metalations of N,N-dimethyl-2,4,6--triisopropylbenzamide (191), methyl 2,4,6-triisopropylbenzoate (192), and methyl 2,4,6-triisopropylthiobenzoate (193), to give the intermediate (194) (Y = NCH_3, O, S) which can be subsequently trapped by electrophilic reagents[154,155].



(191), Y = NCH_3

(192), Y = O

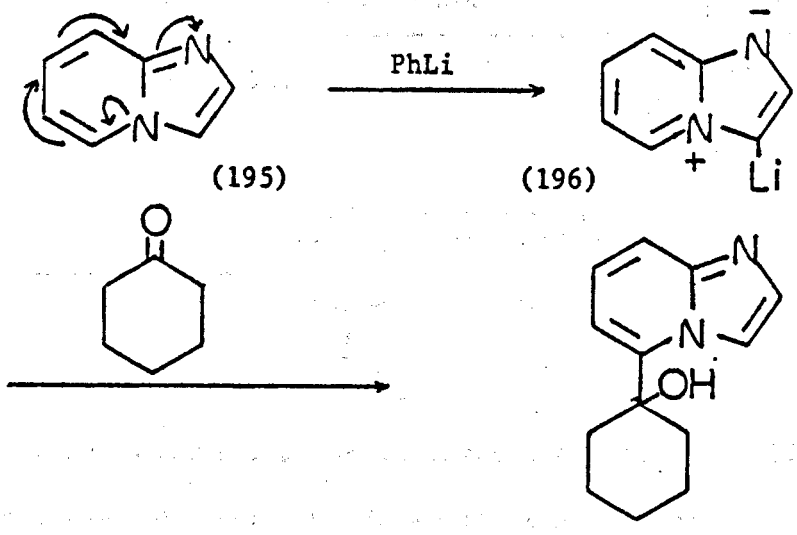
(193), Y = S

(194)

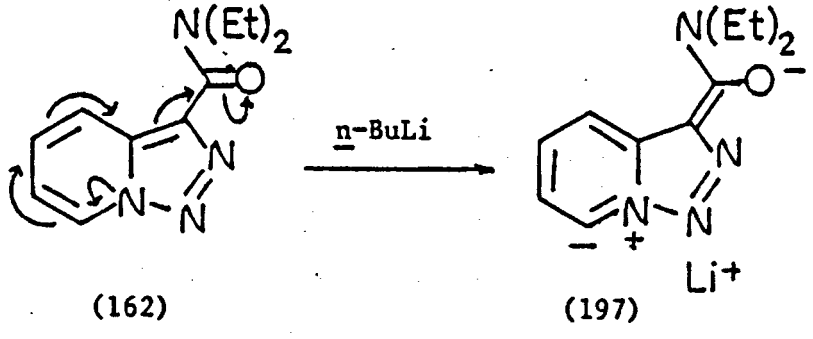
The metalation of (193) is particularly pertinent, since it has been shown that (194) (Y = S) can be formed by proton transfer from (193) to lithiomethyl methylsulphide[156], a result which indicates that the carbonyl group does provide thermodynamic stabilisation for the formal methyl carbanion adjacent to the heteroatom.

With reference to polyazaindenes, base-catalysed hydrogen-deuterium exchange of the protons α to nitrogen in imidazo[1,2-a]-

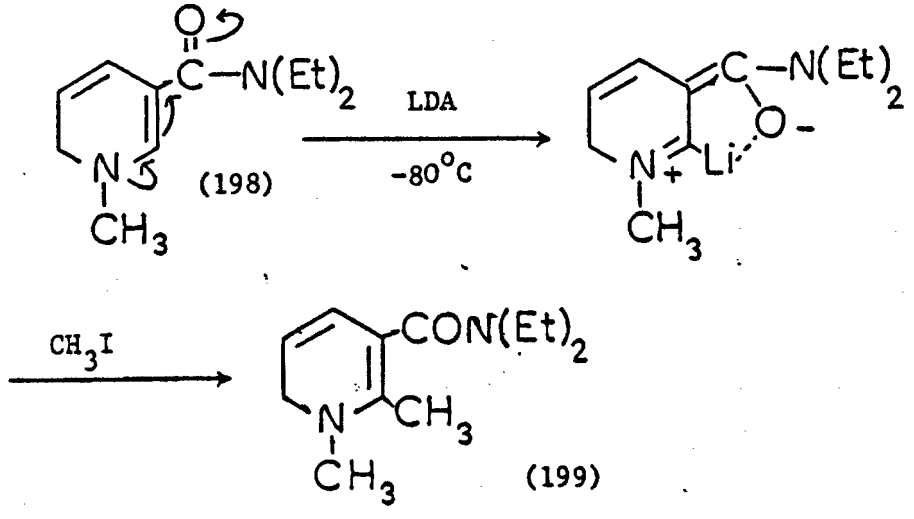
-pyridine (195) has been observed to occur preferentially at the 3-position[157]. Paudler and Shin[158] have shown that compound (195) can be metalated at the same position and that substitution occurs as expected on reaction with cyclohexanone in yields of 15-30%. Dipolar stabilisation is illustrated as a factor contributing to the stability of the intermediate (196).



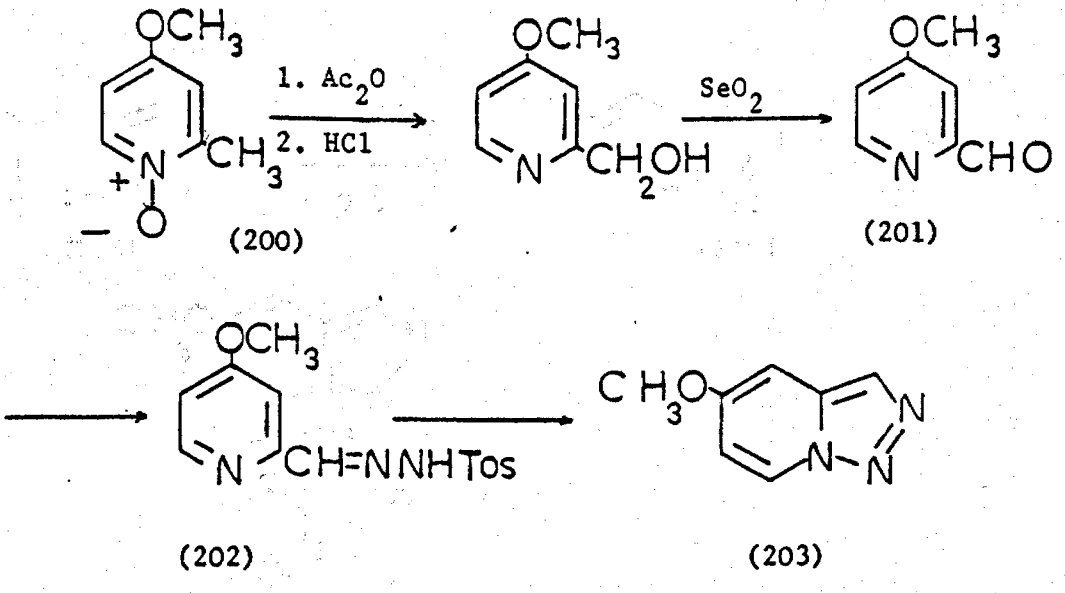
Returning to the amide (162) the preferential substitution at position 7 can be viewed as promoted by dipolar stabilisation of intermediate (197).



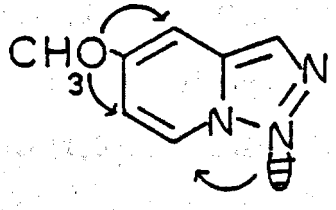
An example of a dipole stabilised carbanion for an amide group is provided by the lithiation of the 3-amidodihydropyridine (198)[159]. This can be lithiated at the 2-position and methylated to give compound (199).



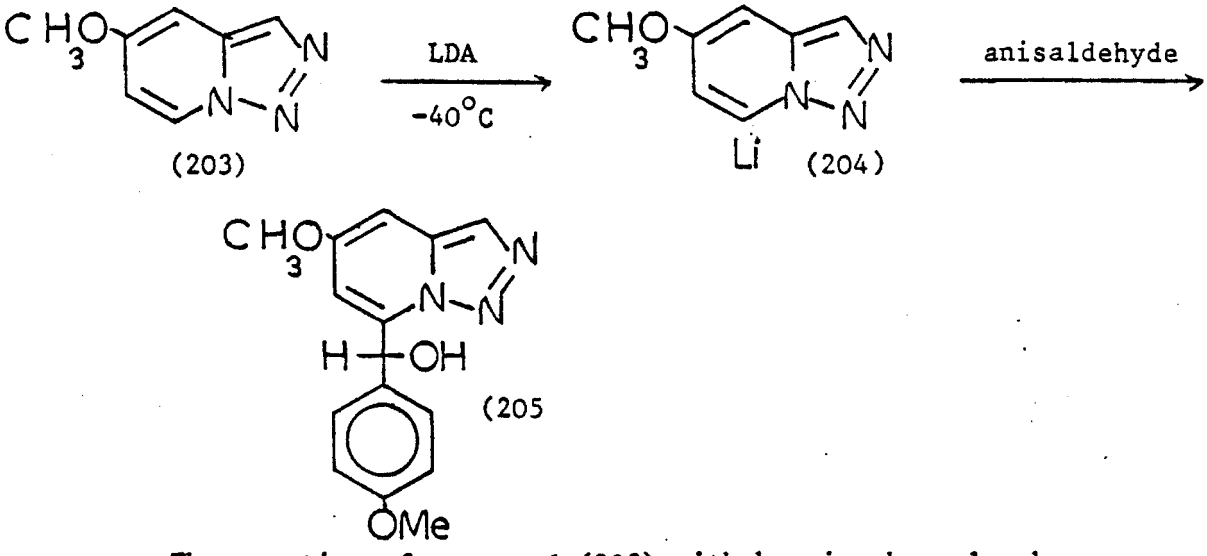
The synthesis of 5-methoxytriazolo[1,5-a]pyridine (203) was achieved by treatment of 4-methoxypyridine-2-carboxaldehyde (201) with p-toluenesulphonylhydrazide. The resulting hydrazone (202) was cyclised by morpholine to give the compound (203). The carboxaldehyde was synthesised by a known procedure[164] starting from 4-methoxy-2-methylpyridine-1-oxide (200).



Again there are two directing groups in compound (203).

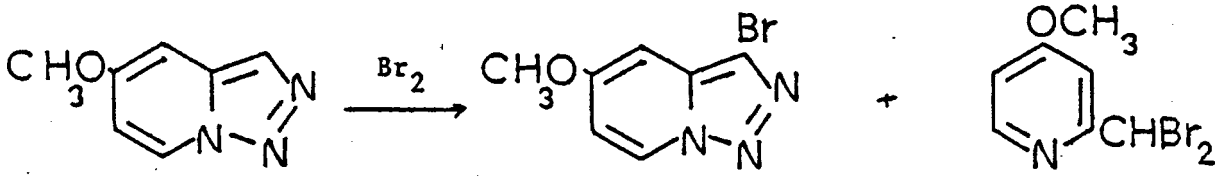


The methoxy group is capable of directing lithiation to either positions 4 or 6, while the peri-nitrogen atom N1 can direct lithiation to position 7. Co-workers at this University have lithiated compound (203) using two moles of lithium diisopropyl--amide. Again lithiation occurred at position 7, since reaction of the lithium derivative (204) with anisaldehyde gave the triazolopyridin-7-yl methanol (205). Other products were present in small amounts, but their structure has yet to be elucidated.



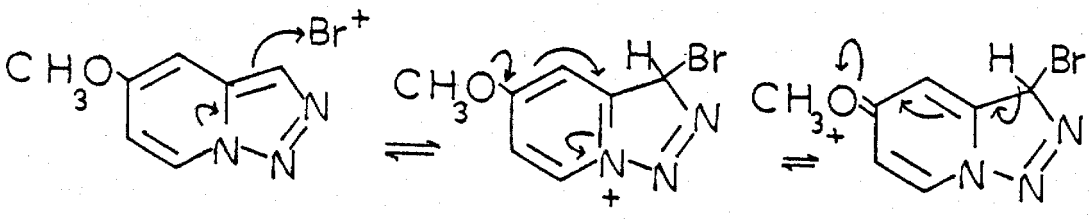
(203) (204) (205

The reaction of compound (203) with bromine has also been investigated by co-workers at this University. Bromination of 5-methoxytriazolo[1,5-a]pyridine (203) with bromine at 0-5°C gave a mixture of 2-dibromomethyl-4-methoxypyridine (206) and 3-bromo--5-methoxytriazolo[1,5-a]pyridine (207) in a ratio of approximately 1:4.

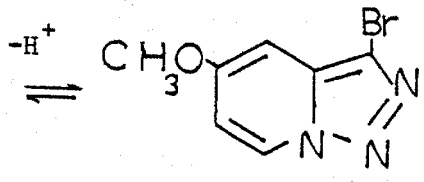


(203) (207) (206)

The formation of the bromo compound (207) can be explained as follows: The cyclic form (208) in the electrophilic substitution mechanism is stabilised by the methoxyl group to give resonance structures such as (209).



(208) (209)



(203)

Experimental

Preliminary experiments on lithiation of [1,2,3]triazolo[1,5-a]pyridine

During the course of this research all the materials were purified as follows:-

Tetramethylethylenediamine and diisopropylamine were distilled from potassium hydroxide. Tetrahydrofuran was purified by refluxing with and then distilling from sodium-benzophenone ketyl. Diethyl ether was dried by distillation from sodium wire. All coreactants were distilled prior to use. The n-butyllithium was obtained as a 1.6M solution in hexane from Aldrich Chemical Co. Limited. The molarity of the n-butyllithium was constantly checked using two methods:

(i) N.M.R. determination[160]

(ii) Using 2,5-dimethoxybenzyl alcohol, a self indicating standard.[161]

The latter method was found to be the most reliable. All experiments were carried out under "oxygen free" nitrogen[122] or argon. Experiments to determine the most suitable lithiating agent were carried out as follows:-

A solution of triazolopyridine (usually 1g, 0.0084 mol) in the solvent of choice (either T.H.F. or diethyl ether) was cooled to various temperatures (by using a refrigeration apparatus or immersing the flask in a mixture of dichloromethane and liquid nitrogen). This was added to an equimolar quantity of the lithiating agent of choice at the same temperature. The reaction was monitored by withdrawing approximately 100 mg and quenching this immediately with D_2O. The solution was immediately extracted with dry dichloromethane, the extract dried over magnesium sulphate, filtered and finally evaporated. The residue was dissolved in deuteriochloroform and the n.m.r. spectrum obtained. Percentage lithiation could be calculated from integral values.

Table 2.6.

Compound no 126	Co-reactant	Amount n-BuLi (ml)	Molarity n-BuLi	Amount diisopropylamine used (ml)	Amount triazolopyridine used (g)	Amount co-reactant (ml)	% yield prod.
(a)	octaldehyde	15.8	1.07	2.6	2	2.62	30
(b)	benzaldehyde	14.2	1.18	2.6	2	1.70	30
(c)	p-methoxy benzaldehyde	14.5	1.16	2.6	2	2.05	69
(d)	p-nitro benzaldehyde	13.0	1.30	2.6	2	2.54g	20
(e)	4-acetyl pyridine	14.2	1.18	2.6	2	1.86	40
(f)	cyclohexanone	15.8	1.07	2.6	2	1.74	25
(g)	benzophenone	14.2	1.18	2.6	2	3.06g	52
(h)	methylvinyl ketone	13.0	1.30	2.6	2	1.36	38

Experimental. Part A

General procedure for lithiation of triazolo[1,5-a]pyridine

Reaction with aldehydes and ketones

A solution of n-butyllithium (amount (ml), molarity) in hexane, was added to an equimolar amount of diisopropylamine at -40°C. An equimolar solution of triazolo[1,5-a]pyridine in ether was added with stirring, which was continued at -40°C for six hours, during which a deep red colour developed. Addition of an equimolar amount of the carbonyl coreactant caused a colour change to yellow; the mixture was allowed to come to room temperature and stirred overnight, then hydrolysed by a solution of ammonium chloride in ammonia (specific gravity 0.80). See table 2.6 for details of amounts used. The purification procedures for each compound will then be discussed.

1-(Triazolopyridin-7-yl)octan-1-ol (126a)

After hydrolysis the aqueous layer was extracted with dichloromethane (4 x 200 ml). The organic extract was dried over magnesium sulphate, filtered and evaporated to yield 3.8g of a brown oil. The oil was absorbed onto alumina (16g, IV) and chromatographed on a column of alumina (120g, IV). Elution with petroleum ether (b.p. 60-80°C) gave octaldehyde (0.4g) and with benzene-petroleum ether (1:1) gave triazolopyridine (0.3g). Elution with dichloromethane-benzene (1:4) gave the octanol (126a) as an unstable light brown oil (30%). When this reaction was carried out using an argon 'blanket', the octanol was obtained in 55% yield (2.3g).

B.pt. Unstable to distillation

Analysis: Accurate mass determination.

$C_{14}H_{21}N_3O$ requires M^+ = 247. 16845

found M^+ = 247. 1687

N.M.R. ($CDCl_3$)	δ8.00 ppm,	s,	1H,	H3	
	7.60,	dd,	1H,	H4	$J_{4,5}$ = 9 Hz
					$J_{4,6}$ = 1 Hz
	7.20	dd,	1H,	H5	$J_{5,4}$ = 9 Hz
					$J_{5,6}$ = 7 Hz
	6.95	dd,	1H,	H6	$J_{6,5}$ = 7 Hz
					$J_{6,4}$ = 1 Hz
	5.35	tr,	1H,	CH	
	4.00	br.s,	1H,	OH, Ex D_2O	
	0.75-2.3,	m,	15H,	octyl protons	

I.R. ($CHCl_3$) ν_{max} 3390 (br, OH), 2930, 2850, 1790, 1640, 1310, 925 cm^{-1}

U.V. (95% EtOH) λ_{max} 282 nm (sh)

Mass spectrum, m/e, 247(54) M^+, 219(6), 149(100), 148(33), 144(15), 134(34), 130(23), 123(12), 121(60), 120(43), 119(7), 118(17), 106(30), 93(50), 92(67), 91(32), 78(41), 77(18), 70(81), 69(22), 66(12), 65(51), 57(31).

α-(Triazolopyridin-7-yl)benzyl Alcohol (126b)

After hydrolysis the aqueous layer was extracted with dichloromethane (4 x 200 ml). The organic extract was dried over magnesium sulphate, filtered and evaporated to yield 3.8g of a light brown oil. Using medium pressure chromatography with ethylacetate-petroleum ether (b.pt. 60-80°C) (3:1) as eluant, the following were eluted;

Fractions (40 ml) 5-6, benzoin(benzoylphenylcarbinol)(0.2g), benzaldehyde (0.2g)

Fractions 6-9, the benzyl alcohol (126b) (1.1g) 30%

Fractions 10-11, triazolopyridine (0.2g)

When this reaction was repeated using an argon blanket or 'oxygen-free' nitrogen, the benzylalcohol was obtained in 53% yield (2.0g). The alcohol (126b) was a pale yellow oil, but trituration with petroleum ether (b.pt. 40-60°C) gave a yellow powder.

M.pt. 123.5-124.5°C (cyclohexane)

Analysis: Found: C, 69.59%; H, 4.99%; N, 18.98%

$C_{13}H_{11}N_3O$ requires: C, 69.32%; H, 4.92%; N, 18.66%

^{1}H N.M.R. ($CDCl_3$) δ8.07 ppm, s, 1H, H3

7.69 dd, 1H, H4, $J_{4,5}$ = 8.8 Hz, $J_{4,6}$ = 1.1 Hz.

7.36-7.62, m, 5H, benzene protons

7.30, dd, 1H, H5, $J_{5,6}$ = 6.8 Hz, $J_{5,4}$ = 8.8 Hz.

6.72 dd, 1H, H6, $J_{6,5}$ = 6.8 Hz, $J_{6,4}$ = 1 Hz.

6.50 d, 1H, CH, J_{CH-OH} = 4.5 Hz

4.70 d, 1H, OH, J_{OH-CH} = 4.5 Hz

^{13}C N.M.R. ($CDCl_3$) Multiplicities in off-resonance shown in parenthesis. δ133.69 ppm (s), 125.57(d), 125.23(d), 116.47(d), 112.75(d) -triazolo-pyridine carbon atoms, 139.92 (s, benzene quaternary), 138.36 (s, quaternary carbon), 128.22(d), 128.12(d), 126.88(d)-benzene carbon atoms, 71.01(d, CHCOH7).

I.R. ($CHCl_3$) ν_{max} 3650, 3590, 3440 (br, OH), 1635 (benzene ring) cm^{-1}

U.V. (95% EtOH) λ_{max} 281 nm (sh).

Mass spectrum, m/e, 225(100) M^+, 197(34), 196(94), 180(52), 179(13), 178(11), 169(42), 168(100), 167(63), 141(36), 128(13), 117(17), 115(23), 107(100), 105(81), 92(52), 91(44), 79(100), 77(100), 65(38), 64(34), 57(33), 51(42).

α-(Triazolopyridin-7-yl)-4-methoxybenzyl alcohol (126c)

Immediately after hydrolysis, a yellow solid was deposited. This was filtered and dried in a vacuum dessicator and shown to be almost pure alcohol (126c) (2.65g, 69%).

M.pt. 171-172°C (benzene)

Analysis: Found, C, 65.77%; H, 5.04%; N, 16.75%

$C_{14}H_{13}N_3O_2$ requires: C, 65.76; H, 5.13%; N, 16.46%

^{1}H N.M.R. ($CDCl_3$) δ8.12 ppm, s, 1H, H3

7.70 dd, 1H, H4, $J_{4,5}$ = 8.8 Hz, $J_{4,6}$ = 1.1 Hz

7.24 dd, 1H, H5, $J_{5,6}$ = 6.9 Hz, $J_{5,4}$ = 8.8 Hz

6.73 dd, 1H, H6, $J_{6,5}$ = 7.0 Hz, $J_{6,4}$ = 1.1 Hz

7.48, 6.93, 2 doublets, AA'BB' system of benzene ring

6.50 d, 1H, CH, J_{CH-OH} = 4.4 Hz

4.49 d, 1H, OH, J_{OH-CH} = 4.6 Hz

3.82 s, 3H, OCH_3

^{13}C n.m.r. ($CDCl_3$) - multiplicities in off-resonance shown in parenthesis δ133.74 ppm (s), 125.6(d), 125.23(d), 116.475(d), 113.71(d) - triazolopyridine carbon atoms, 159.23 (s, quaternary C-OMe), 139.963(s), 130.90(s), 128.20(d), 112.732(d) - (benzene carbon atoms), 71.05 (d, CH(OH)), 55.15 (q, OCH_3).

I.R. ($CHCl_3$) ν_{max} 3580, 3445 (br, OH), 2925, 2840 (OCH_3), 2450, 1610 (benzene ring), 1585, 1300, 1110, 1070, 830 (para-disubstituted benzene) cm^{-1}.

U.V. (95% EtOH) λ_{max} 278 nm (sh)

Mass spectrum, m/e, 255(100) M^+, 227(14), 226(18), 212(21), 199(20), 198(89), 184(21), 183(23), 166(20), 134(27), 120(25), 118(18), 94(16), 91(20), 78(59), 77(39), 65(14).

α-(Triazolopyridin-7-yl)-4-nitrobenzyl alcohol (126d)

After hydrolysis the aqueous layer was extracted with dichloromethane (4 x 200 ml). The organic extract was dried over magnesium sulphate, filtered and evaporated to yield 2.6g of a brown oil. Trituration of this oil with chloroform gave 0.9g (20%) of the alcohol (126d) as a yellow powder. Examination of the residue by N.M.R. spectroscopy revealed the presence of only starting materials.

M.pt. 180-182°C (benzene)

Analysis: Found: C, 57.92%; H, 3.52; N, 20.75;

$C_{13}H_{10}N_4O_5$ requires: C, 57.77%; H, 3.73%; N, 20.75%

^{1}H N.M.R. ($CDCl_3$) δ8.26 ppm, s, 1H, H3

8.2 dd, 1H, H4, $J_{4,5}$ = 9 Hz

7.90 dd, 1H, H6, $J_{6,5}$ = 8 Hz, $J_{6,4}$ = 2 Hz

7.48 dd, 1H, H5

7.79-7.49, 2 doublets, AA'BB' system of benzene ring

6.90 s, 1H, OH, Ex. D_2O

6.61 s, 1H, CH

^{13}C n.m.r. (D_6-DMSO) - multiplicities in off-resonance shown in parenthesis. δ133.54(s), 125.71(d), 123.237(d), 116.96(d), 112.00(d) -triazolopyridine carbon atoms, 148.18 (s, quaternary, C-NO_2), 139.77(s), 68.47 (d, CH(OH)).

I.R. ($CHCl_3$) ν_{max} 3300 (br, OH), 1520 (NO_2 stretch), 1350 cm^{-1}

U.V. (95% EtOH) λ_{max} 275 nm ($\log_{10}\varepsilon$ 4.08)

Mass spectrum, m/e, 270(100) M^+, 241(27), 240(21), 239(17), 224(47), 212(94), 196(38), 195(100), 193(21), 179(34), 168(85), 167(100), 166(100), 153(21), 152(40), 149(19), 141(38), 140(47), 139(64), 120(38), 115(66), 106(42), 105(55), 94(42), 92(100), 91(64), 89(32), 79(21), 77(100), 76(64), 75(42), 66(38), 65(100), 63(100), 57(21).

1-(4-pyridyl)-1-(triazolopyridin-7-yl)ethanol (126e)

After hydrolysis the aqueous layer was extracted with dichloromethane (4 x 200 ml). The organic extract was dried over magnesium sulphate, filtered and evaporated to yield 3.8g of a brown oil. Using medium pressure chromatography with ethyl acetate as eluant, the following were eluted;

Fractions (40 ml) 10-16, triazolopyridine (0.6g)

Fractions 17-36, 4-acetylpyridine (0.6g)

Fractions 55-72, alcohol (126e) (1.6g)

The alcohol was obtained as a tan solid (40%).

M.pt. 125-126°C (cyclohexane)

Analysis: Found: C, 65.45%; H, 5.22%; N, 23.22%

$C_{13}H_{12}N_4O$ requires: C, 64.98%; H, 5.03%; N, 23.32%.

^1H N.M.R. ($CDCl_3$) δ8.08 ppm, s, 1H, H3

7.80 dd, 1H, H4, $J_{4,5}$ = 8.8 Hz

$J_{4,6}$ = 1.3 Hz

7.39 dd, 1H, H5, $J_{5,4}$ = 8.7 Hz

7.30 ppm, m, 4H, pyridine ring protons

7.16 dd, 1H, H6, $J_{6,5}$ = 6.96 Hz

$J_{6,4}$ = 1.4 Hz

6.30 br.s, 1H, OH, Ex. D_2O

2.03 s, 3H, CH_3

^{13}C n.m.r. ($CDCl_3$) - multiplicities in off resonance shown in parenthesis. δ134.13(s), 125.64(d), 125.30(d), 117.49(d), 112.80(d) - triazolopyridine carbon atoms, 153.51(s), 149.47(d, pyridine α carbon atoms), 140.13(s), 119.611 (d, pyridine β carbon atoms), 74.91 (s, C(OH)M), 28.21 (q, CH_3).

I.R. ($CHCl_3$) ν_{max} 3430 (br, OH), 2900, 1600, 1415, 1370, 1325, 1260, 1225, 1215, 1135, 115, 1070, 1040, 1000, 965, 825 cm^{-1}

U.V. (95% EtOH) λ_{max} 274 nm (sh)

Mass spectrum, m/e, 240(29) M^+, 201(25), 200(100), 197(24), 174(100), 173(18), 172(67), 169(25), 157(69), 131(29), 129(67), 128(51), 127(24), 115(24), 92(12), 78(13), 77(29), 63(24), 56(16)

1-(Triazolopyrdiin-7-yl)cyclohexanol (126f)

After hydrolysis the aqueous layer was extracted with dichloromethane (4 x 200 ml). The organic extract was dried over magnesium sulphate, filtered and evaporated to yield 2.6g of a light brown oil. This oil was evaporated onto alumina (12g, IV), and chromatographed on a column of alumina (85g, IV). Elution with benzene-petroleum ether (b.pt. 60-80°C) (1:3) gave cyclohexanone (0.3g). Elution with benzene--petroleum ether (1:1) gave triazolopyridine (0.5g) and the required alcohol (126f) (0.9g, 25%) as a pale yellow powder.

M.pt. 100°C (petroleum ether (b.pt. 60-80°C))

Analysis: Found: C, 66.47%; H, 7.05%; N, 19.63%.

$C_{12}H_5N_3O$ requires: C, 66.34%; H, 6.96%; N, 19.34%.

^{1}H N.M.R. ($CDCl_3$) δ8.09 ppm, s, 1H, H3

7.68 dd, 1H, H4, $J_{4,5}$ = 8.8 Hz

$J_{4,6}$ = 1.3 Hz

7.29 dd, 1H, H5, $J_{5,6}$ = 7.0 Hz

$J_{5,4}$ = 8.7 Hz

6.96 dd, 1H, H6, $J_{6,5}$ = 7.0 Hz

$J_{6,4}$ = 1.3 Hz

5.33 br.s, 1H, OH, D_2O Ex.

1.63-2.47, m, 10H, cyclohexane protons

^{13}C N.M.R. ($CDCl_3$) - multiplicities in off resonance shown in parenthesis. δ134.44 ppm (s), 125.73(d), 125.09(d), 116.20(d), 110.10(d) -triazolo-pyridine carbon atoms, 144.06(s), 34.64(tr), 25.74(tr), 21.27(tr), 72.47 (q, C(OH)).

I.R. ($CHCl_3$) ν_{max} 3470 (br, OH), 2940, 2860, 2460, 1925, 1635, 1390, 1350, 1320, 1135, 1090, 975 cm^{-1}

U.V. (95% EtOH) λ_{max} 285 nm ($\log_{10}\epsilon$ 3.62)

Mass spectrum, m/e, 219(81), 190(38), 175(19), 173(24), 162(24), 161(17), 148(10), 146(52), 145(15), 144(76), 143(74), 142(93), 133(33), 132(31), 119(22), 118(26), 91(52), 81(34), 79(21), 78(22), 65(26), 63(34), 55(22).

Diphenyl(triazolopyridin-7-yl)methanol (126g)

Immediately after hydrolysis the alcohol (126g) was deposited as a yellow solid (2.65g, 52%).

M.pt. 186.5-187.5°C (cyclohexane)

Analysis: Found: C, 75.64%; H, 4.83%; N, 13.93%.

$C_{19}H_{15}N_3O$ requires: C, 75.73%; H, 5.02%; N, 13.95%.

^{1}H N.M.R. ($CDCl_3$) δ8.07 ppm, s, 1H, H3

7.73 dd, 1H, H4, $J_{4,5}$ = 8.6 Hz, $J_{4,6}$ = 1.0 Hz

7.30 m, 10H, benzene ring protons

6.77 br.s, 1H, OH, D_2O Ex.

6.32 dd, 1H, H6, $J_{6,5}$ = 6.95 Hz $J_{6,4}$ = 1.2 Hz

^{13}C N.M.R. ($CDCl_3$) - multiplicities in off resonance shown in parenthesis. δ134.44 ppm (s), 125.28(d), 125.01(d), 116.98(d), 116.19(d) - triazolopyridine carbon atoms, 141.47(s), 142.59(s), 127.94(d), 127.75(d), 127.12 (d) - benzene carbon atoms, 81.19 (s, $\underline{C}(OH)(Ph)_2$).

I.R. ($CHCl_3$) ν_{max} 3430 (br, OH) 1635, 1600, 1445, 1375, 1315, 1110, 1020, 970, 910, 875 cm^{-1}.

U.V. (95% EtOH) λ_{max} 283 nm (sh)

Mass spectrum, m/e, 218(100), 191(44), 171(17), 161(24), 157(24), 155(19), 148(22), 147(85), 144(68), 135(44), 134(93), 133(29), 130(51), 129(95), 122(41), 120(93), 119(97), 118(24), 117(27), 108(56), 106(37), 105(97), 94(24), 91(90), 84(32), 76(34), 71(19), 69(37), 65(88), 57(49), 55(63), 44(93).

2-(Triazolopyridin-7-yl)but-3-en-2-ol (126h)

After hydrolysis the aqueous layer was extracted with dichloromethane (4 x 200 ml). The organic extract was dried over magnesium sulphate, filtered and evaporated to yield 2.6g of a light brown oil. Using medium pressure chromatography, with ethyl acetate-petroleum ether (b.pt. 60-80°C) (3:1) as eluant, the following were eluted:

Fractions (40 ml) 11-12, alcohol (126h) (1.2g, 38%)

Fractions 15-24, triazolopyridine (0.4g)

Further purification of the alcohol was achieved by P.L.C. (multiple elution) using ethylacetate-toluene (1:9) as solvent.

B.pt. - unstable to distillation

Analysis: Found: C, 63.25%; H, 5.98%; N, 21.31%.

$C_{10}H_{11}N_3O$ requires: C, 63.47%; H, 5.86%; N, 22.21%.

^{1}H N.M.R.

δ8.11 ppm,	s,	1H,	H3	
7.73	dd,	1H,	H4,	$J_{4,5}$ = 8.7 Hz
				$J_{4,6}$ = 1.3 Hz
7.31	dd,	1H,	H5,	$J_{5,6}$ = 6.9 Hz
				$J_{5,4}$ = 8.0 Hz
7.07	dd,	1H,	H6,	$J_{6,5}$ = 6.9 Hz
				$J_{6,4}$ = 1.2 Hz
6.16-6.44,	q,	1H,	alkene proton	
5.2 -5.46,	tr,	2H,	alkene protons	
				J_{AB} = 0.85 Hz
				J_{BC} = 10.62 Hz
				J_{AC} = 16.70 Hz
5.9	br.s,	1H,	OH,	Ex.D_2O
1.9	s,	3H,	CH_3	

^{13}C N.M.R. ($CDCl_3$) - multiplicities in off-resonance shown in parenthesis. δ134.27 ppm (s), 125.54(d), 125.21(d), 116.50(d), 111.83(d) - triazolopyridine carbon atoms, 141.34(d), 114.58(tr), 73.99(s, C(OH)), 25.75 (q, CH_3).

I.R. ($CHCl_3$) ν_{max} 3420 (br, OH), 1660, 1320, 1220, 1040, 980, 930 cm^{-1}

U.V. (95% EtOH) λ_{max} 283 nm ($\log_{10}\varepsilon$ 3.77)

Mass spectrum, m/e, 189(48) M^+, 188(100), 172(100), 162(83), 161(100), 160(100), 147(39), 146(100), 143(50), 142(33), 134(42), 137(39), 132(67), 130(33), 128(35), 121(100), 119(100), 118(100), 117(100), 115(56), 106(92), 104(56), 95(23), 92(100), 89(64), 88(100), 84(100), 79(81), 78(83), 69(42), 65(100), 63(100), 55(100).

Attempts to produce the 1,4 addition product (128) with methyl vinyl ketone. Conversion of lithio species to the copper reagent (127)

(i) Using cuprous halides

A solution of n-butyllithium (13.0 ml of 1.3M, 0.0168 mol) in hexane, was added to diisopropylamine (2.35 ml, 0.0168 mol) at -40°C. A solution of triazolopyridine (1) in ether (80 ml) was added with stirring, which was continued at -40°C for 6 hours, during which time a deep red colour developed. To this solution was added freshly prepared cuprous iodide[100] (1.6g, 0.0084 mol). There was no immediate colour change, stirring was continued at -40°C for a further one hour. Methyl vinyl ketone (1.36 ml, 0.0168 mol) was added, the solution turned yellow in colour immediately. The mixture was allowed to come to room temperature and stirred overnight, then hydrolysed by a solution of

ammonium chloride in ammonia (specific gravity 0.880). After hydrolysis the aqueous layer was extracted with dichloromethane (4 x 200 ml). The organic extract was dried over magnesium sulphate, filtered and evaporated to yield 2.0g of a light brown oil. Further extraction of the aqueous layer with a continuous extraction apparatus gave no further material. The brown oil was evaporated onto alumina (10g, IV), and chromatographed on a column of alumina (60g, IV). Elution with benzene-petroleum ether (1:3) gave triazolopyridine (0.2g) and the 1,2 addition product (126h) (1.0g, 31%). Continued elution using dichloromethane as eluant gave no further material.

(ii) Using dimethylsulphide-cuprous bromide complex

Preparation of DMS-CuBr complex

Prepared by the method of House[119]

M.pt. 122-130°C

Lit. m.pt. 124-129°C[119]

The 7-lithiotriazolopyridine species (124) was prepared as previously described using the same quantities. To this was added the dimethylsulphide-cuprous bromide complex (1.7g, 0.0084 mol) in a mixture of ether (10 ml) and dimethylsulphide (10 ml). A yellow colour developed immediately. The solution was stirred for a further one hour at -40°C. Methyl vinyl ketone (1.36 ml, 0.0168 mol) was added. The mixture was allowed to come to room temperature and stirred overnight, then hydrolysed (ammonium chloride/ammonia 0.880). Extraction with dichloromethane (4 x 200 ml), drying over magnesium sulphate followed by filtration and evaporation yielded a brown oil (2.3g). This was evaporated onto alumina (10g, IV) and chromatographed on a column of alumina (60g, IV). Elution with benzene-petroleum ether (b.pt. 60-80°C)

(1:3) gave only triazolopyridine (1.8g). No further material was eluted from the column even using dichloromethane as eluant.

Conversion of the lithio species (124) to the Grignard reagent (129)

Preparation of magnesium bromide

An ethereal solution of 1,2-dibromoethane (3.8g, 0.02 mol) was added dropwise to magnesium turnings (1.22g, excess). The resulting solution was filtered under a dry nitrogen atmosphere,
This solution was then added dropwise to an ethereal solution (80 ml) of 7-lithiotriazolopyridine (0.0168 mol, prepared as previously described). No change in the colour of the red solution was observed. The resulting solution was stirred at -40°C for a further two hours. Methyl vinyl ketone (1.36 ml, 0.0168 mol) was added. The mixture was allowed to come to room temperature and stirred overnight. The normal work-up procedure gave a brown oil (3g).

Medium pressure chromatography with ethylacetate-petroleum ether (b.pt. 60-80°C) (3:1) as eluant gave the alcohol (126h) (1.1g, 36%) and triazolopyridine (0.4g). No further material was obtained from the column using ethylacetate as eluant. As can be seen, there is no significant increase in the yield of the alcohol (126h) produced.

Attempted alkylation of 7-lithiotriazolopyridine (124)

With methyliodide

The 7-lithio species (124) was prepared as previously described using 2g of triazolopyridine (0.0168 mol). After addition of the co-reactant (0.0168 mol) and work up (as previously described), n.m.r. spectroscopy indicated only the presence of starting materials.

With benzyl bromide

The 7-lithio species (124) was prepared as previously described using 2g of triazolopyridine (0.0168 mol). Addition of the co-reactant (0.0168 mol) and work up as previously described gave a brown oily mass (4.8g) which later solidified. N.m.r. revealed the presence of starting materials. Peaks due to diisopropylamine were also present. This indicated the possibility of salt formation between benzylbromide and diisopropylamine.

A sample of the solid was shaken with water and extracted with dichloromethane (2 x 50 ml). The organic extract was dried over magnesium sulphate, filtered and evaporated. N.m.r. spectroscopy revealed the presence of triazolopyridine and benzylbromide. N.m.r. spectroscopy on the aqueous extract (in D_2O) gave peaks due to both diisopropylamine and benzylbromide. The peaks are probably due to the formation of the salt $R^1R^2R^3N^+Br^-$ where R^1 = H, R^2 = isopropyl and R^3 = benzyl.

Reactions of 7-lithiotriazolopyridine (124)

Reaction with solid carbon dioxide

The 7-lithio species (124) was prepared as previously described using 2g of triazolopyridine (0.0168 mol). After six hours the reaction mixture was poured onto a tenfold excess of solid carbon dioxide in a dry nitrogen bag. The colour changed immediately from red to yellow. The mixture was allowed to come to room temperature and stirring was continued overnight. The mixture was then hydrolysed with dilute sulphuric acid. The aqueous layer was extracted with dichloromethane (4 x 100 ml). The organic extract was dried over magnesium sulphate, filtered and evaporated to yield 1.6g of a yellow oil, which was identified by n.m.r. spectroscopy as triazolopyridine.

Reaction with bromine

The 7-lithio species (124) was prepared as previously described using 2g of triazolopyridine (0.0168 mol). To this was added bromine (2.68g, 0.0168 mol). The colour changed immediately from red to bright yellow. After hydrolysis the normal work-up procedure was followed and evaporation yielded 4.4g of a violet solid. Extraction of this solid with benzene gave the bromopyridine (134) (1.1g, 20%) as an off-white powder.

M.pt. 131-133°C (cyclohexane)

Analysis: Found: C, 21.76%; H, 1.08%; N, 4.28%.

$C_6H_4Br_3N$ requires: C, 21.85%; H, 1.22%; N, 4.25%.

^1H N.M.R. ($CDCl_3$) δ7.2-7.85 ppm, m, 3H, pyridine ring protons

6.55 s, 1H, CH.

I.R. ($CHCl_3$) ν_{max} 1585, 1565, 1200, 1150, 1120, 1080, 985, 800 cm^{-1}

U.V. (95% EtOH) λ_{max} 225 nm (sh)

277 nm ($\log_{10}\varepsilon$ 3.83)

Mass spectrum, m/e, 253(100), 251(110)(M^+-Br) 250(100), 249(100), 233(52), 232(29), 217(92), 216(85), 215(92), 214(83), 189(62), 187(79), 186(100), 170(100), (M^+-Br_2), 168(100), 159(44), 158(62), 157(48), 156(42), 149(44), 144(100), 130(42), 119(71), 109(62), 97(100), 89(81), 88(87), 87(39), 85(100), 78(100), 75(100), 69(100), 67(66), 65(62).

Reaction with 1,2-dibromoethane

The 7-lithio species (124) was prepared as previously described using 2 g of triazolopyridine (0.0168 mol). To this was added 1,2-dibromoethane (freshly distilled and dried over calcium chloride) (1.45 ml, 0.0168 mol). Normal work-up procedure yielded a pale brown oil (2.2 g). N.m.r. spectroscopy revealed only the presence of triazolopyridine.

With benzonitrile

The 7-lithio species (124) was prepared as previously described using 3 g of triazolopyridine (0.0252 mol). To this was added benzonitrile (2.57 ml, 0.0252 mol). Normal work-up procedure yielded a semi-solid orange oil (4.4 g). This was evaporated onto alumina (17 g, IV), and chromatographed on a column of alumina (135 g, IV). Elution with benzene-petroleum ether (b.pt 60-80°C) (1:5) gave benzonitrile (0.4 g), benzene-petroleum ether (3:2) gave triazolopyridine (0.6 g). Further elution with diculoromethane-benzene mixtures gave unidentifiable oils (1.2 g).

With cyanogen bromide

The 7-lithio species (124) was prepared as previously described using 2 g of triazolopyridine (0.0168 mol). Addition of an ethereal solution (10 ml) of cyanogen bromide (1.78 g, 0.0168 mol) produced an immediate colour change from red to bright yellow. Normal work-up procedure yielded a brown semi-solid (3.1 g). N.m.r. spectroscopy revealed only the presence of triazolopyridine.

With ethyl chloroformate

The 7-lithio species (124) was prepared as previously described using 2 g of triazolopyridine (0.0168 mol). After the addition of ethyl chloroformate (1.6 ml, 0.0168 mol), normal work-up procedure yielded a yellow oil (3.3 g). Trituration of this oil with diethylether gave a yellow solid (0.86 g, 19%) which was later identified as the ketone (139).

Mpt. indistinct, > 290°C.

Analysis: Found: C, 59.02%; H, 2.88%; N, 32.27%

$C_{13}H_8N_6O$ measures: C, 59.09%; H, 3.05%; N, 31.81%

^1H N.M.R. (D_6-DMSO)

δ8.32 ppm, dd, 1H, H4, $J_{4,5}$ = 9.4 Hz, $J_{4,6}$ = 1.4 Hz.

8.29, s, 1H, H3

7.87, dd, 1H, H6, $J_{6,5}$ = 7.0 Hz, $J_{6,4}$ = 1.3 Hz.

7.62, dd, 1H, H5, $J_{5,6}$ = 6.9 Hz, $J_{5,4}$ = 8.6 Hz.

^{13}C N.M.R. (D_6-DMSO) - multiplicities in off-resonance shown in parenthesis.

δ133.47 ppm (s), 126.49(d), 125.27 (d), 122.812 (d), 119.89 (d)-triazolopyridine carbon atoms, 179.41(s).

I.R. (Nujol mull) ν_{max} 1665(C=O), 1620, 1325, 1090, 885 cm^{-1}.

U.V. (95% EtOH) λ_{max} 238 nm ($\log_{10}\varepsilon$ 4.31)
276 nm ($\log_{10}\varepsilon$ 3.99)
366 nm ($\log_{10}\varepsilon$ 3.70)

Mass spectrum, m/e, 264(6) M^+, 263(25), 236(21)(M-28), 209(14), 181(18), 179(35), 159(31), 154(16), 153(16), 149(21), 147(21), 132(37), 130(67), 121(27), 120(25),

106(46), 104(27), 103(21), 100(8),
93(18), 91(18), 82(42), 80(42),
78(29), 64(21), 63(42), 57(21).

Medium pressure chromatography on the residue (2.4 g), with ethylacetate-petroleum ether (b.pt. 60-80°C)(4:1), gave ethylchloroformate (1.3 g) and triazolopyridine (0.4 g). Further elution with ethyl acetate gave no further material.

This experiment was repeated using half of one equivalent of ethyl chloroformate (0.8 ml, 0.0084 mol) but failed to increase the yield of the ketone (139).

Attempted decarbonylation of the ketone (129)

The ketone (0.05 g) was placed in a small sample tube. This was immersed in a beaker containing transparent silicone oil which was heated gradually. At 190°C evolution of a gas was observed. Attempted extraction of the residue failed, extensive decomposition had occurred.

With Dimethylformamide

To the lithium reagent from triazolopyridine (3g, 0.025 mol) was added dry dimethylformamide (1.9 ml, 0.025 mol). The colour of the mixture changed immediately from red to bright yellow. After stirring overnight, the mixture was hydrolysed with 2N hydrochloric acid. The resulting deep red solution was stirred for one hour. This was then extracted with dichloromethane (4 x 200 ml). The organic extract was dried over magnesium sulphate, filtered and evaporated to yield a brown oil (1.5g). Using medium pressure chromatography, with benzene-petroleum ether (b.pt. 60-80°C)(1:1)

as eluent, 7-hydroxymethyltriazolopyridine (144) (1.1g, 30%) was eluted.

M. pt. 127-129°C (benzene)

Analysis: Found: C, 56.25%; H, 4.62%; N, 28.59%.

$C_7H_7N_3O$ requires: C, 56.37%; H, 4.73%; N, 28.18%.

^1H N.M.R. ($COCl_3$)

δ8.15 ppm, s, 1H, H3

7.87, dd, 1H, H4, $J_{4,5}$ = 8.7 Hz, $J_{4,6}$ = 1 Hz

7.44, dd, 1H, H5, $J_{5,6}$ = 8.6 Hz, $J_{5,4}$ = 8.5 Hz

7.23, dd, 1H, H6, $J_{6,5}$ = 6.7 Hz, $J_{6,4}$ = 1.3 Hz

5.19, br.s., 2H, CH_2.

^{13}C N.M.R. (D_6-acetone) - multiplicities in off-resonance shown in parenthesis

δ134.46 ppm (s), 126.05 (d), 125.60 (d), 116.52 (d), 111.59 (d) - triazolopyridine carbon atoms,

139.56 (s), 59.25 (tr, CH_2).

I.R. ($CHCl_3$) ν_{max} 3420(br, OH), 1930, 1710, 1645 cm^{-1}

U.V. (95% EtOH) λ_{max} 282 nm ($\log_{10}\varepsilon$ 3.91).

Mass spectrum, m/e, 149(84)M^+, 121(18), 120(18), 94(20), 93(100), 92(60), 90(12), 76(20), 66(100), 65(84), 64(76), 63(56), 52(24).

The aqueous layer was evaporated to yield 1.7g of a light tan oil. This was redissolved in water and continuously extracted with chloroform for several days, however nothing could be extracted from the aqueous layer.

I.R. ($CHCl_3$) ν_{max} 3300(br, OH), 1735, 1705, 1655, 1595, 1150, 900 cm^{-1}.

U.V. (95% EtOH) λ_{max} 229 nm ($\log_{10}\varepsilon$ 4.04)
278 nm ($\log_{10}\varepsilon$ 3.96)
303 nm (sh).

Mass spectrum, m/e, 378(41), 376(88), 374(57), 304(31), 302(55), 300(22), 246(48), 236(83), 210(24), 209(22), 168(22), 135(100), 134(100), 120(100), 108(74), 100(64), 93(53), 91(93), 90(34), 89(86), 81(83), 80(38), 79(90), 78(38), 76(100), 64(40), 63(69), 62(71), 56(24).

Diphenyl-(6-dibromomethylpyridin-2-yl)methanol (147g)

Obtained from the alcohol (126g) (4g) in 76% yield (4.3g) as a light brown oil. Trituration with petroleum ether (b.pt. 40-60°C) gave a tan powder.

M.pt. 118-120°C (absolute ethanol)

Analysis: Found: C, 52.98%; H, 3.48%; N, 3.33%

$C_{19}H_{15}Br_2NO$ requires: C, 52.68% H, 3.49%; N, 3.23%.

^1H N.M.R. ($CDCl_3$)

δ7.73 ppm, m, 2H, pyridine β protons

7.28, br.s., 10H, benzene protons

7.04, q, 1H, pyridine γ proton

6.64, s, 1H, CH

5.87, br.s., 1H, OH. Ex.D_2O

I.R. ($CHCl_3$) ν_{max} 3660, 3600, 3400 (br, OH), 1585, 1570 cm^{-1}

U.V. (95% EtOH) λ_{max} 274 nm ($\log_{10}\varepsilon$ 4.03).

Mass spectrum, m/e, 418(45), 417(100), 415(100), 413(100), 356(67), 354(100), 353(100), 352(100), 351(100), 350(100), 334(50), 332(50), 276(100), 274(100), 272(100), 270(100), 255(67), 206(50), 201(50), 194(50), 183(78), 182(100), 180(67), 168(100), 167(100), 165(100), 151(67), 142(67), 138(48), 127(83), 114(92), 106(100), 97(53), 93(37), 91(100), 89(35), 81(100), 77(100), 69(90), 67(67), 65(77), 63(100), 57(100).

General procedure for conversion of dibromomethylpyridines into pyridine-2-carboxaldehydes.

The dibromomethylpyridine (ca. 1.2g in 25 ml of ethanol) was mixed with silver nitrate (2.1 mol equiv.) in hot water (∿ 7 ml). The mixture was boiled for 15 minutes, then cooled, and concentrated hydrochloric acid (7 ml) added. The silver salts were removed by filtration, the filtrate was evaporated under reduced pressure, and the residue was treated with saturated aqueous sodium hydrogen carbonate. Extraction with dichloromethane (4 x 50 ml), followed by drying with magnesium sulphate, filtering and evaporation gave the virtually pure pyridine-2-carboxaldehyde.

General procedure for reactions between triazolopyridines and bromine

The triazolopyridine was dissolved in dichloromethane (2g in ca. 25 ml) and cooled to 0-5°C, and bromine (1 mol. equiv.) in dichloromethane was added dropwise. Vigorous gas evolution occurred and stirring was continued after addition was complete (1 hr.). The solution was shaken with aqueous sodium hydrogen carbonate, then water, separated, and dried over magnesium sulphate. Filtration and evaporation gave the substantially pure dibromo--methylpyridine.

(6-dibromomethylpyridin-2-yl)-(p-methoxyphenyl)methanol (147c)

Obtained from the alcohol (126c) (2g) in 98% yield (3.0g) as a brown oil. Further purification was achieved using P.L.C. Multiple elution with ethylacetate-toluene (1:20) as eluent gave an analytically pure sample.

Analysis: Found: C, 43.61%; H, 3.51%; N, 3.55%

$C_{14}H_{13}Br_2NO_2$ requires: C, 43.44%; H, 3.38%; N, 3.62%

^1H N.M.R. ($CDCl_3$)

δ8.19-7.90 ppm, m, 2H, pyridine β protons

7.1, m, 1H, pyridine γ proton.

6.94-7.37, 4H, AA'BB' system, benzene protons.

6.20, s, 1H, $\underline{CH}Br_2$

5.60, s, 1H, $\underline{CH}OH$

3.76, s, 3H, CH_3

4.7, s, 1H, OH, Ex.D_2O.

α-(6-formylpyridin-2-yl)-4-methoxybenzyl alcohol (148c)

Obtained from the dibromomethyl compound (147c)(1.22g) in 78% yield (0.6g). The carboxaldehyde was an oil, characterised as its 2,4-dinitrophenylhydrazone.[162]

M.pt. 189-92°C (absolute ethanol)

Analysis: Found: C, 56.54%; H, 3.87%; N, 16.49%

$C_{20}H_{17}N_5O_6$ requires: C, 56.73%; H, 4.05%; N, 16.54%.

^{1}H N.M.R. ($CDCl_3$)

δ9.90 ppm, s, 1H, CHO

7.80, m, 2H, pyridine β protons

7.50, m, 1H, pyridine γ proton

6.80-7.30, AA'BB' system benzene ring protons

5.75, s, 1H, CH

4.75, br.s., 1H, OH, D_2O.Ex.

3.70, s, 3H, CH_3

I.R. ($CHCl_3$) ν_{max} 3400(br, OH), 3170, 2820, 1710(CHO), 1600, 1455, 1380, 1175, 990 cm^{-1}.

U.V. (95% EtOH) λ_{max} 230 nm (sh)

272 nm ($\log_{10}\epsilon$ 3.82)

Mass spectrum, m/e, 214(12), 201(29), 187(17), 186(10), 180(17), 142(25), 137(79), 136(100), 135(100), 131(21), 119(14), 110(35), 107(100), 106(31), 105(31), 92(39), 88(100), 86(100), 84(100), 79(100), 78(90), 77(98), 65(29), 64(25), 55(23).

Diphenyl-(6-formylpyridin-2-yl)methanol (148g)

Obtained from the dibromomethyl compound (147g)(3g) in quantitative yield (2.2g). The carboxaldehyde was a brown oil characterised as its 2,4-dinitrophenylhydrazone[162].

M.pt. 197-199°C (absolute ethanol)

Analysis: Found: C, 64.07%; H, 3.97%; N, 14.88%

$C_{25}H_{19}N_5O_5$ requires: C, 63.96%; H, 4.08%; N, 14.92%.

^{1}H N.M.R. ($CDCl_3$)

δ9.90 ppm, s, 1H, CHO

7.30-7.80, m, 3H, pyridine protons

7.28, s, 10H, benzene protons

5.90, br.s., 1H, OH, D_2O.Ex.

I.R. ($CHCl_3$) ν_{max} 3400 (br, OH), 3060, 2830, 1710, 1590, 1490, 1250, 1040, 1000, 970 cm^{-1}

U.V. (95% EtOH) λ_{max} 265 nm ($\log_{10}\varepsilon$ 3.86)
270 nm (sh)

Mass spectrum, m/e, 289(9)M^+, 273(15), 212(40), 184(34), 183(89), 182(100), 181(77), 155(36), 154(28), 152(40), 150(36), 132(11), 130(17), 128(19), 108(100), 107(32), 106(100), 105(100), 96(41), 95(21), 94(43), 91(26), 88(100), 86(100), 85(100), 84(100), 82(68), 78(87), 76(52), 69(100), 68(21), 67(51), 65(32), 55(57).

Bis-2-(6-dibromomethylpyridyl)ketone (149)

The ketone (139) (0.25g, 0.00094 mol) was dissolved in dichloromethane (15 ml) and cooled to 0°C, and bromine (0.15 g, 0.00094 mol) in dichloromethane (10 ml) was added dropwise. Stirring was continued until addition was complete (1 hr.). The solution was then shaken with aqueous sodium hydrogen carbonate, then water, separated, and then dried over magnesium sulphate. Filtration and evaporation gave the substantially pure bis-dibromomethylpyridyl ketone (149) in 40% yield (0.2g) as a red oil. Previously prepared in 5% yield by Newkome[111].

Experimental. Part B.

7-methyltriazolo[1,5-a]pyridine(153)

Two methods of preparation were used:

(i) via the hydrazone.

A mixture of 6-methyl-2-pyridine-2-carboxaldehyde (20.0g, 0.165 mol) and hydrazine hydrate (32 ml) were heated together on a water bath at 90-100°C for 90 minutes. The solution was then allowed to cool and 30% sodium hydroxide solution (32 ml) was added with stirring. The mixture was extracted with dichloro--methane (4 x 300 ml), the organic extract dried over potassium hydroxide, filtered and evaporated to yield the hydrazone (151) (24.4g ∿ 100%).

M.pt. 80-82°C (benzene-petroleum ether (b.pt. 60-80°C) (1:1))

Analysis: Found: C, 63.10%; H, 6.49%; N, 30.31%

$C_7H_9N_3$ requires: C, 62.20%; H, 6.71%; N, 31.09%.

This compound has been previously prepared[163]. No melting point reported.

The hydrazone (151) (20g), potassium ferricyanide (107.3g) and sodium hydrogen carbonate (27.4g) in water (800 ml) were heated on a water bath at 90-100°C for 30 minutes. There was a great deal of efffervescence and a black oil separated out. The mixture was allowed to cool and 30% sodium hydroxide was added (70 ml). The mixture was 'salted out' using sodium chloride and thoroughly extracted with dichloromethane (6 x 500 ml). The organic extract was dried over magnesium sulphate, filtered and evaporated to yield the crude triazolopyridine (193) (12.2g, 62%).

Distillation gave pure 7-methyltriazolopyridine (153), b.pt. 94°C at 0.05 mm, (9g, 46%).

M.pt. 40-42°C

Analysis: Found: C, 63.05%; H, 5.15%; N, 31.29%

$C_7H_7N_3$ requires: C, 63.14%; H, 5.36%; N, 31.56%

^{1}H N.M.R. ($CDCl_3$)

δ8.10 ppm, s, 1H, H3

7.63, dd, 1H, H4, $J_{4,5}$ = 9Hz

7.20, dd, 1H, H5, $J_{5,6}$ = 7Hz, $J_{5,4}$ = 9Hz

6.79, dd, 1H, H6, $J_{6,5}$ = 7Hz

2.88, s, 3H, CH_3

^{13}C N.M.R. ($CDCl_3$) - multiplicities in off-resonance shown in parenthesis

δ133.54 ppm(s), 125.67(d), 124.98(d), 115.01(d), 113.84(d) - triazolopyridine carbon atoms, 135.24(s), 17.33(q, CH_3)

I.R. ($CHCl_3$) ν_{max} 3380, 1920, 1640, 1550, 1525, 1425, 1325, 1210, 1180, 1150 970 cm^{-1}

U.V. (95% EtOH) λ_{max} 281 nm ($\log_{10}\varepsilon$ 3.88)

Mass spectrum, m/e, 133(100)M^+, 123(49), 122(81), 118(33), 106(25), 105(100), 104(100), 103(23), 94(58), 93(94), 92(56), 91(39), 90(25), 79(100), 78(100), 77(100), 76(42), 66(52), 65(100), 64(66), 63(100), 62(44), 61(21), 52(100).

(ii) via the tosylhydrazone (152)

To a methanolic solution (10 ml) of 6-methyl-2-pyridine-2--carboxaldehyde (5g, 0.0412 mol) was added p-toluenesulphonylhydrazide (7.7g, 0.0412 mol) in methanol (50 ml). The mixture was warmed gently and then cooled in an ice-bath. The tosylhydrazone separated as pink crystals. They were filtered and washed with cold methanol, and finally dried in a vacuum dessicator (over P_2O_5). The yield obtained was 82% (9.8g).

M.pt. 84-86°C (petroleum ether (b.pt. 40-60°C) - dichloromethane (4:1)).

Analysis: Found: C, 57.35%; H, 5.16%; N, 14.17%

$C_{14}H_{15}N_3O_2S$ requires: C, 58.12%; H, 5.23%; N, 14.53%

The tosylhydrazone (7g) was dissolved in morpholine (40 ml) and heated on a water bath at 90-100°C for 60 minutes. The excess morpholine was then removed under reduced pressure. The resulting yellow solid was treated with diethylether (200 ml). The morpholine sulphinate precipitate was filtered off and the filtrate evaporated to yield 7-methyltriazolopyridine (153) (2.3g, 71%).

Preliminary experiments on the lithiation of 7-methyltriazolo-pyridine (153)

Reaction with lithium deuteroxide

To a solution of 7-methyltriazolopyridine (153) (0.2g) in D_2O, in an n.m.r. tube, was added a small piece of lithium metal. The n.m.r. spectrum was checked regularly to see if there was any change in the spectrum.

Reaction of 7-methyltriazolopyridine (153) with sodamide

Sodium metal (0.17g, 0.0074 mol) was dissolved in dry liquid ammonia (20 ml, dried by passing through a potassium hydroxide drying tower). To this solution was added a small amount of Iron(III) nitrate. $9H_2O$ as a catalyst. The colour of the solution changed from the characteristic deep blue colour of sodium dissolved in liquid ammonia to the grey colour of sodamide. The ammonia condenser was removed and dry 'oxygen-free' nitrogen was passed into the flask, excess liquid ammonia was allowed to boil off. To the sodamide was added dry diethylether (30 ml). To this ethereal solution of sodamide was added 7-methyltriazolopyridine (1g, 0.0074 mol) in diethylether (20 ml). No change in colour was observed. The mixture was then boiled under reflux for one hour. With stirring, freshly distilled benzyl chloride (0.86 ml, 0.0074 mol) was added. The mixture was stirred for a further hour. Hydrolysis with ammonium chloride in ammonia (specific gravity 0.880), followed by extraction with dichloromethane (2 x 400 ml), drying the organic extract over magnesium sulphate, filtering and evaporation gave a crude product (2.0g). This was shown by n.m.r. spectroscopy to contain only starting materials (i.e. 7-methyl--triazolopyridine (153) and benzyl chloride).

Lithiation of 7-methyltriazolopyridine (153)

(i) Using 'oxygen-free'nitrogen as blanket gas

Preparation of 1-(p-methoxyphenyl)-2-(triazolopyridin-7-yl)ethanol (155)

A solution of 7-methyltriazolopyridine (153) (2g, 0.015 mol)

in dry ether (60 ml) was added at -40°C to a mixture of n-butyllithium (10.5 ml, 1.43M in hexane) and diisopropylamine (2.1 ml, 0.015 mol). After 6 hours at -40°C an intense red colour had developed, changing instantly to yellow when anisaldehyde (1.83 ml, 0.015 mol) was added. The mixture was stirred overnight at room temperature, hydrolysed with ammonium chloride in ammonia (specific gravity 0.880) and separated. Extraction of the aqueous layer with dichloromethane (4 x 200 ml) followed by drying over magnesium sulphate, filtering and evaporation gave a crude product (4.1g). Medium pressure chromatography (elution with ethyl acetate--petroleum ether (b.pt. 60-80°C)(2:3)) gave anisaldehyde (0.2g), p-methoxybenzyl alcohol (0.1g) and 7-methyltriazolopyridine (0.2g). Elution with an increased proportion of ethylacetate gave the methoxyphenylethanol (155) (2.3g, 57%).

M.pt. 117-118°C (benzene).

Analysis: Found: C, 67.02%; H, 5.57%; N, 15.88%

$C_{15}H_{15}N_3O_2$ requires: C, 66.90%; H, 5.61%; N, 15.61%

^{1}H N.M.R. ($CDCl_3$)

δ8.13 ppm, s, 1H, H3

7.74, dd, 1H, H4, $J_{4,5}$ = 8.5Hz, $J_{4,6}$ = 1Hz

6.8-7.4, m, 6H, H5, H6, benzene ring protons

5.35, m, 1H, CH

3.76, s, 3H, CH_3

3.51, m, 2H, CH_2

^{13}C N.M.R. (D_6-DMSO) - multiplicities in off-resonance shown in parenthesis

δ133.64 ppm(s), 125.32(d), 125.08(d), 115.26(d),

113.24(d) - triazolopyridine carbon atoms, 158.32(s, C-OMe), 136.59(s), 136.20(s), 126.57(d), 115.14(d) - benzene carbon atoms, 69.03 (d, CH(OH)), 54.98 (q, OCH_3), 41.26(tr)

I.R. ($CHCl_3$) ν_{max} 3400 (br, OH), 2840, 1645, 1615, 1590, 1555, 1470, 1445, 1330, 1305, 1250, 1175, 1105, 1040, 970 cm^{-1}

U.V. (95% EtOH) λ_{max} 281 nm ($\log_{10}\varepsilon$ 3.94)

Mass spectrum, m/e, 269(11)M^+, 183(13), 182(19), 181(11), 137(52), 135(87), 133(100), 109(43), 107(21), 106(11), 105(71), 104(52), 94(43), 93(11), 92(19), 91(11), 79(24), 78(63), 77(78), 69(17), 67(11), 66(11), 65(21), 64(17), 55(21), 53(11), 52(17), 51(32).

Treatment of compound (155) with bromine. Preparation of 2-(6-dibromomethylpyridin-2-yl)-1-(p-methoxyphenyl)ethanol (156)

To a cooled (0-5°C) dichloromethane solution (20 ml) of the alcohol (155) (1g, 0.0037 mol) was added bromine (0.6g, 0.0037 mol) in dichloromethane with stirring. Stirring was continued for one hour. The mixture was then shaken with aqueous sodium hydrogen carbonate, then water, and then thoroughly extracted with dichloromethane (2 x 200 ml). The organic extract was dried over magnesium sulphate, filtered and evaporated to yield the almost pure dibromomethyl compound (156) (1.3g, 87%). An analytically pure sample was obtained by P.L.C. Multiple elution with ehtyl acetate-toluene (1:20) gave the pure dibromomethyl compound (156).

B.pt. Undetermined

Analysis: Found: C, 44.62%; H, 3.64%; N, 3.49%

$C_{15}H_{15}Br_2NO_2$ requires: C, 44.92%; H, 3.77%; N, 3.49%

^1H N.M.R. ($CDCl_3$)

δ6.8-7.8 ppm, m, 7H, pyridine and benzene ring protons.

6.7, s, 1H, $C\underline{H}Br_2$

5.2, tr, 1H, $C\underline{H}(OH)$

3.8, s, 3H, CH_3

3.2, d, 2H, CH_2

I.R. (liquid film) ν_{max} 3400 (br, OH), 3000, 2950, 1615, 1595, 1520, 1460, 1300, 1250, 1175, 1030 cm^{-1}

U.V. (95% EtOH) λ_{max} 225 nm ($\log_{10}\varepsilon$ 4.40)
272 nm ($\log_{10}\varepsilon$ 3.98)

Mass spectrum, m/e, 266(89), 264(100), 262(100), 251(19), 241(85)M-Br_2, 222(59), 223(53), 213(64), 211(57), 208(57), 200(85), 192(42), 191(47), 186(100), 185(100), 184(100), 180(57), 149(100), 138(60), 137(100), 135(100), 119(42), 108(100), 107(68), 92(100), 91(100)

2-(6-formylpyridin-2-yl)-1-(p-methoxyphenyl)ethanol (157)

The dibromomethylpyridine (156) (1.15g, 0.0028 mol) in ethanol (25 ml) was mixed with silver nitrate (1.22g, 0.0058 mol) in hot water (7 ml). The mixture was boiled for 15 minutes then cooled,

concentrated hydrochloric acid (8 ml) added. The silver salts were removed by filtration, the filtrate was evaporated under reduced pressure, and the residue treated with saturated aqueous sodium hydrogen carbonate. Extraction with dichloromethane (2 x 200 ml), drying of the organic extracts over magnesium sulphate, filtering and evaporation gave virtually pure product (157) (0.5g, 68%).

M.pt. 103-108°C (absolute ethanol)

Analysis: Found: C, 70.10%; H, 5.60%; N, 5.22%

$C_{15}H_{15}NO_3$ requires: C, 70.02%; H, 5.88%; N, 5.44%

^1H N.M.R. ($CDCl_3$)

δ10.1 ppm, s, 1H, CHO

7.1-7.9, m, 7H, pyridine and benzene ring protons.

6.9, tr, 1H, CH(OH)

3.8, m, 5H, OCH_3 and CH_2

I.R. ($CHCl_3$) ν_{max} 3400 (br, OH), 1710 (CHO), 1610, 1580 cm^{-1}

U.V. (95% EtOH) λ_{max} 225 nm ($\log_{10}\varepsilon$ 4.32)

325 nm ($\log_{10}\varepsilon$ 4.38)

Mass spectrum, m/e, 257(1)M^+, 240(30), 239(100), (M^+-CO), 238(100), 225(90), 224(26), 211(38), 209(36), 207(34), 196(40), 195(90), 167(80), 152(30), 151(18), 149(52), 137(34), 135(100), 107(54), 79(22), 78(30), 77(50).

(ii) Using nitrogen with traces of oxygen present.

The experiment was performed using exactly the same quantities as previously. Work up gave a crude product (4.4g). Medium pressure chromatography (elution with ethylacetate--petroleum ether (b.pt. 60-80°C) (2:3)) gave anisaldehyde (0.8g), p-methoxybenzylalcohol (0.2g), and 7-methyltriazolopyridine (0.3g). Elution with ethylacetate-petroleum ether (3:1) gave 7-hydroxy--methyltriazolopyridine (144) (0.8g, 35%) and a small amount of 1,2-bis(triazolopyridin-7-yl)ethane (158) (0.1g, 2%).

M.pt. 211-212°C (benzene)

Analysis: Found: C, 62.95%; H, 4.40%; N, 32.00%

$C_{14}H_{12}N_6$ requires: C, 63.62%; H, 4.58%; N, 31.80%

^{1}H N.M.R. ($CDCl_3$)

δ8.1 ppm, s, 1H, H3

7.6, dd, 1H, H4, $J_{4,5}$ = 9Hz, $J_{4,6}$ = 1Hz

7.1, dd, 1H, H5

6.7, dd, 1H, H6, $J_{6,5}$ = 7Hz, $J_{6,4}$ = 1Hz

3.9, s, 4H, CH_2

I.R. ($CHCl_3$) ν_{max} 1935, 1645, 1560, 1330, 1150, 1105, 970 cm^{-1}

U.V. (95% EtOH) λ_{max} 280 nm ($\log_{10}\varepsilon$ 4.25).

Mass spectrum, m/e, 264(39)M^+, 235(27), 234(61), 209(24), 208(100), 207(45), 206(36), 205(30), 193(24), 192(27), 191(15), 181(24), 180(48), 179(30), 178(15), 169(24), 168(24), 156(36), 154(61), 149(18),

141(24), 133(30), 132(24), 130(24),
117(30), 104(42), 103(30), 95(24),
93(30), 91(27), 79(33), 78(66),
77(73), 65(45), 64(30), 63(51),
51(78).

Attempts to improve yields of compounds (144) and (158)

Compound (144)

From 7-methyltriazolopyridine (153) (2g, 0.015 mol), 7-lithiomethyltriazolopyridine (154) was synthesised as previously described. Dry air (dried by passing through concentrated sulphuric acid) was bubbled into the solution. However after work-up there was no significant increase in the yield of 7-hydroxymethyltriazolo--pyridine obtained (35%).

Compound (158)

A solution of 7-methyltriazolopyridine (153) (2g, 0.015 mol) in ether (60 ml) was added at -40°C to a mixture of n-butyllithium (11 ml, 1.4 M) and diisopropylamine (2.1 ml, 0.015 mol). After 6 hours the characteristic red colour had developed. Iodine (1.91g, 0.0075 mol) was added. The colour went bright yellow immediately. The solution was stirred for a further hour at -40°C. The mixture was then allowed to come to room temperature and stirred overnight. It was then boiled under reflux for 30 minutes and hydrolysed with ammonium chloride in ammonia (specific gravity 0.880). The solution was extracted with dichloromethane (2 x 200 ml) and the extract washed with sodium thiosulphate solution. The organic

extract was then dried over magnesium sulphate, filtered and evaporated to yield a crude product (1.2g) which was shown by n.m.r. spectroscopy to contain 7-hydroxymethyltriazolopyridine (144) (50%).

Experimental. Part C.

Preparation of the cyanhydrin of pyridin-2-aldehyde (170)

M.pt. 83.85°C (benzene)

lit. m.pt.[147] 88-98°C.

Oxidation of the cyanhydrin (170).

A mixture of dimethylsulphoxide (1.17g, 0.0149 mol) and dichloromethane (10 ml) were cooled to -50°C. To this was added trifluoroacetic anhydride (2.33g, 0.011 mol) in dichloromethane (7 ml) over a period of ten minutes. During the addition a white precipitate formed. The cyanhydrin (1.0g, 0.0074 mol) in (20 ml) was then added over a period of ten minutes. The contents of the flask were maintained at -50°C for a further thirty minutes. Triethylamine (4 ml) was then added over a ten minute period. After addition, the mixture was allowed to come to room temperature. All the solvents were removed under reduced pressure to yield the cyanoketone (171) (0.7g, 71%); ν_{max} ($CHCl_3$) 1740 cm^{-1}, M^+, 134, δ8.7 ppm (1H, d, pyridine α-proton) and δ7.5-8.2 ppm (3H, m, pyridine β and γ protons).

Attempted formation of the tosylhydrazone (172)

The cyanoketone (171) (0.7g, 0.0053 mol) was dissolved in methanol (10 ml). To this was added a methanolic solution (20 ml) of p-toluenesulphonylhydrazide (0.98g, 0.0053 mol). The mixture was warmed gently but no solid was deposited on cooling. The solution was boiled under reflux for one hour. T.L.C. (ethyl acetate as eluent) showed only the presence of starting materials.

Synthesis of the methyl ester (174) via the Pinner Synthesis

The cyanoketone (171) (0.8g, 0.0061 mol) was dissolved in methanol (50 ml) to which a small amount of water (0.1 ml) had been added. Hydrogen chloride gas was passed into the methanolic solution. When the solution was warm, the flow of gas was diminished and the mixture was boiled under reflux for eight hours. The methanol was removed under reduced pressure and the residue was neutralised with saturated aqueous sodium hydrogen carbonate. Extraction with dichloromethane (3 x 100 ml), separation, drying over magnesium sulphate. Filtration and evaporation gave the methyl ester (174) (0.3g, 30%). Continuous extraction of the aqueous layer with chloroform gave no further material.

Attempted formation of the tosylhydrazone (175)

The ester (174) (0.3g, 0.0018 mol) was dissolved in methanol (4 ml). To this was added a methanolic solution (5 ml) of p-toluenesulphonylhydrazide (0.36g, 0.0018 mol). The mixture was warmed gently but no solid was deposited on cooling. The solution was boiled under reflux for one hour. T.L.C. (ethyl acetate-toluene (1:1) as eluant) showed only the presence of starting materials.

Preparation of ethyl-2-pyridyl acetate

Prepared by the method of Woodward and Kornfield.

B.pt. 120-60°C/60 mm

Lit. B.pt.[150] 135-137°C/28 mm

Preparation of 3-ethoxycarbonyltriazolopyridine (177)

Sodium (5.6g, 0.24 mol) was dissolved in absolute ethanol (350 ml) under a dry nitrogen atmosphere. To this was added dropwise ethyl-2-pyridylacetate (40g, 0.24 mol) in absolute ethanol (100 ml). The solution was kept at a temperature of 15-20°C. Tosylazide (52.5g, 0.26 mol) was added dropwise. The mixture was stirred for 30 minutes. After 15 minutes a creamy white precipitate formed. After 30 minutes, water (20 ml) was added and the precipitate dissolved, upon addition of a further amount of water (80 ml), an oil separated out. The mixture was extracted with dichloromethane (4 x 100 ml). The organic extracts were dried over magnesium sulphate, filtered and evaporated to yield the product (177) (21.5g, 46%) as a yellow solid.

M.pt. 110-111°C (absolute ethanol)

Analysis: Found: C, 56.13%; H, 4.47%; N, 22.24%

$C_9H_9N_3O_2$ requires: C, 56.54%; H, 4.75%; N, 21.98%

^1H N.M.R. ($CDCl_3$)

δ8.84 ppm, dd, 1H, H7

8.27, dd, 1H, H4

7.57-7.18, m, 2H, H5 and H6

4.52, q, 2H, CH_2

1.49, tr, 3H, CH_3

^{13}C N.M.R. ($CDCl_3$) - multiplicities in off-resonance shown in parenthesis.

δ134.711 ppm (s), 125.70 (d), 129.02 (d), 118.98 (d), 116.25 (d) - triazolopyridine carbon atoms,

160.97 (s), 60.96 (tr), 14.43 (q).

I.R. ($CHCl_3$) ν_{max} 1730, 1710, 1650 (ester C = O), 1530, 1070 cm^{-1}

U.V. (95% EtOH) λ_{max} 245 nm ($\log_{10}\varepsilon$ 3.75)
286 nm ($\log_{10}\varepsilon$ 4.17)
300 nm (sh)

Mass spectrum, m/e, 191(4)M^+, 186(100), 165(44), 155(91), 149(52), 135(76), 123(37), 122(41), 121(30), 119(22), 111(41), 109(41), 107(100), 95(48), 94(52), 93(57), 92(65), 91(100), 81(46), 79(52), 78(59), 69(50), 67(44), 65(100), 63(37), 57(80).

Attempts to prepare 3-methoxycarbonyltriazolopyridine (179).

(i) using sodium ethoxide in ethanol as base.

Preparation of methyl-2-pyridylacetate

B.pt. 130-150°C/40 mm

Lit. B.pt.[150] 122-125°C/21 mm

Sodium (0.76g, 0.033 mol) was dissolved in absolute ethanol (45 ml) under a dry nitrogen atmosphere. To this was added dropwise methyl-2-pyridyl acetate (5g, 0.033 mol) in absolute ethanol (10 ml). The solution was kept at a temperature of 15-20°C. Tosylazide (7.2g, 0.036 mol) was added dropwise. The mixture was stirred for 30 minutes. As before, a creamy white precipitate formed which dissolved upon addition of water (20 ml). Upon addition of more water (80 ml), an oil separated out. The mixture was extracted with dichloromethane (2 x 100 ml).

The organic extracts were dried over magnesium sulphate, filtered and evaporated to yield 3-ethoxycarbonyltriazolopyridine (179) (1.6g). Continuous extraction of the aqueous layers gave no more product, only p-toluenesulphonamide was isolated.

(ii) Using potassium methoxide in methanol as base.

Potassium (1.3g, 0.0033 mol) was dissolved in absolute methanol (30 ml) under a dry nitrogen atmosphere. To this was added methyl-2-pyridyl acetate (5g, 0.033 mol) in methanol (15 ml). The solution was kept at a temperature of 15-20°C. Tosylazide (7.2g, 0.036 mol) was added dropwise. Before addition was complete a creamy white precipitate formed which dissolved upon addition of water (20 ml). Upon addition of more water (80 ml), an oil separated out. The mixture was extracted with dichloromethane (2 x 100 ml). The organic extracts were dried over magnesium sulphate, filtered and evaporated to yield a crude product (9.1g). Trituration of this semi-solid with petroleum ether (b.pt. 40-60°C) gave the salt (180) (2.6g, 24%) as pure crystals.

M.pt. 141-142°C (absolute ethanol)

Analysis: Found: C, 57.15%; H, 5.73%; N, 4.22%

$C_{16}H_{19}NO_5S$: C, 57.02%; H, 5.68%; N, 4.15%

^1H N.M.R. (CD_3OD)

δ9.1 ppm, dd, 1H, pyridine α-proton

8.0-8.5, m, 3H, pyridine β and γ protons.

7.1-7.5, AA'BB' benzene ring protons

4.6, s, 2H, CH_2

4.3, s, 3H, $\overset{+}{N}-\underline{CH}_3$

3.7, s, 3H, $CO_2\underline{CH}_3$

2.3, s, 3H, CH_3

Mass spectrum gave molecular ion at 337 m.u.

Examination of the oil, left after trituration, by n.m.r. spectroscopy showed the prescence of very small amounts of the salt (180) and large amounts of ethyl toluene-4-sulphonate (5.1g). Acidification of the aqueous layer with 2N hydrochloric acid, followed by extraction with dichloromethane (2 x 100 ml) drying over magnesium sulphate, filtration and evaporation gave some p-toluenesulphonamide (0.3g).

Independent synthesis of salt (180)

The methyl ester (2g, 0.013 mol) was dissolved in anhydrous benzene (15 ml). This solution was added dropwise to methyl toluene-4-sulphonate (2.46g, 0.013 mol) in anhydrous benzene (20 ml). The mixture was boiled under reflux for two hours and then allowed to cool overnight. Pink crystals were deposited which were shown by n.m.r. spectroscopy and melting point determination to be exactly the same as the salt (180). The yield of crystals obtained was 90% (4.0g), m.pt. 139-141°C.

(iii) Using lithium diisopropylamide as the base.

To a stirred solution of diisopropylamine (4.6 ml), 0.045 mol) and n-butyllithium (23 ml of 1.4M in hexane) in ether (40 ml) was added the methyl ester (5g, 0.033 mol) in ether (80 mls). The temperature of the mixture was kept at -40°C. Upon addition of the ester the solution went a deep crimson in colour. Stirring was continued for 4 hours. Tosylazide (6.5g, 0.033 mol) was added slowly, with stirring. The red colour changed to yellow. The mixture was allowed to come to room temperature and stirred overnight.

The mixture was hydrolysed with ammonium chloride in ammonia (specific gravity 0.880) and extracted with dichloromethane (4 x 100 ml). The organic extracts were dried over magnesium sulphate, filtered and evaporated to yield a crude product (6.1g). This was evaporated onto alumina (25g, IV) and chromatographed on a column of alumina (150g, IV). Elution with petroleum ether (b.pt. 60-80°C) gave ethyl toluene-4-sulphonate (1.5g) and benzene-petroluem ether (b.pt. 60-80°C) (2:3) gave the methyl ester (178) starting material (0.5g). The remainder of the weight was due to the salt (180), but this was not eluted from the column even with methanol.

Attempts to synthesise triazolopyridine (1) by diazo group transfer

(i) Using lithium diisopropylamide as base

To a solution of diisopropylamine (7.5 ml, 0.053 mol) and n-butyllithium (38 ml, 1.39 M in hexane) in ether (20 ml), at a temperature of -40°C, was added 2-methylpyridine (5g, 0.053 mol) with stirring. A deep orange colour developed. Tosylazide (10.5g, 0.053 mol) was added with stirring after 1 hour the colour changed to brown. The mixture was allowed to come to room temperature and stirred overnight. Hydrolysis with ammonium chloride in ammonia (specific gravity 0.880), followed by extraction with dichloromethane (4 x 200 ml), drying over magnesium sulphate, filtering and evaporation gave a brown oil (6g). N.m.r. spectroscopy showed only the presence of 2-methyl pyridine.

(ii) Using phenyllithium as base

A picolyllithium solution was prepared (0.1 mol)[150] and cooled to below 30°C. Tosylazide (19.7 g, 0.1 mol) was added slowly with stirring. There was considerable frothing, the ether solvent boiled away, more ether was added. The mixture was stirred for 30 minutes and then hydrolysed with ammonium chloride in ammonia (specific gravity 0.880). Extraction with dichloromethane (5 x 200 m), drying over magnesium sulphate followed by filtration and evaporation gave a brown oil (10g) identified by n.m.r. spectroscopy as 2-methylpyridine.

3-Triazolo[1,5-a]pyridinecarboxylic acid (168)

The ester (177) (2.14g, 0.011 mol) was dissolved in ethanol (40 ml) and 2N sodium hydroxide (6 ml) was added. The mixture was heated at 50°C for 1 hour. A white solid was deposited. The mixture was then acidified with 2N hydrochloric acid, the solid dissolved. The mixture was extracted with dichloromethane (3 x 100 ml) and the organic extracts dried over magnesium sulphate, filtered and evaporated to yield the relatively pure acid (168) (1.7g, 93%) as a white powder.

M.pt. 153-155°C (absolute ethanol)

Analysis: Found: C, 51.18%; H, 2.96%; N, 25.35%

$C_7H_5N_3O_2$ requires: C, 51.54%; H, 3.09%; N, 25.76%

^1H N.M.R. (D_6-DMSO)

δ9.2 ppm, dd, 1H, H7

8.0, dd, 1H, H4

7.0-7.7, m, 2H, H5, H6

8.4, br.s, 1H, OH, Ex.D_2O

^{13}C N.M.R. (D_6-DMSO) - multiplicites in off-resonance shown in parenthesis.

δ161.82 ppm(s), 134.23(s), 128.90(s), 129.87(d), 126.37(d), 118.30(d), 116.69(s)

I.R. (Nujol Mull) ν_{max} 1680, 1635, 1470 cm^{-1}

U.V. (95% EtOH) λ_{max} 237 nm ($\log_{10}\varepsilon$ 3.78)
286 nm ($\log_{10}\varepsilon$ 4.07)
300 nm (sh)

Mass spectrum, m/e, 163(13)M^+, 149(52), 119(100), 111(37), 108(67), 107(85), 97(43), 95(49), 93(52), 92(65), 91(100), 90(100), 81(49), 79(100), 78(100), 77(63), 76(49), 69(59), 67(80), 65(100), 64(100), 63(100), 57(78).

3-triazolo[1,5-a]pyridine carbonyl chloride (169).

The acid (168) (2g, 0.0123 mol) was suspended in anhydrous benzene (200 ml). To this was added thionylchloride (0.9 ml, 0.0123 mol) with a few drops of dry pyridine. The mixture was boiled under reflux for 3 hours. The solvent and excess thionyl chloride were then removed under reduced pressure to yield a yellow solid (2.3g) (100%) identified by n.m.r. spectroscopy and i.r. (1735, C=O) as the acid chloride (169). Further characterisation was not undertaken.

N,N-Diethyltriazolo[1,5-a]pyridine-3-carboxamide (162)

(a) via the ester (179)

The ester (179) (0.5g) was dissolved in diethylamine (20 ml). This was placed in a Carius tube and sealed. The tube was heated at 160°C for 7 hours. The tube was then opened and the excess diethylamine evaporated to yield a black oil (0.5g). The n.m.r. spectrum of the oil revealed only traces of the starting ester (179).

(b) via the acid chloride (169).

The acid chloride (169) (2g, 0.011 mol) was dissolved in anhydrous benzene (190 ml). This was added slowly to a cooled solution of diethylamine (4 ml, excess) in benzene (20 ml) over a period of two hours with vigorous stirring. The mixture was stirred overnight and then shaken with water (2 x 40 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 100 ml). The combined organic extracts were dried over magnesium sulphate, filtered and evaporated to yield a brown oil (2.3g, 95%) later identified as the required tertiary amide (162).

M.pt. 31-34°C

B.pt. 200°C/0.2 mm

Analysis: Found: C, 60.34%; H, 6.60%; N, 25.36%

$C_{11}H_{14}N_4O$ requires: C, 60.35%; H, 6.47%; N, 25.67%

^{1}H N.M.R. ($CDCl_3$) δ8.70 ppm, dd, 1H, H7

8.45, dd, 1H, H4

6.90-7.50, m, 2H, H5 and H6

3.90, br.q, 4H, CH_2

1.30, tr, 6H, CH_3

^{13}C N.M.R. ($CDCl_3$) - multiplicities in off-resonance shown in parenthesis

δ160.83 ppm (s), 135.67 (s), 133.09 (s), 127.26 (d), 124.86 (d), 120.58 (d), 115.98 (d), 42.18 (tr), 13.82 (q)

I.R. ($CHCl_3$) ν_{max} 3500, 1640 (C=O), 1530, 1390, 1380, 1160, 1070 cm^{-1}

U.V. (95% EtOH) λ_{max} 245 nm ($\log_{10}\varepsilon$ 3.89)

277 nm (sh)

287 nm ($\log_{10}\varepsilon$ 4.10)

305 nm (sh)

Mass spectrum, m/e, 218(100)M^+, 190(37), 175(100), 162(100), 161(100), 147(100), 133(72), 132(22), 131(17), 121(37), 120(100), 119(100), 108(44), 107(100), 105(100), 100(28), 93(65), 92(100), 91(100), 90(100), 80(37), 79(100), 78(100), 71(100), 65(83), 63(100), 56(100)

Lithiation of the amide (162).

Preparation of 7-(α-hydroxy-p-methoxytolyl)-N,N-dimethyltriazolo-[1,5-a]pyridine-3-carboxamide (185)

using 2 equivalents of lithium diisopropylamide

To a solution of diisopropylamine (2.56 ml, 0.018 mol) and n-butyllithium (14 ml, 1.3M in hexane) in ether (50 ml) at -40°C was added the amide (162) (2g, 0.0097 mol) dropwise. The mixture was stirred for 6 hrs at -40°C. The co-reactant, p-anisaldehyde (1.13 ml, 0.0097 mol) was added and the solution changed colour from red to yellow immediately. The mixture was allowed to come to room temperature and stirred overnight. The mixture was hydrolysed with ammonium chloride in ammonia (specific gravity 0.880). The mixture was then extracted with dichloromethane (4 x 100 ml). The organic extracts were dried over magnesium sulphate, filtered and evaporated to yield a brown oil (4.5g). This was evaporated onto alumina (20g, IV) and chromatographed on a column of alumina (135g, IV). Elution with benzene gave the starting amide (162) (0.2g) and some p-methoxybenzylalcohol (0.1g). Elution with benzene-dichloromethane (1:3) gave the disubstituted triazolopyridine (185) (1.0g, 31%).

M.pt. 148-149°C (benzene)

Analysis: Found: C, 63.78%; H, 6.17%; N, 15.92%

$C_{19}H_{22}N_4O_3$ requires: C, 64.43%; H, 6.26%; N, 15.81%

^{1}H N.M.R. ($CDCl_3$) δ8.2 ppm, dd, 1H, H4

6.90-7.50, m, 2H, H5 and H6

6.80-7.20, AA'BB' system of benzene ring protons

6.50, br.s, 1H, CH

5.00, br.s, 1H, OH, D_2O.Ex.

3.90, br.q, 4 H, CH_2

3.70, s, 3H, OCH_3

1.30, tr, 6H, CH_3

I.R. ($CHCl_3$) ν_{max} 3400 (br, OH), 1630 (C=O), 1540, 1390, 1100, 1040, 850 cm^{-1}

U.V. (95% EtOH) λ_{max} 245 nm (sh)
280 nm (sh)
290 nm ($\log_{10}\varepsilon$ 4.08)
310 nm ($\log_{10}\varepsilon$ 4.08)

Mass spectrum, m/e, 253(100), 241(35), 240(100), 237(37), 236(38), 221(39), 214(76), 213(100), 206(26), 196(100), 195(22), 186(37), 185(96), 181(26), 136(33), 134(31), 120(37), 119(28), 118(43), 117(33), 108(19), 105(47), 93(46), 90(41), 78(33), 77(48), 67(48).

Using only one equivalent of lithium diisopropylamine (half the quantities previously used) a brown oil (4.1g) was obtained. This was evaporated onto alumina (20g, IV) and chromatographed on a column of alumina (120g, IV). Elution with benzene-petroleum ether (b.pt. 60-80°C) gave anisaldehyde (0.8g), benzene-petroleum ether (b.pt. 60-80°C) (3:2) gave the starting amide (0.2g) and benzene eluted p-methoxybenzyl alcohol (0.2g). No further material was eluted from the column.

Synthesis of 4-methoxy-pyridine-2-carboxaldehyde (201)

Prepared by the method of Furukawa[164]

B.pt. 100-120°C/0.02 mm

Lit. B.pt.[164] 125-130°C/25 mm

Preparation of the hydrazone (202)

The aldehyde (2.93g, 0.0214 mol) (201) was dissolved in methanol (20 ml). To this solution was added p-toluenesulphonyl--hydrazide (3.96g, 0.0214 mol) in methanol (30 ml). The mixture was warmed gently and then cooled in ice. The hydrazone separated as pink crystals. These were filtered and washed with a small amount of cold methanol, and finally dried in a dessicator. The yield of the hydrazone was 35% (2.3g).

M.pt. 96-98°C (methanol)

Analysis: Found: C, 54.8%; H, 4.7%; N, 13.9%

$C_{14}H_{15}N_3O_3S$ requires: C, 55.1%; H, 4.9%; N, 13.8%

Cyclisation of the hydrazone (202)

The hydrazone (2.1g, 0.0068 mol) was dissolved in morpholine (15 ml) and heated on a water bath at 90-100°C for 1 hr. The excess morpholine was then removed under reduced pressure and the residue treated with ether. The morpholine sulphinate precipitate was filtered off and the filtrate evaporated to yield 5-methoxy--triazolopyridine (203) (0.7g, 68%) as a red liquid which solidified on cooling.

M.pt. 99-101°C (cyclohexane)

Analysis: Found: C, 55.84%; H, 4.59%; N, 28.14%

$C_7H_7N_3O$ requires C, 56.37%; H, 4.73%; N, 28.18%

^1H N.M.R. ($CDCl_3$)

δ8.7 ppm, dd, 1H, H7

7.8, s, 1H, H3

6.6-6.8, m, 2H, H4, H6

3.9, s, 3H, OCH_3

I.R. ($CHCl_3$) ν_{max} 2820 (C-H Stretch), 1650, 1550, 1170 (C-O Stretch), 1020, 810 cm^{-1}

U.V. (95% EtOH) λ_{max} 260 nm ($\log_{10}\varepsilon$ 3.94)

267 nm ($\log_{10}\varepsilon$ 3.94)

Mass spectrum, m/e, 149(100)M^+, 123(40), 122(44), 121(100), 120(58), 108(14), 107(36), 106(100), 93(80), 92(64), 91(100), 80(100), 79(100), 78(100), 77(36), 76(14), 67(100), 66(100), 65(100), 64(100), 63(100), 62(100), 61(100).

CHAPTER THREE

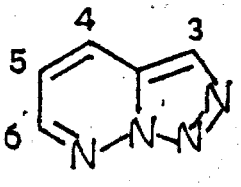
APPLICATION OF DIRECTED LITHIATION REACTIONS TO OTHER FUSED [1,2,3] TRIAZOLE SYSTEMS

Introduction

From chapter two it has been seen that the directed lithiation reaction is a very useful synthetic tool for functionalising the pyridine ring of triazolopyridine. This chapter describes investigations of the possible use of this reaction in functionalising other heterocycles, notably the [1,2,3]triazolopyrimidines and -pyrazines. The synthesis and chemical behaviour of these systems will now be reviewed. The [1,2,3]triazolo[1,5-b]pyridazine system will also be discussed.

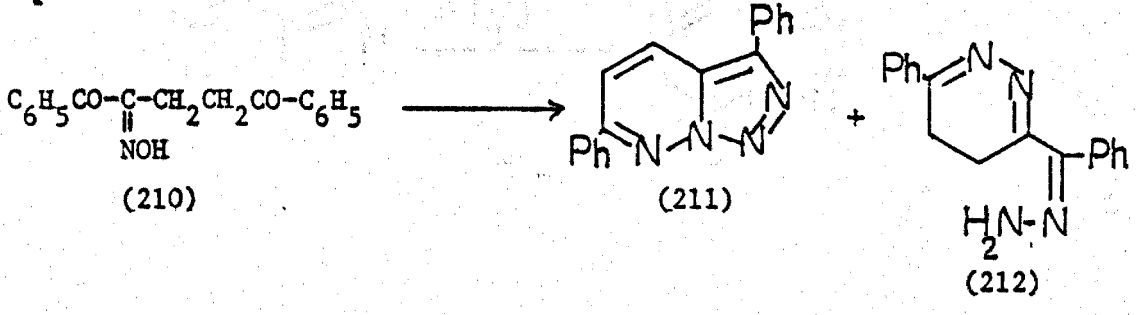
3.1. Review of the synthesis and chemistry of [1,2,3]triazolopyrimidines, pyrazines and pyridazines

(a) [1,2,3]Triazolo[1,5-b]pyridazine (213)



(213)

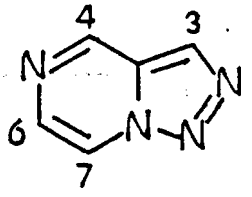
The only representative of this system was obtained by Evans, Johns and Markham[165]. When the oxime (210) was treated with excess hydrazine, 3,6-diphenyltriazolo[1,5-b]pyridazine (211) was obtained in 45% yield together with the hydrazone (212).



(210) (211) (212)

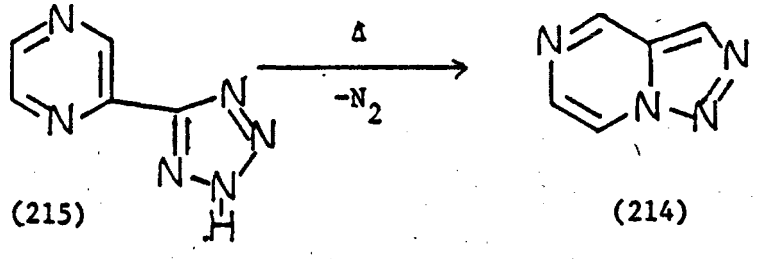
The bicyclic compound was also obtained if only one equivalent of hydrazine was used and if acetic acid was used instead of hydrochloric acid in the cyclisation step.

(b) [1,2,3]Triazolo[1,5-a]pyrazine (214)



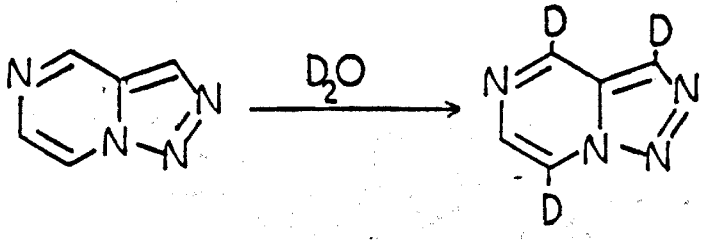
(214)

This heterocycle has been synthesised by Wentrup[28] by thermolysis of 5-(2-pyrazinyl)tetrazole (215) at 400°C/10^{-5} min. This is the only synthesis available to date.

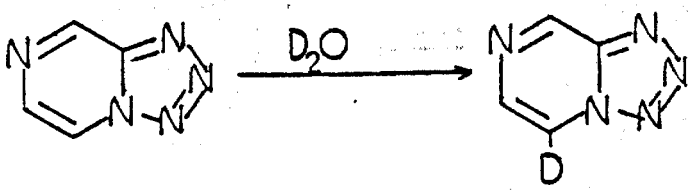


(215) (214)

The heating of compound (214) in D_2O at 100°C caused exchange of three protons. By monitoring the reaction by N.M.R. spectroscopy the relative rates of exchange were determined: H7 > H3 > H4. The approximate half--lives at 100°C were $t_{\frac{1}{2}}$ ≈ 24h for H7, $t_{\frac{1}{2}}$ ≈ 40h for H3, and $t_{\frac{1}{2}}$ ≈ 50h for H4.

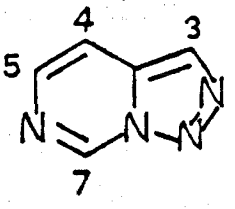


The fastest exchanging proton H7 of compound (214) finds a parallel in H5 of tetrazolo[1,5-a]pyrazine (216), which exchanged rapidly in D_2O yielding compound (217) ($t_{\frac{1}{2}}$ ≈ 12h at 94°C).[166]

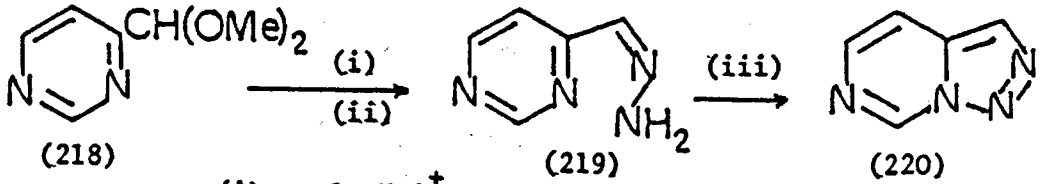


(216) (217)

(c) [1,2,3]Triazolo[1,5-c]pyrimidine (220)



This compound has been synthesised using 4-pyrimidinecarboxaldehyde dimethylacetal (218).[167] The hydrolysis of compound (218) with aqueous sulphuric acid proved difficult and attempts to isolate the aldehyde resulted in its decomposition. Nevertheless the hydrazone (219) was prepared without isolating the aldehyde. By treatment with lead tetra-acetate in benzene at room temperature, the hydrazone (219) reacted almost immediately giving the triazolopyrimidine (220).



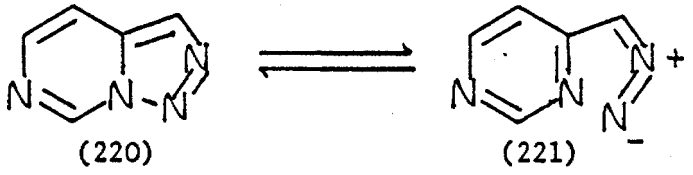
(218) (219) (220)

(i) 1. H_3O^+

(ii) 2. N_2H_4

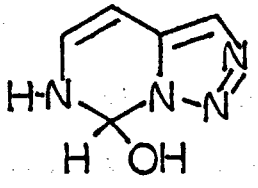
(iii) $Pb(OAc)_4$

Attempts to obtain evidence for the existence of the diazo tautomer (221) failed.



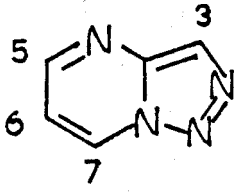
(220) (221)

The I.R. spectra in chloroform solution or in the solid state showed no absorption between 2000 and 2200 cm^{-1} (diazo gp) thus ruling out the presence of the tautomer (221) under these conditions. Trifluoroacetic acid is known to favour the open-chain tautomer in the azidoazine-tetrazoloazine isomerisation which is similar to the equilibrium (220) $\rightleftharpoons$ (221).[168] However, upon addition of traces of trifluroacetic acid to a solution of compound (226) in dimethylsuphoxide or in chloroform the covalent hydrate (222) was formed instead of the expected diazo tautomer (221).

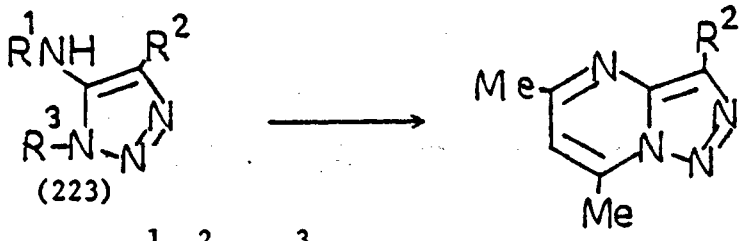


(222)

(d) [1,2,3]Triazolo[1,5-a]pyrimidine



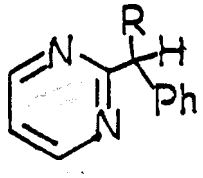
Heating the 4-substituted-5-amino-1H-1,2,3-triazoles (223a,b) and acetylacetone with piperidine in ethanol gave the [1,2,3]triazolo-[1,5-a]pyrimidine derivatives (224a,b) in high yield.[169,170]



(223) (224)

	R^1	R^2	R^3
a;	H	Ph	H
b;	H	$CONH_2$	H

Opening of the triazole ring in the triazolopyrimidine (224a) occurs in hot glacial acetic acid alone or in the presence of acetyl chloride, or in trifluoroacetic acid, yielding the 2-substituted pyrimidine derivatives (225a), (225b) and (225c) respectively.



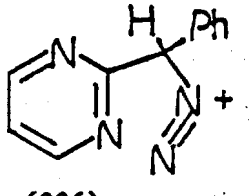
(225)

a; OAC

b; Cl

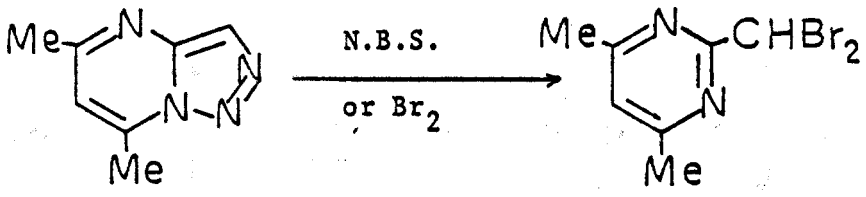
c; $OCOCF_3$

In contrast, heating the amide (223b) with acetylacetone in glacial acetic acid yields the triazolopyrimidine derivative (224b), which is stable to prolonged treatment with acetic or trifluoroacetic acid. This reactivity of the triazole ring towards acidic reagents can be explained by the formation of a diazonium cation such as structure (226) and



(226)

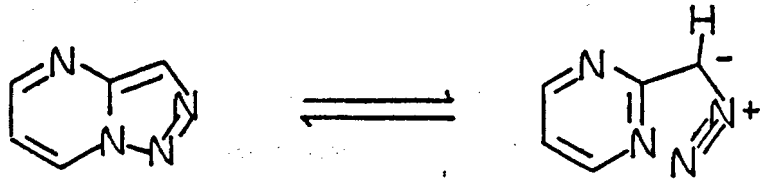
reaction of the derived carbonium ion with the solvent. Ring opening also occurs when these systems are treated with halogenating agents.[171] When 5,7-dimethyltriazolo[1,5-a]pyrimidine (227) was treated with N-bromosuccinimide (NBS) or bromine in dichloromethane, 2-dibromomethyl--4,6-dimethylpyrimidine (228) was the major product.



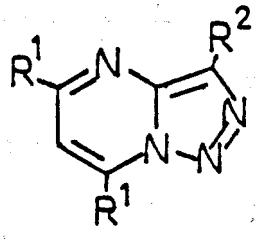
(227) (228)

Similar results were obtained using N-chlorosuccinimide (NCS). Again the possible existence of a diazomethane tautomer is obvious.

Tennant[172] has demonstrated simple examples of diazoalkylidene-amine-1,2,3-triazole equilibria in a fused system by variable temperature ^1H n.m.r. studies of a series of [1,2,3]triazolo[1,5-a]pyrimidines.



The triazolopyrimidines (224a,b) and (229,c,d) all lacked I.R. diazo absorption at ca. 2200 cm^{-1} demonstrating that at room temperature they exist entirely in the fused triazole form.



(224a), R^1 = Me, R^2 = Ph

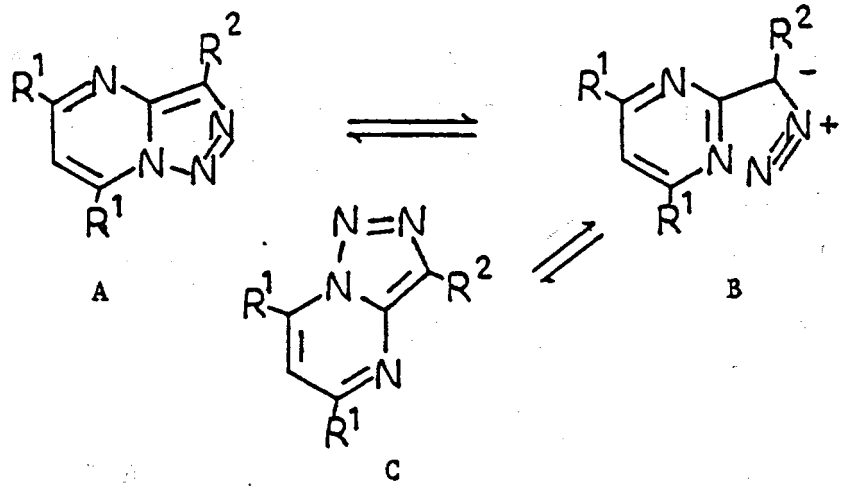
(224b), R^1 = Me, R^2 = $CONH_2$

(229c), R^1 = H, R^2 = $CONH_2$

(229d), R^1 = N, R^2 = Ph

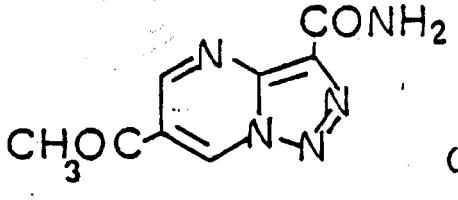
At room temperature, the ^1H n.m.r. spectrum of amide (229c) exhibited three double doublets centred at δ9.64 ppm, δ8.98 ppm and δ7.46 ppm. However the low field doublets changed progressively on warming and ultimately coalesced at 100°C, before sharpening up to a doublet centred at δ9.03 ppm (2H). The high field doublet of doublets coalesced likewise and eventually emerged as a triplet centred at δ7.26 ppm. These changes

which reversed completely on cooling may be attributed to the rapid interconversions (A ⇌ B ⇌ C) at elevated temperatures.



A B C

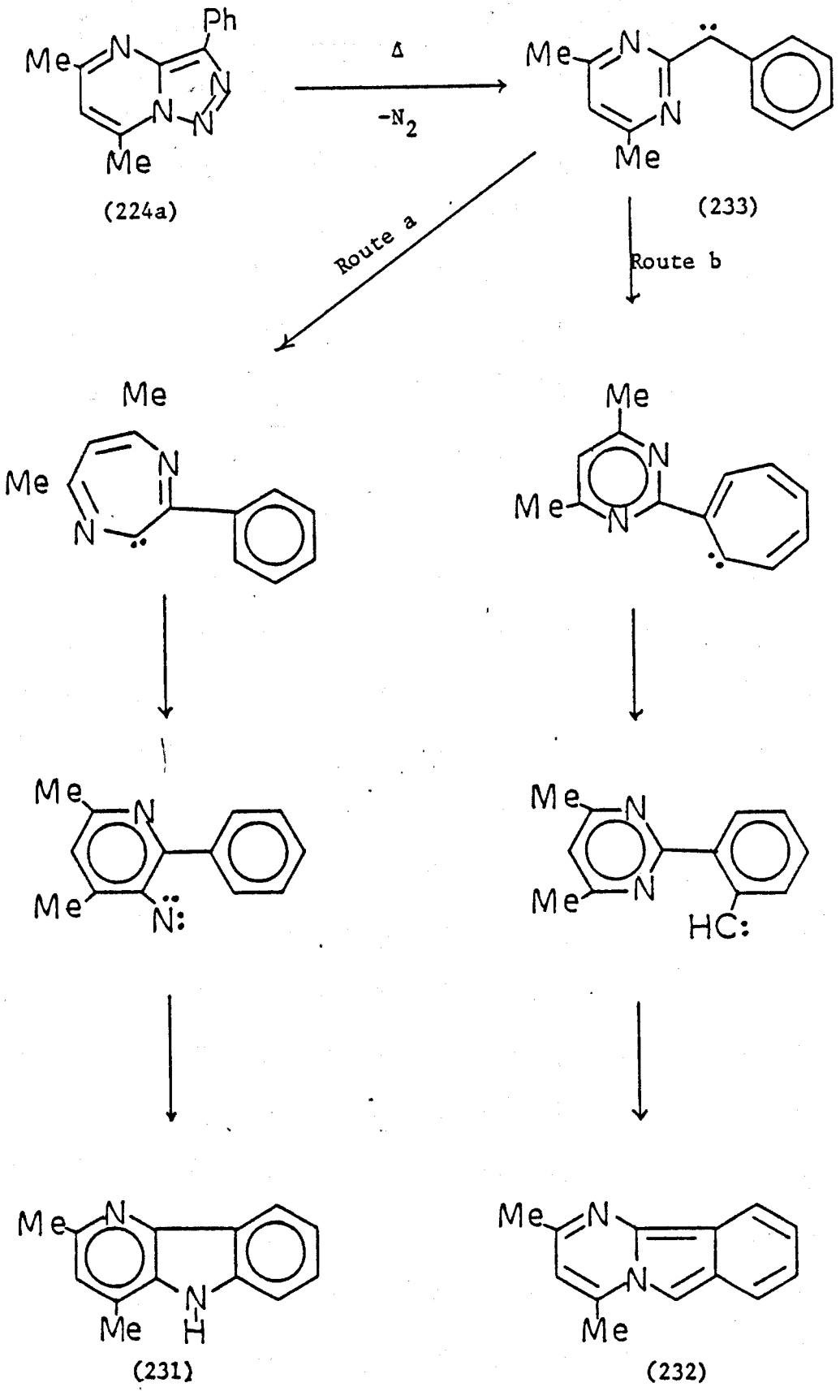
These suggestions are supported by the appearance of I.R. diazo absorption at 2100 cm^{-1} in a sample of compound (230) kept at 80°C for 20h.



(230)

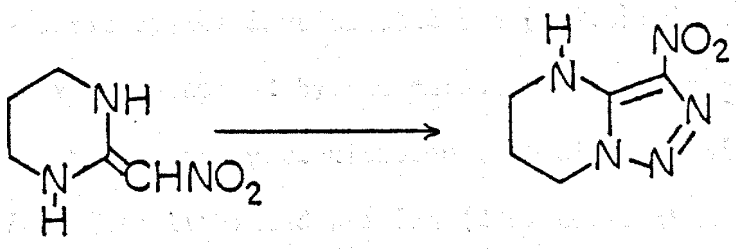
Gas phase thermolysis of 5,7-dimethyl-3-phenyltriazolo[1,5-a]pyrimidine (224a) results in two products, 2,4-dimethyl-5H-pyrido[3,2-b]indole (231; 14%) and 2,4-dimethylpyrimido[2,1-a]isoindole (232; 72%).[36] The formation of compounds (231) and (232) in the thermolysis demonstrates that the derived phenyl-2-pyrimidylcarbene (233) can undergo expansion of both the pyrimidine and benzene rings. The latter (route b) is favoured by a factor of approximately 5. See figure 3.1.

The triazolopyrimidine ring system can also be synthesised by treating the diamine (234) with p-chlorobenzenesulphonyl azide in acetonitrile for 7 days at room temperature to give compound (235) in 35% yield.[173]



(231) (232)

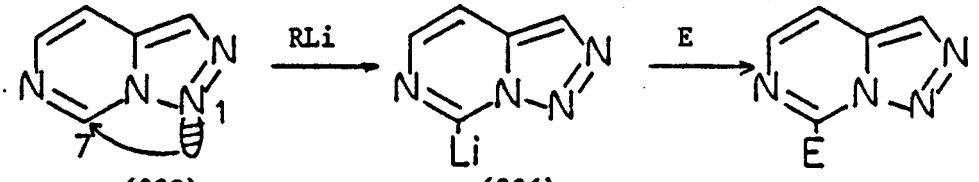
Scheme 3.1



(234) (235)

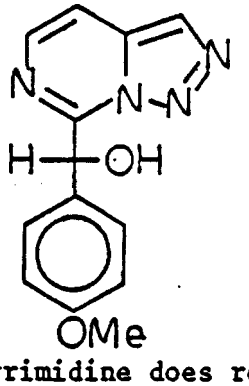
Discussion

The first system investigated was [1,2,3]triazolo[1,5-c]pyrimidine (220). This was prepared by the method of Maury et al.[167] in 60% yield. It was thought that the peri-nitrogen atom N1 might direct lithiation to position 7. This lithiated species (236) could then undergo reaction with various electrophiles in a manner similar to triazolopyridine (1).



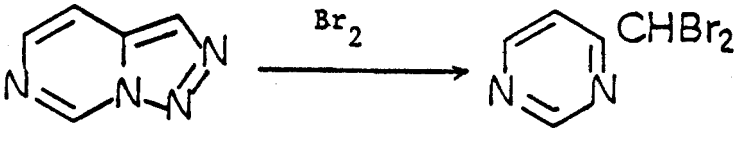
(220) (236)

Lithiation of compound (220), under the same conditions as those used for triazolopyridine, with lithium diisopropylamide as base (reaction time - 6 hours and a reaction temperature of -40°C), failed to give any of the expected product (237) using anisaldehyde as co-reactant. Only starting materials were recovered.



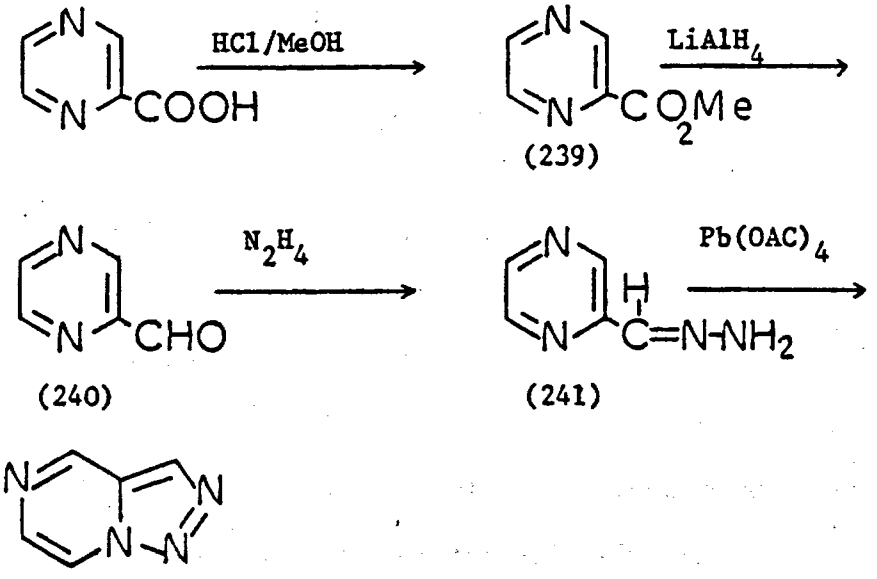
(237)

However triazolo[1,5-c]pyrimidine does react with bromine to give the previously synthesised 4-dibromomethylpyrimidine (238)[174] but in a far greater yield (70%).



(220) (238)

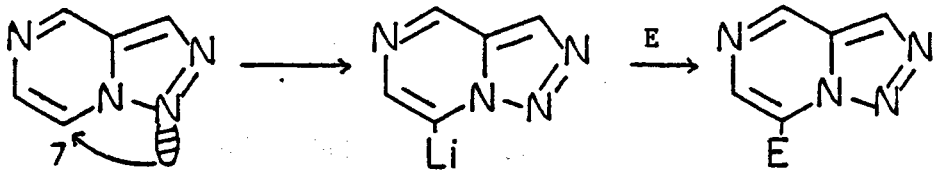
Triazolo[1,5-a]pyrazine (214) has only been synthesised by thermolysis of 5(2-pyrazinyl)tetrazole.[28] A much more effective synthesis was devised using 2-pyrazinecarboxylic acid. The reaction sequence is shown in scheme 3.2.



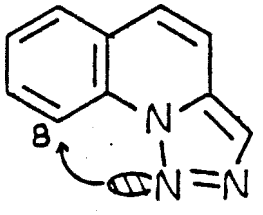
Scheme 3.2

Pyrazine-2-carboxaldehyde (240) was synthesised by a known procedure, involving a selective reduction of the methyl ester (239) using lithium aluminium hydride at -70°C.[175] The methyl ester was easily prepared from 2-pyrazinecarboxylic acid.[176] The yield of pyrazine-2-carboxaldehyde obtained was only 12%. However some difficulty was encountered in separating 2-pyrazinecarboxaldehyde (b.pt. 51°C/3 mm) from the methyl ester (b.pt. 59°C/0.01 mm). Partial separation was achieved using a 'spinning band' distillation column.

Reaction of 2-pyrazinecarboxaldehyde with hydrazine hydrate gave the hydrazone (241) which on oxidation with lead tetraacetate gave the triazolopyrazine (214) in 78% yield (from 2-pyrazinecarboxaldehyde). Again the possibility arises that the peri-nitrogen atom N1 could direct lithiation to position 7 of the triazolopyrazine system.

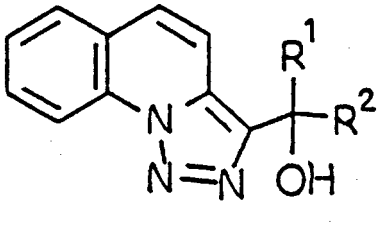


Initial experiments with lithium diisopropylamide as base have failed to achieve any lithiation at position 7. Anisaldehyde was again used as co-reactant. Only starting materials were recovered. Dr. Belen Abarca in Spain[177] has applied this lithiation reaction to [1,2,3]triazoloquinoline (242). It was thought that the peri-nitrogen atom N1 might direct lithiation to position 8 on the quinoline ring.



(242)

However lithiation of compound (242) using lithium diisopropylamide at -40°C, followed by quenching with aldehydes and ketones such as anisaldehyde, acetone and acetaldehyde gave 3-substituted triazoloquinolines (243) not 8-substituted derivatives.



(243)

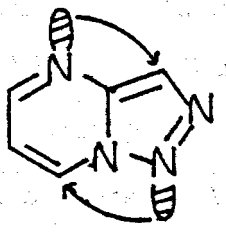
a; $R^1 = CH_3$, $R^2 = CH_3$

b; $R^1 = H$, $R^2 = CH_3$

c; $R^1 = H$, $R^2 = 4\text{-}MeOC_6H_4$

This is another example where the lithiating agent removes the most acidic proton, thus the 'acid-base' mechanism is operative (see chapter two) as opposed to the 'coordination only' mechanism of lithiation.

An interesting case that has yet to be investigated is [1,2,3]triazolo[1,5-a]pyrimidine (244).



(244)

In this molecule there are two nitrogen atoms (N1 and N4) which both have lone pairs of electrons. Directed lithiation could hence occur either at position 3 or position 7.

Experimental

Preparation of [1,2,3]Triazolo[1,5-c]pyrimidine (220)

Prepared by the method of Maury and Paugam[167] in 60% yield.

M.pt. 130-132°C (benzene-petroleum ether (b.pt. 60-80°C))

Lit. m.pt.[167] 130-131°C (benzene-petroleum ether)

Lithiation of [1,2,3]Triazolo[1,5-c]pyrimidine (220)

A solution of n-butyllithium (8.7 ml of 1.44M in hexane; 0.0125 mol) was added to diisopropylamine (1.86 ml, 0.0125 mol) at -40°C under an argon atmosphere. A solution of triazolo[1,5-c]pyrimidine (220) (1.5g, 0.0125 mol) in dry ether (60 ml) was added with stirring which was continued at -40°C for 6h during which time a deep red colour developed. Anisaldehyde (1.52 ml, 0.0125 mol) was added and the colour changed to yellow. The mixture was allowed to come to room temperature and stirred overnight. The mixture was then hydrolysed by a solution of ammonium chloride in ammonia (specific gravity 0.880). The hydrolysed mixture was extracted with dichloromethane (3 x 100 ml). The organic extracts were dried over magnesium sulphate, then filtered and evaporated to yield a brown oil (2.8g). N.M.R. spectroscopy revealed only the presence of starting materials, triazolopyrimidine and anisaldehyde.

Preparation of 4-dibromomethylpyrimidine (238)

This compound has previously been prepared by Brown et al.[174] All spectral data was recorded but no b.pt. given.

The triazolopyrimidine (1g, 0.0083 mol) was dissolved in dichloromethane (25 ml) and cooled to 0-5°C, and bromine (0.38g, 0.0083 mol) was added dropwise. Stirring was continued after the addition was complete (1h). The solution was shaken with aqueous

sodium hydrogen carbonate, then water, and dried over magnesium sulphate. Filtration and evaporation gave the dibromomethylpyrimidine (1.5g, 70%), (238).

Preparation of 2-methoxycarbonylpyrazine (239)

Prepared by the method of Hall and Spoerri[176] in 81% yield.

M.pt. 59°C

Lit. m.pt.[176] 59°C

Preparation of pyrazine-2-carboxaldehyde (240)

Prepared by the method of Rutner and Spoerri[175] in 12% yield.

B.pt. 51°C/3 mm

Lit. b.pt.[175] 59°C/6 mm.

Preparation of the hydrazone (241)

The aldehyde (240) (1.6g, 0.0148 mol) was dissolved in water (10 ml). To this was slowly added hydrazine hydrate (10 ml) in water (20 ml). The mixture was allowed to stand for 24h. It was then extracted with dichloromethane (4 x 100 ml), the organic extract was dried over magnesium sulphate, filtered and evaporated to give the hydrazone (241) as a white solid in 78% yield (1.4g).

M.pt. 88-91°C (cyclohexane/benzene)

Analysis: Found: C, 48.60%; H, 4.95%; N, 46.12%.

$C_5H_6N_4$ requires: C, 49.17%; H, 4.95%; N, 45.88%.

Preparation of [1,2,3]Triazolo[1,5-a]pyrazine (214)

Lead tetraacetate (5g) was dissolved in anhydrous benzene (100 ml) and kept under a dry nitrogen atmosphere. To this was added the

hydrazone (241) (1.2g, 0.0098 mol) in anhydrous benzene (200 ml). The mixture was stirred for 20 minutes. The benzene was removed under reduced pressure to yield a brown oil (5g). This was quickly passed down a column of alumina (100g, IV) using dichloromethane as eluant. Triazolopyrazine (214) was obtained in quantitative yield (1.2g).

M.pt. 123-125°C (cyclohexane/benzene)

Lit. m.pt.[28] 126-12.65°C (ethyl acetate)

All spectral data recorded by Wentrup apart from the ^{13}C data.

^{13}C N.M.R. ($CDCl_3$) - multiplicities in off-resonance shown in parenthesis.

143.16(d), 131.42(d), 122.15(d), 116.62(d).

No quaternary carbon atom visible.

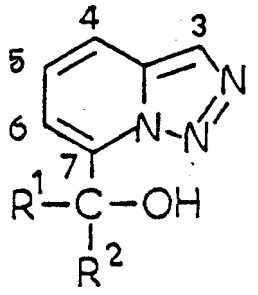
Lithiation of [1,2,3]Triazolo[1,5-a]pyrazine (214)

A solution of n-butyllithium (5 ml of 1.3M in hexane, 0.0066 mol) was added to diisopropylamine (0.94 ml, 0.0066 mol) at -40°C under an argon atmosphere. A solution of triazolo[1,5-a]pyrazine (214) (0.8g, 0.0066 mol) in dry ether (60 ml) was added with stirring which was continued at -40°C for 6h during which time a red-brown colour developed. Anisaldehyde (0.81 ml, 0.0066 mol) was added. The mixture was allowed to come to room temperature and stirred overnight. The mixture was then hydrolysed by a solution of ammonium chloride in ammonia (specific gravity 0.880). The hydrolysed mixture was extracted with dichloromethane (4 x 100 ml). The organic extracts were dried over magnesium sulphate, then filtered and evaporated to yield a brown oil (1.5g). N.M.R. spectroscopy revealed only the presence of starting materials, triazolopyrazine (214) and p-anisaldehyde.

CHAPTER FOUR

THE SPECTRAL PROPERTIES OF SUBSTITUTED TRIAZOLOPYRIDINES

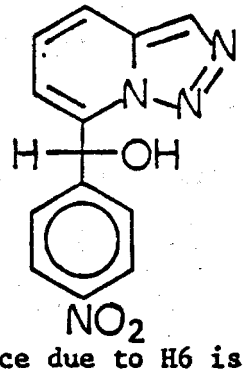
^{1}H N.M.R.



(126a-h)

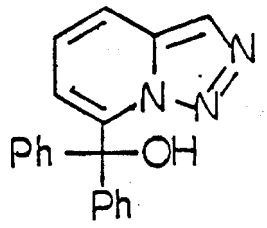
In the synthesis of the triazolopyridin-7-yl methanols (126a-h) the site of lithiation and hence the position of the new substituent was established by ^{1}H N.M.R. spectroscopy. The N.M.R. spectra of the methanols (126a-h) exhibited a loss of the broadened doublet of doublets at δ8.7 ppm due to H7 and a loss of the long range coupling (J = 1 Hz) shown by H3 coupling with the epi-proton H7.

In most cases the effect of the substituents on the proton shifts on the triazolopyridine moiety are negligible. Two noteworthy exceptions are the following:-



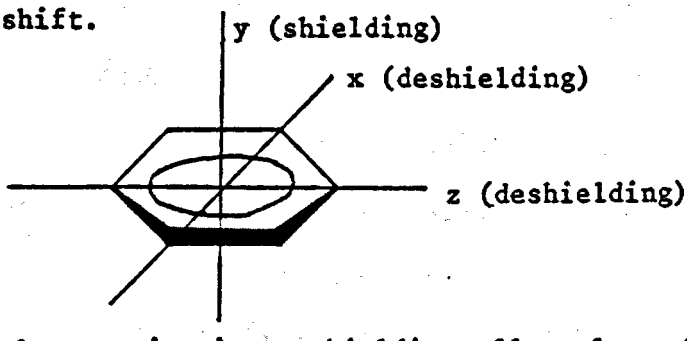
(126d)

In this molecule the resonance due to H6 is moved downfield from δ7.0 ppm (in unsubstituted triazolopyridine (1)) to δ7.9 ppm. All the other proton resonances show a less marked downfield shift. In most of the other cases the CH(OH) resonances occur in the region of δ6.1-6.5 ppm, in this molecule however the resonance occurs at δ6.9 ppm. All these effects are due to the strongly electron withdrawing power of the nitro group.

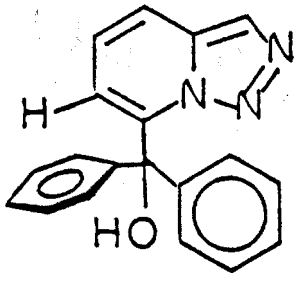


(126g)

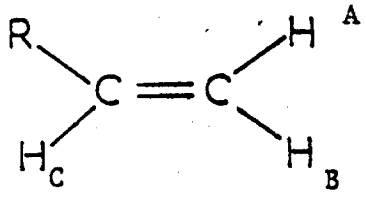
The N.M.R. spectrum of this compound exhibits a doublet of doublets at δ6.32 ppm with the coupling constants J6.95 Hz and J1.2 Hz. Both these coupling constants are consistent with resonance being due to H6. The coupling constants are thus $J_{6,5}$ = 6.95 Hz and $J_{6,4}$ = 1.2 Hz. In triazolopyridine (1) these coupling constants are $J_{6,5}$ = 6.5 Hz and $J_{6,4}$ = 1.25 Hz. However relative to triazolopyridine (1) the resonance due to H6 is moved upfield to δ6.32 ppm from a normal value of δ7.0 ppm. This can be explained by remembering the effects of the ring current (Y) on the phenyl substituents. Along the sixfold axis of the benzene ring, the extra magnetic field produced by the ring current opposes the applied field, giving a high field shift. Conversely, at the proton (X,Z) on the benzene ring, thering current field adds to the external field giving a low field shift.



Thus proton H6 must be experiencing a shielding effect from the phenyl substituents. The arrangement of the phenyl groups must be as shown.



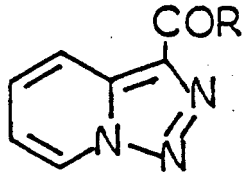
In the secondary triazolopyridin-7-yl methanols (126b,c) some coupling between the hydroxyl proton and the α-proton was present, $J_{CH(OH)}$ = 4.5 Hz. In the tertiary triazolopyridin-7-yl methanol (126h) the vinylic coupling constants are



J_{AB}(gem) = 0.85 Hz, typical values -3 to +7 Hz[178]

J_{BC}(cis) = 10.62 Hz, typical values 3 to 18 Hz

J_{AC}(trans) = 16.70 Hz, typical values 12 to 24 Hz

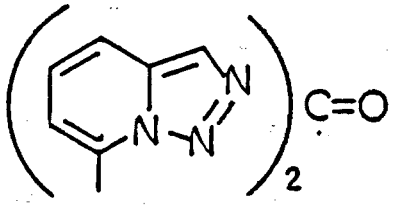


(168), R = OH

(177), R = OEt

(162), R = $N(Et)_2$

The N.M.R. spectra of the 3-substituted triazolopyridine showed a loss of the singlet at δ8.0 ppm due to H3. In all cases the resonance due to H4 was moved downfield, the shift was typically 0.6 ppm (δ7.7 ppm → δ8.3 ppm). All the other resonances were moved downfield but to a lesser extent. This effect is due to the deshielding ability of the carbonyl group. This effect is also observed in the ketone (139).

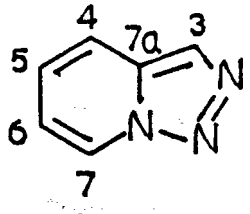


(139)

The resonance due to H6 is moved downfield to δ7.9 ppm, a shift of 0.9 ppm relative to unsubstituted triazolopyridine. Again all the other resonances were moved downfield but to a lesser extent.

^{13}C N.M.R.

The ^{13}C N.M.R. spectrum of triazolopyridine has been previously reported[179] and the chemical shifts and assignments are presented in table 4.1.*



C3	C4	C5	C6	C7	C7a
118.7	116.1	126.1	116.1	126.1	134.5

* recorded in acetone - D_6

Table 4.1.

However chemical shifts and assignments carried out during the course of this research differ from those previously published.[179] The ^{13}C N.M.R. spectrum of triazolo[1,5-a]pyridine (1) was recorded in acetone-D_6, benzene-D_6 and in $CDCl_3$. The acetone solution gave the least useful results because of overlap in the signals. Most of the measurements were made with solutions in $CDCl_3$. The chemical shifts are recorded in table 4.2.

	Chemical shifts δ values ppm					
Multiplicities in off-resonance	115 d	117.6 d	124.7 d	125 d	125.2 d	133.32 s

Table 4.2.

The signal at δ133.32 ppm appears as a singlet in the 'off-resonance' spectrum and is obviously due to the quaternary carbon atom, C7a. The preparation of 3-deuteriotriazolopyridine[28] led to the assignment of shift to carbon atom 3. In the fully decoupled spectrum of

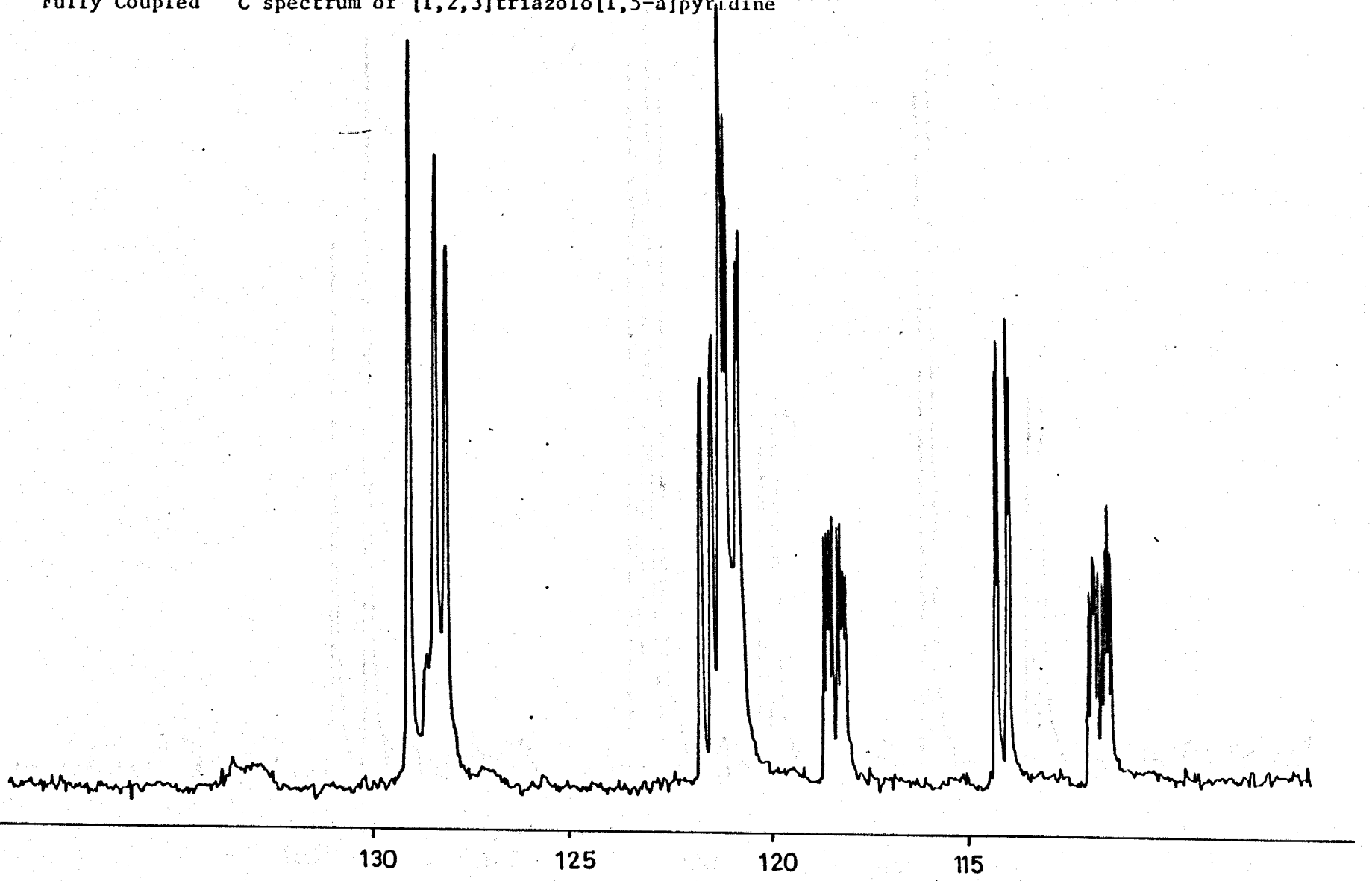
3-deuteriotriazolopyridine the signal at δ125.2 ppm is missing (assigned as δ118.7 ppm in the previous report[179]). In 7-deuteriotriazolopyridine (125) the missing signal is that at δ124.7 ppm; this peak is noticeably smaller than the others in the fully decoupled spectrum of triazolopyridine (1), (presumably due to the nuclear quadrupole of the neighbouring nitrogen atom). The assignment of the remaining three signals depends on an inspection of the coupling constants (table 4.3) for triazolopyridine (1) and 7-deuteriotriazolopyridine (125). Both the fully coupled spectra are reproduced here. The spectra were performed at a frequency of 100 MHz by Dr. C.H. Spencer at the University of Sheffield.

Compound	Chemical shift ppm	All in Hz			
		$^{1}J_{CH}$	$^{2}J_{CH}$	$^{3}J_{CH}$	$^{4}J_{CH}$
Triazolopyridine (1)	125.2	184.33	-	-	-
	125.0	174.56	7	1	-
	124.7	172.73	-	-	-
	117.6	170.90	7.6	1.2	-
	115.0	167.85	7.5	1.2	1
	133.34	-	-	-	-
7-deuteriotriazolopyridine (125)	125.23	189.20	-	-	-
	124.96	175.17	-	1	-
	117.60	170.59	7.5	∿1	-
	114.87	167.80	7.5	∿1	-
	133.35	-	-	-	-

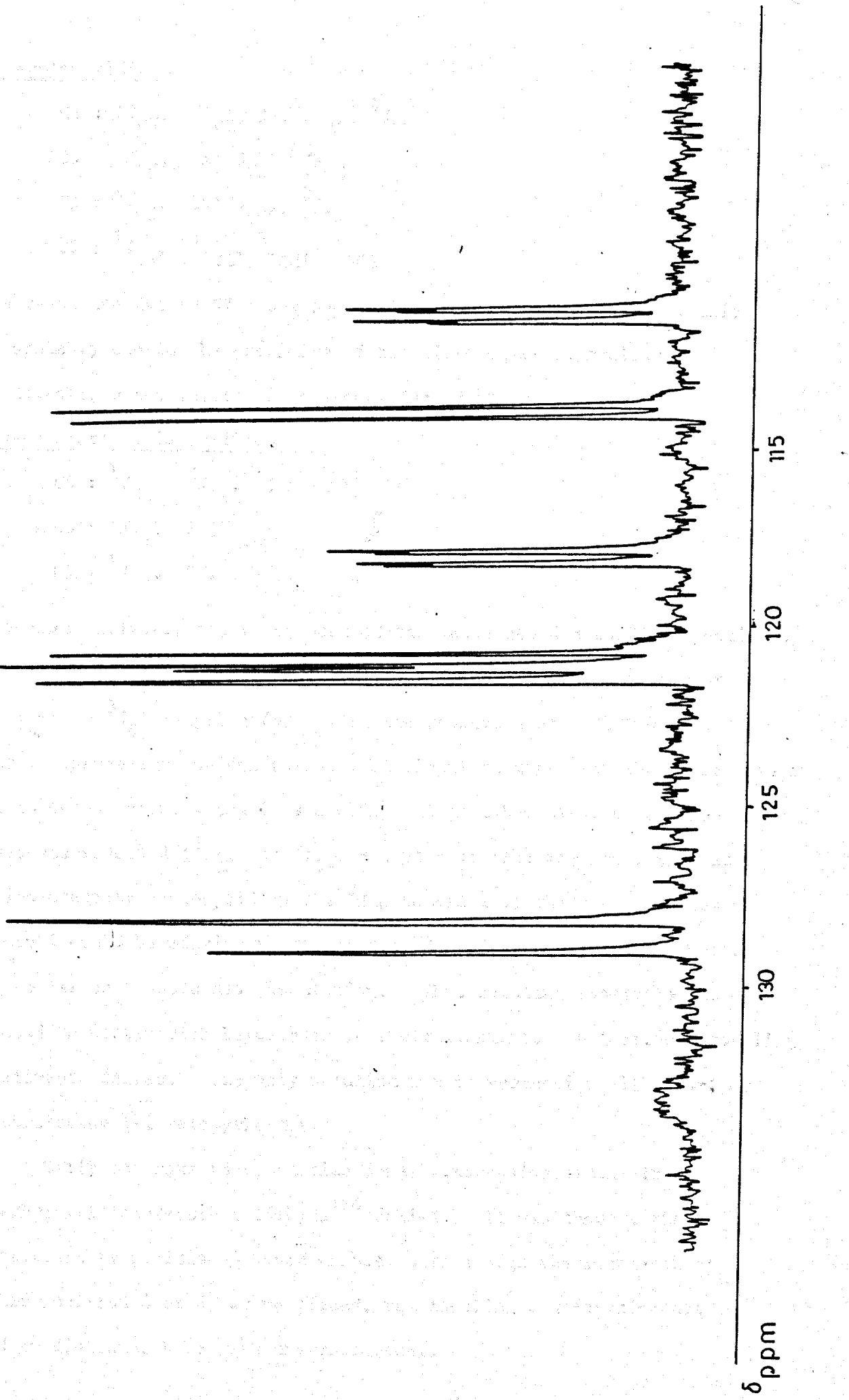
Table 4.3.

In a 1st order spectrum, the coupling constants each carbon resonance should show are given below.

Fully Coupled ^{13}C spectrum of [1,2,3]triazolo[1,5-a]pyridine



Fully Coupled ^{13}C spectrum of 7-deuteriotriazolo[1,5-a]pyridine



Triazolopyridine

C4 : $^{1}J_{CH}$, $^{2}J_{CH}$, $2x(^{3}J_{CH})$, $^{4}J_{CH}$

C5 : $^{1}J_{CH}$, $2x(^{2}J_{CH})$, $^{3}J_{CH}$

C6 : $^{1}J_{CH}$, $2x(^{2}J_{CH})$, $^{3}J_{CH}$

C7 : $^{1}J_{CH}$, $^{2}J_{CH}$, $^{3}J_{CH}$, $^{4}J_{CH}$

The resonance due to C7 shows no coupling constants except $^{1}J_{CH}$, this is probably due to the proximity of the nitrogen atoms nuclear quadrupole, which results in a broadening of the resonance.

7-Deuteriotriazolopyridine

C4 : $^{1}J_{CH}$, $^{2}J_{CH}$, $2x(^{3}J_{CH})$

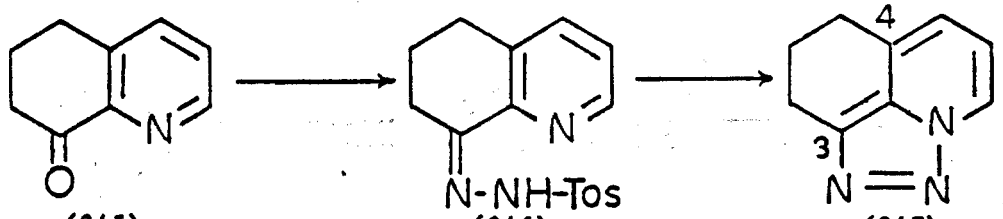
C5 : $^{1}J_{CH}$, $2x(^{2}J_{CH})$

C6 : $^{1}J_{CH}$, $^{2}J_{CH}$, $^{3}J_{CH}$

From this analysis, the assignment of the resonance due to C5 is possible. From the spectrum of 7-deuteriotriazolopyridine, it can be seen that there is no $^{3}J_{CH}$ coupling ($\sim$7 Hz) in the resonance at $\sim$ δ125.0 ppm. This resonance must be due to C5. Distinguishing between the resonances due to carbon atoms 4 and 6 is a difficult task because the coupling constants involved ($^{2}J_{CH}$ and $^{4}J_{CH}$) are of a similar magnitude ($\sim$ 1 Hz). In 7-deuteriotriazolopyridine the $^{2}J_{CH}$ coupling of the resonance due to carbon 6 would be missing, but also the $^{4}J_{CH}$ coupling of the resonance due to carbon 4 would also be missing. Thus coupling constants cannot be used to distinguish between these two resonances. Selective decoupling experiments failed. The only solution was to synthesise either 4-, or 6-substituted triazolopyridines.

Early attempts to synthesise 5-methyltriazolopyridine from 4-methylpyridine-2-carboxaldehyde[180] failed. It was thought that a substituent at position 5 would enable us to assign the resonance at either position 4 or 6, as mentioned, the coupling constants cannot be used to distinguish between the resonances.

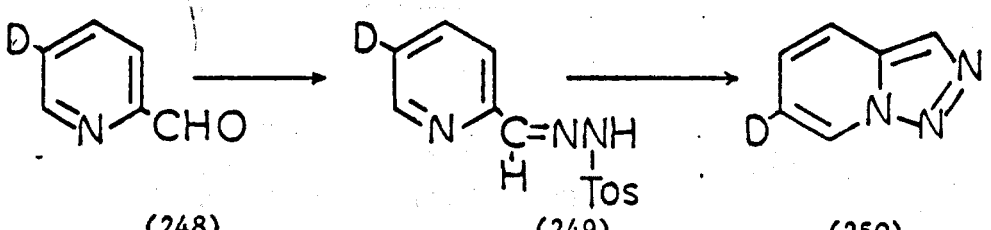
Mr. J. Young of Croda Synthetic Chemicals supplied a sample of 8-oxo-5,6,7,8-tetrahydroquinoline (245). This readily reacted with p-toluenesulphonylhydrazide to form the hydrazone (246). It can be seen that cyclisation of this hydrazone would give a 3,4-disubstituted triazolopyridine (247) which might be used to complete the assignment for carbon atom 4.



(245) (246) (247)

However heating the hydrazone (246) in morpholine did not give enough product for any characterisation or N.M.R. studies to be undertaken.

The only certain method of assigning the resonances due to C4 and C6 is to prepare the corresponding deuterio derivative. Attempts at preparing 5-deuteriopyridine-2-carboxaldehyde (248) are currently under way at these laboratories. The reaction of this carboxaldehyde with p-toluenesulphonylhydrazide followed by heating the hydrazone (249) in morpholine would give 6-deuteriotriazolopyridine (250).

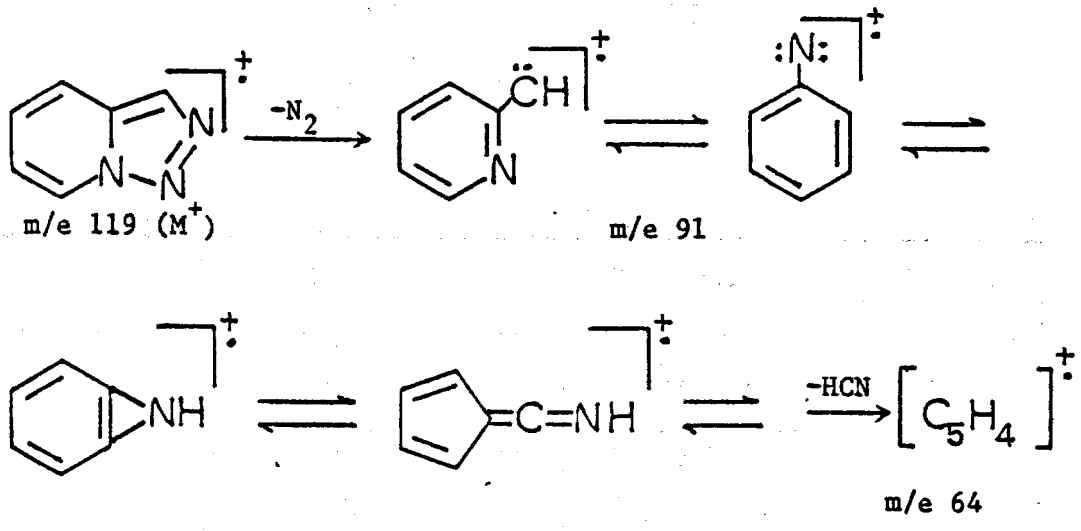


(248) (249) (250)

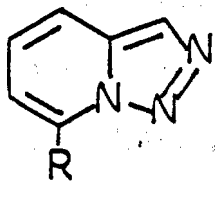
Mass Spectra

The mass spectrum of triazolo[1,5-a]pyridine (1) has been reported[29]. Apart from a strong molecular ion, the principal feature is a peak at 91 m.u. due to a C_6H_5N radical ion. This ion, or inter-converting ions, which is obtained from many other compounds, hetero-

cyclic and non-heterocyclic, has been studied by the technique of collision induced decomposition (CID)[181].



Several accurate mass spectra of the triazolopyridin-7-yl methanols were obtained from P.C.M.U. Harwell, and their fragmentation pathways observed in more detail. The following compounds were investigated



(126g), R = $Ph_2C(OH)$

(126a), R = $\underline{n}$-$C_7H_{13}CH(OH)$

(126c), R = 4-$MeOC_6H_4CH(OH)$

(126d), R = 4-$NO_2C_6H_4CH(OH)$

(155), R = 4-$MeOC_6H_4CH(OH)CH_2$

(126f), R = $(C_6H_{10})OH$

In most cases, the most frequent fragmentation pattern was that due to loss of molecular nitrogen from the molecular ion in a manner similar to the parent compound, giving ions of the general structure

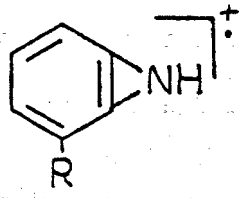
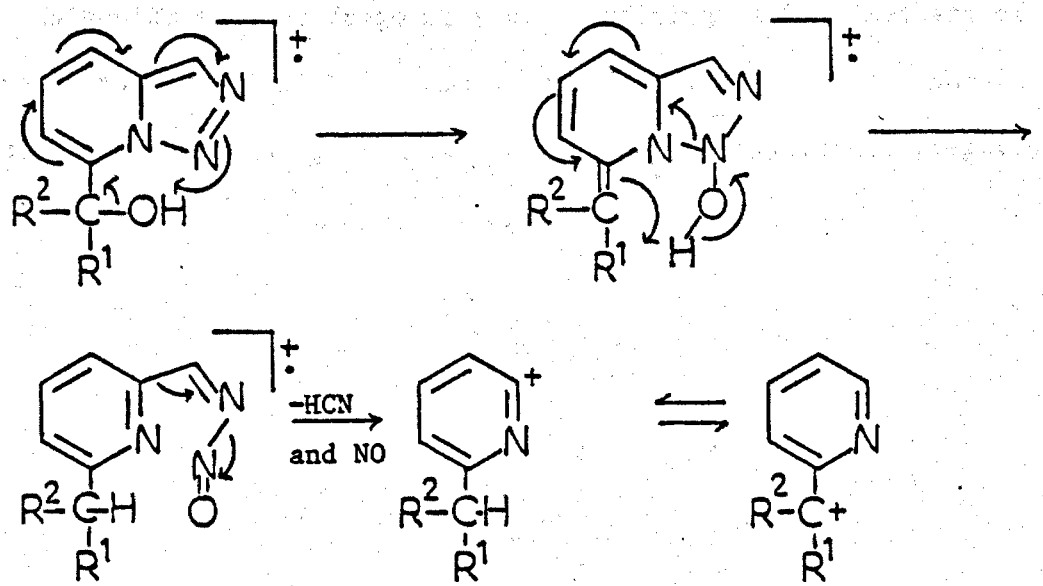
(251 a-f)  etc.

Table 4.4

Compound	R	$M^+ - N_2$, m/e	% Relative intensity
(a)	$Ph_2C(OH)$	$C_{19}H_{15}NO$, 273	37
(b)	$n\text{-}C_7H_{13}CH(OH)$	$C_{14}H_{21}NO$, 219	6
(c)	$4\text{-}MeOC_6H_4CH(OH)$	$C_{14}H_{13}NO_2$, 227	4
(d)	$4\text{-}NO_2MeOC_6H_4CH(OH)$	$C_{13}H_{10}N_2O_3$, 242	3
(e)	$4\text{-}MeOC_6H_4CH(OH)CH_2$	$C_{15}H_{15}NO_2$, 241	5
(f)	$(C_6H_{10})OH$	$C_{12}H_{15}NO$, 189	6

Fragmentation of the side chain then began with an initial loss of 17 m.u. (-OH) from the ions (251). An alternative fragmentation pathway observed in compounds (126c), (126d), (126f) and (126g) involved the loss of a CHN_2O fragment. In some cases, notably compounds (126c), (126d) and (126f) this is the major pathway. One possible explanation is the following rearrangement,



(252) (253)

Rearrangement of the molecular ions leads to a species (252). Loss of HCN and NO gives a carbonium ion (253).

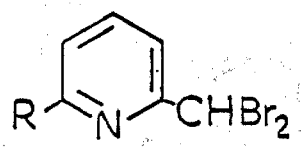
Table 4.5 shows the relative intensities of these ions.

Comp.	$M^+ - CHN_2O$, m/e	Rel. int. %
(126c)	$C_{13}H_{12}NO$, 198	74
(126d)	$C_{12}H_9N_2O_2$, 213	38
(126g)	$C_{18}H_{14}NO$, 244	3
(126f)	$C_{11}H_{14}NO$, 160	12

Table 4.4

These results are rather surprising, because for compounds (126f) and (126g) loss of HCN and NO would give tertiary carbonium ions which would be more stable than the secondary carbonium ions formed by compounds (126c) and (126d). Thus for compounds (126f) and (126g) this pathway would seem the more favourable, although it can be seen as only a minor pathway. Compound (126d) has an electron withdrawing nitro group on the phenyl ring, this would be expected to further destabilise the secondary carbonium ion, whilst the methoxy group on compound (126c) would further stabilise the carbonium ion.

Molecular ions or fragment ions containing various numbers of bromine atoms give rise to isotope patterns. These patterns should be visible in the mass spectra of the dibromomethylpyridines prepared.



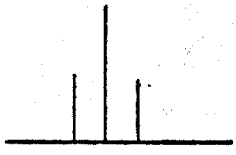
(147c), R = $HC(OH)4\text{-}MeOC_6H_4$

(147g), R = $C(OH)Ph_2$

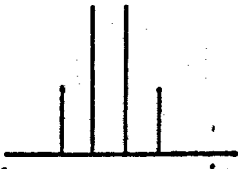
(156), R = $CH_2CH(OH)4\text{-}MeOC_6H_4$

(134), R = Br

For the dibromomethylpyridines (147c and g, 156), containing two bromine atoms the following pattern should be observed

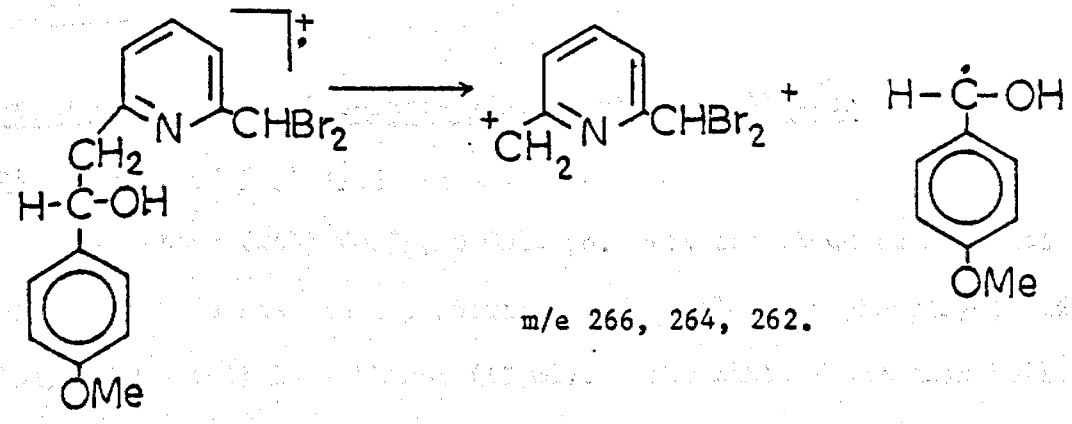


For compound (134) which contains three bromine atoms the expected pattern would be



All the peaks are spaced two mass units apart.

For compound (147c) no molecular ion is visible and nowhere in the spectrum is the expected isotope pattern observed. For compound (147g), the ion due to $[M^+ - 17(OH)]$ shows the expected pattern with peaks at 413, 415 and 417 m.u. No molecular ion is observed. For compound (156), the ion due to $[M^+ - C_8H_3O_2(137)]$ shows the expected pattern with peaks at 262, 264 and 266 M.U. This ion is probably due to the following fragmentation.



m/e 266, 264, 262.

Compound (134), which contains three bromine atoms, gives no molecular ion. 4-dibromomethylpyrimidine (238) gives a strong molecular ion (M^+ 223) which exhibits the expected isotopic pattern.

Experimental

Reaction of 8-oxo-5,6,7,8-tetrahydroquinoline (245) with p-toluenesulphonylhydrazide

The ketone (245) (0.5g, 0.0034 mol) was dissolved in methanol (5 ml). To this was added a solution of p-toluenesulphonylhydrazide (0.63g, 0.0034 mol) in methanol (15 ml). The mixture was then boiled gently under reflux and cooled in an ice bath. Pink crystals were deposited, these were filtered and washed with a small quantity of cold methanol. The yield of the hydrazone was 76% (0.81g).

M.pt. 173-174°C (methanol)

Analysis: Found: C, 60.30%; H, 5.18%; N, 13.25%

$C_{16}H_{17}N_3O_2S$ requires: C, 60.44%; H, 5.43%; N, 13.33%

Attempted cyclisation of the hydrazone (246)

The tosylhydrazone (0.7g) (246) was dissolved in morpholine (40 ml) and heated on a water bath at 90-100°C for 90 minutes. The excess morpholine was then removed under reduced pressure and the residue treated with ether. A yellow solid was deposited. This was filtered. The filtrate was evaporated to yield a yellow oil (0.4g). T.L.C. indicated the presence of 3 products (eluant ethylacetate-toluene 1:1). P.L.C. using ethylacetate-toluene (2:3) as eluant gave 3 bands. The first band (R_f 0.2) was shown by N.M.R. spectroscopy to be unreacted hydrazone (246) (0.1g), the second band (R_f 0.33) was shown by N.M.R. spectroscopy to be possibly the product (247) (50 mg). However further purification was not possible. The final band (R_f 0.4) gave unidentifiable oils.

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