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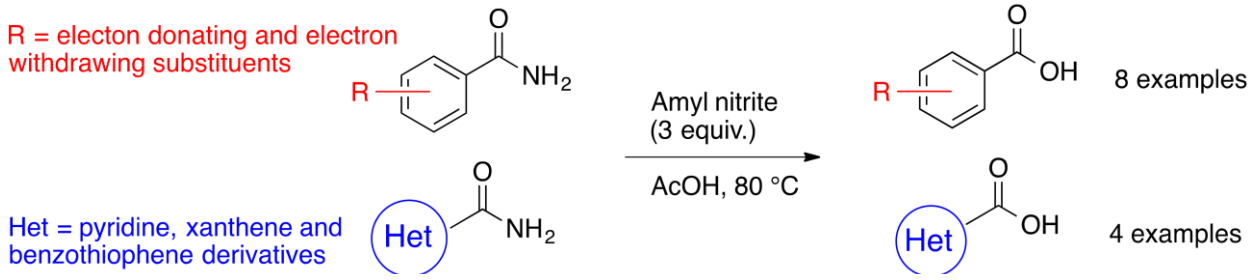

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Amyl nitrite-mediated conversion of aromatic and heteroaromatic primary amides to carboxylic acids

Garrett T. Potter,[a] Gordon C. Jayson,[b] Gavin J. Miller[c] and John M. Gardiner[a*]

[a] *Manchester Instutute of Biotechnology, School of Chemistry, Faculty of EPS, The University of Manchester 131 Princess Street, Manchester M1 7DN, UK.*
[b] *Institute of Cancer Sciences,, The University of Manchester, Wilmslow Road, Manchester M20 4BX, UK.*
[c] *School of Chemistry, Faculty of EPS, The University of Manchester, Oxford Road, Manchester M13 9PL, UK.*

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ABSTRACT

A series of aromatic and heteroaromatic primary amides can be converted directly to carboxylic acids by heating with amyl nitrite in acetic acid. Most conversions proceeded in reasonable to excellent yield on a range of substrates containing various other functional groups. This reagent system is thus applicable for direct hydrolysis of a range of different types of primary carboxamides. The reaction with a phenolic aromatic substrate afforded two alternative nitration products as the major outcomes, evidencing alternative reaction pathways resulting from the free phenolic OH.

1. Introduction

The transformation of primary amides into carboxylic acids is frequently required in organic synthesis. Classical approaches necessitate strongly acidic or alkaline conditions. Due to the forcing nature of these conditions and limitations on functional group compatibility, there is an ongoing interest in developing alternative reagents for primary amide hydrolysis that are compatible with a wider range of other functionalities. Biocatalytic amide hydrolysis is widely employed, though synthetic examples for primary amides are few.[1a-f]

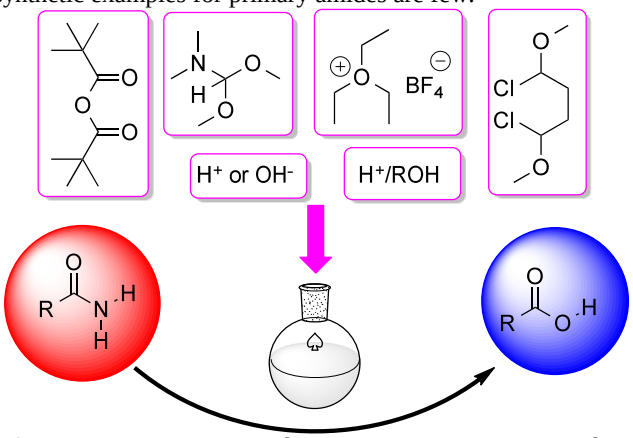
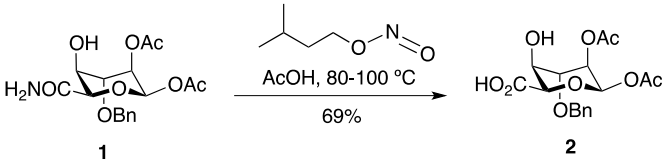


Figure 1. Reagents used to convert primary amides to carboxylic acids in one step or via isolated amide-derived intermedates.[2-5]

Though there have been advances in *ester* hydrolysis,[1d] Figure 1 summarizes a range of reagents previously employed to effect direct primary amide *hydrolysis*.[2-5] Several of these methods also involve multiple steps, via conversions through intermediates, reducing the overall efficiency. For example conversion to an acyl pyrrole[5a] which can then undergo methanolysis, conversion to a bis-carbamate enabling subsequent mild basic hydrolysis to the carboxylate,[5b] conversion to an *N*-acyl phthalimide with succinic anhydride and subsequent hydrolysis.[5c,d] As part of a program to develop a scalable synthesis of L-iduronic acid-containing carbohydrates,[6] we required mild reaction conditions for the transformation of L-iduronamide **1** into L-iduronic acid **2** (Scheme 1). Of particular interest was the potential use of nitrosyl type reagents.[7] Amyl nitrite (isopentyl nitrite) is a mild, non-toxic reagent, which we found to be effective for the conversion of primary amide **1** into carboxylic acid **2** in good yield.. This reaction could be scaled to produce >50 g batches of the desired acid **2** in good yields and was tolerant of acetal, acyl and benzylic ether protecting groups.



1 2

Scheme 1. Conversion of L-iduronamide **1** into acid **2**.[6]

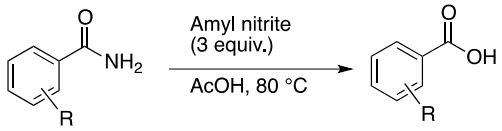
*Corresponding author. Tel +44 (0)161 306 4530; e-mail: gardiner@manchester.ac.uk

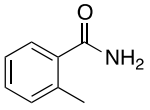
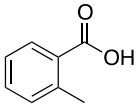
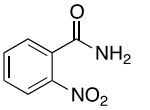
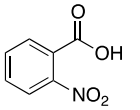
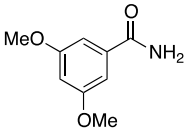
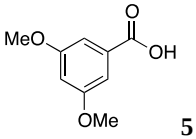
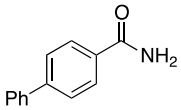
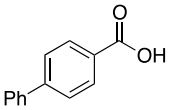
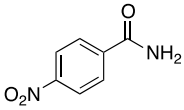
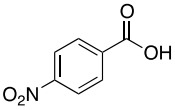
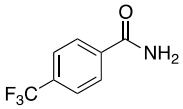
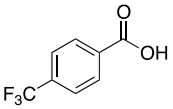
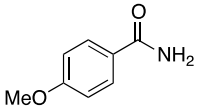
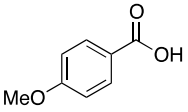
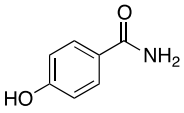
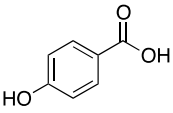
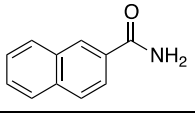
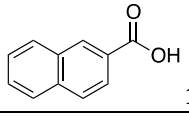
This was also found to be applicable to the analogous glucuronamide providing a route to glucuronic acids, so we sought to evaluate the scope of this reagent for the conversion of non-carbohydrate primary amides to carboxylic acids. We report herein the compatibility of this reagent system for the hydrolysis of a range of aryl (Table 1) and heteroaryl primary amides (Table 2).

2. Results and Discussion

A diversity of aromatic and heteroaromatic substrates were considered for evalution which encompassed a range of different electron withdrawing and donating groups, different regiochemistry of substituents and fused aryl and heteroaryl variants.

Table 1
Conversion of aromatic primary amides to carboxylic acids



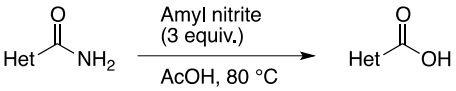
Entry	Aromatic amide	Carboxylic acid	% Yield[a]
1		 **3**	50[b]
2		 **4**	31[c]
3		 **5**	33[d]
4		 **6**	94[d]
5		 **7**	57[e]
6		 **8**	86[d]
7		 **9**	94[b]
8		 **10**	13[f]
9		 **11**	90[f]

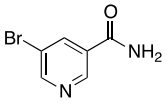
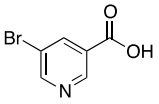
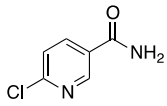
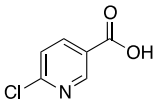
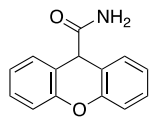
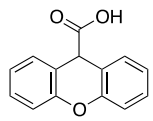
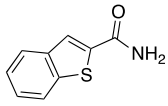
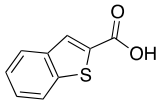
[a] Isolated yield.
[b-f] Reaction time (h): [b]=12, [c]=13, [d]=24, [e]=6, [f]=21

Although the amyl nitrite-mediated conversion proved applicable to all primary amides tested, there were significant differences in yields obtained, and in one case two major alternative side-products/reactions were evident, accounting for the low isolated yield of the anticipated carboxylic acid product.

Steric and electronic effects may influence some of these differences. Direct comparison of *p*-nitro benzamide (**7**, isolated in 57% yield) against *o*-nitro benzamide (**2**, isolated in 31% yield) could be accounted for by steric influences. In general, *p*-substituted benzamides (**6**, **8**, **9** and **11**) were good substrates (all were isolated in >85% yield) whilst the *o*-Me substituted (**3**, 50% yield) and doubly *m*-OMe substituted amides (**5**, 33% yield), were significantly poorer substrates. However, proposing an acylium intermediate for this type of reaction,[6] is not consistent with electronic effects, since a *p*-trifluoromethyl substrate was also converted in high yield.

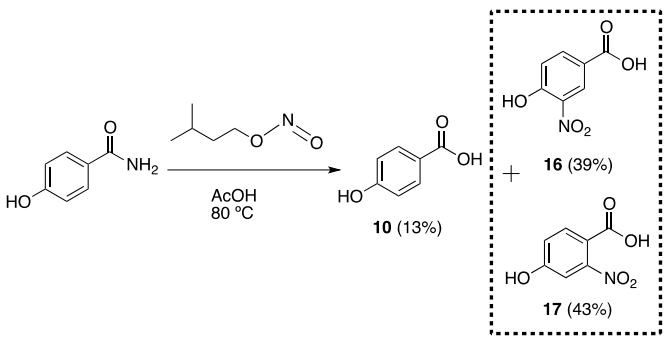
Table 2
Conversion of heteroaromatic primary amides to carboxylic acids



Entry	Heterocyclic amide	Heterocyclic carboxylic acid		% Yield[a]
1			**12**	98[b]
2			**13**	53[c]
3			**14**	30[b]
4			**15**	47[b]

[a] Isolated yield. [b-c] Reaction time (h): [b]=24, [c]=6

For the selected series of hetereoaromatic substrates covering pyridine, xanthene and benzothiophene examples (Table 2, entries 2-4), the yields were generally modest (compounds **13**, **14** and **15** all formed in >30%). However, a 3-substituted pyridine (entry 1, Table 2) proved a very effective substrate (98% isolated yield of **12**).



Scheme 2. Formation of nitrated side-products **16** and **17**.

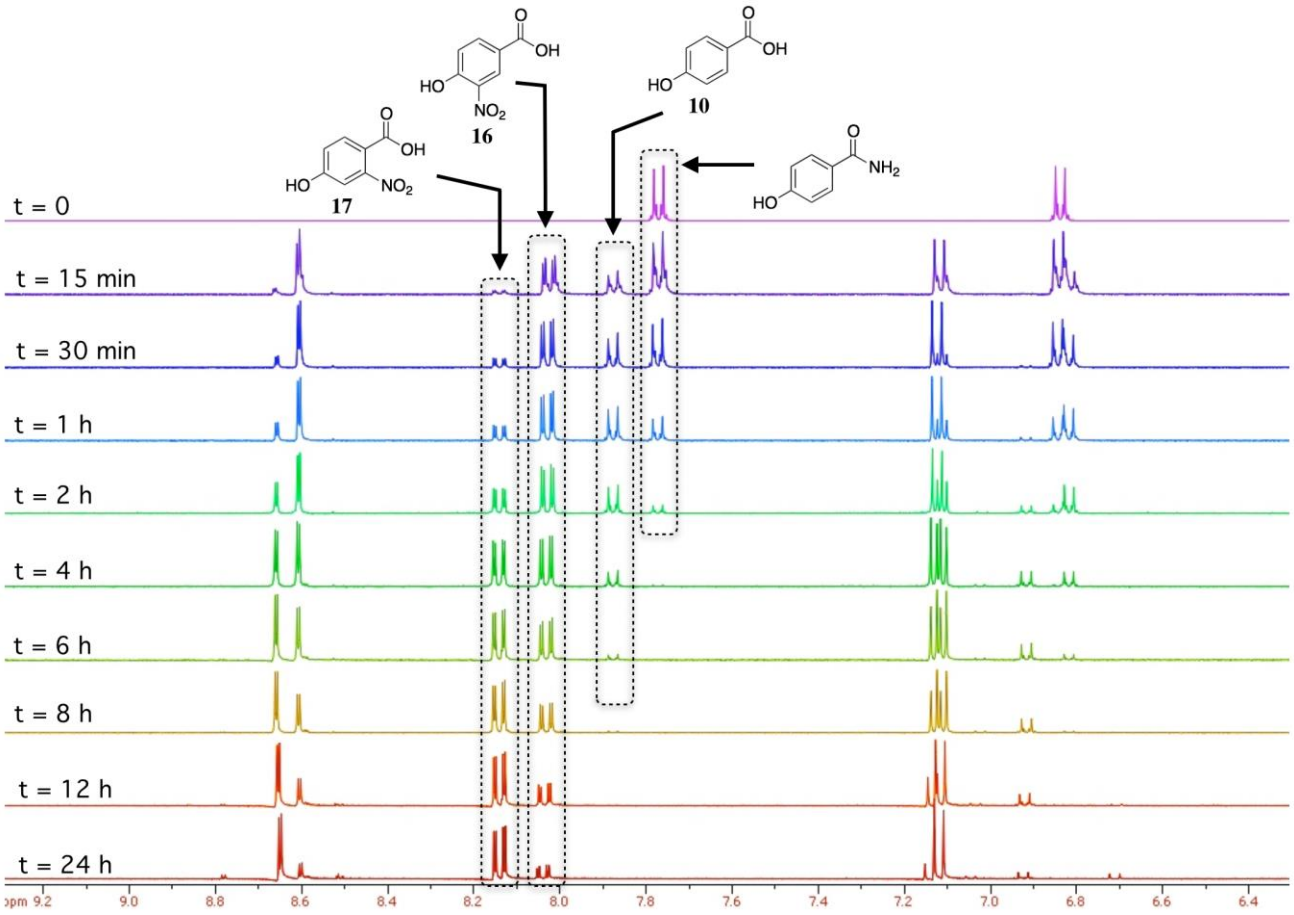


Figure 2. ^{1}H NMR (400 MHz) monitoring of the reaction to form **10**, **16** and **17**.

Of particular note was the low isolated yield (13%) of *p*-OH substituted benzoic acid **10**. This was dramatically different to the outcome with related *p*-anisole derivative where the expected hydrolysis product **9** was obtained in 94% yield. Further investigation of this reaction established that two other by-products accounted for the low isolated yield (Scheme 2).

These were identified as *m*- and *o*-nitro substituted benzoic acids, **16** and **17** respectively, each obtained in similar quantities of around 40%.[8]

^{t}BuONO has previously been used as a mild and chemoselective method to nitrate phenols, and the formation of **16** could occur *via* a similar process involving generation of a phenolic *O*-nitroso intermediate and subsequent *C*-nitration (suggested to occur through phenoxide radical/NO_2 generation).[9] This prior work reported that anisole substrates were resistant to aromatic nitration, which is consistent with our outcome here, and thus indirectly is in support of proposing amyl nitrite forming an initial reactive intermediate with the free phenol.

Whilst this mechanism could account for the formation of **16**, we were also interested in the formation of the major by-product, **17**. We followed the progress of the reaction to track the formation of **17** using ^{1}H NMR spectroscopy (Figure 2). The results from this study demonstrated that **17** was formed as the thermodynamic product of the reaction after prolonged heating in neat AcOH (24 h) and that the kinetic product of nitration, under our conditions, was **16**.

The mechanism for the conversion of **16** to **17** is not clear. There is precedent for homoaromatic 1,2 or 1,4 migration of nitro groups (through Wheland-type intermediates),[10] which could be effected by prolonged heating in neat AcOH. However, additional experiments heating isolated **16** in AcOH showed no conversion to **17**, supporting a need for amyl nitrite and perhaps an alternative *m*-nitration mechanism. Further investigation of this nitration process is currently underway.

3. Conclusions:

We have investigated the application of a commercially available, non-toxic reagent, amyl nitrite, for a mild conversion of primary aromatic and heteroaromatic amides into carboxylic acids. Whilst yields are varied and dependent on the aryl or heteroaryl substitution, this work clearly indicates that amyl nitrite/AcOH should be considered as a viable reagent system for effecting primary amide hydrolysis, not just in carbohydrates but in a broader range of aromatic and heteroaromatic systems. We have also observed and isolated two nitration by-products using a phenolic substrate. This established phenolic *o*-nitration as the kinetic product and that this is converted on prolonged heating, dependent on the presence of amyl nitrite, to the *m*-nitrated phenol.

Acknowledgements:

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Supplementary Material

Supplementary data (representative experimental procedures, characterization data, and copies of NMR) associated with this article can be found, in the online version, at http://….

References and notes

1. (a) Faber, K. (**2011**). *Biotransformations in Organic Chemistry*, (6th edn), Springer-Verlag, Berlin, Heidleberg. (b) Pollard, D. J.; Woodley, J. M. *TRENDS in Biotechnol.* **2006**, *25*, 65-73. (c) Martínková, L.; Křen, V. *Biocat. and Biotrans.* **2002**, *20*, 73-93. (d) Bernet, N.; Thiery, A.; Maestracci, M.; Arnaud, A.; Rios, G. M.; Galzy, P. *J. Indust. Microbiol.* **1987**, *2*, 129-136. (e) Antibody catalysis: Gao, G.; Lavey, B. J.; Lo, C.-H. L.; Datta, A.; Wentworth, Jr. P.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *120*, 2211–2217. (f) Biocatalytic resolutions: Chen, P.; Gao, M.; Wang, D.-X.; Zhao, L.; Mei-Xiang Wang, X. *Chem. Commun.* **2012**, *48*, 3482–3484 and refs. therein. (g) Esterolytic conversion: Kita, Y.; Nishii, Y.; Onoue, A.; Mashima, K. *Adv. Synth. Catal.* **2013**, *355*, 3391–3395 and refs therein.
2. Anelli, P. L.; Brocchetta, M.; Palano, D.; Visigalli, M. *Tetrahedron Lett.* **1997**, *38*, 2367−2368.
3. Kiessling, A. J.; McClure, C. K. *Synth. Commun*. **1997**, *27*, 923− 937.
4. Greenlee, W. J.; Thorsett, E. D. *J. Org. Chem*. **1981**, *46*, 5351− 5353.
5. (a) Lee, S. D.; Brook, M. A.; Chan, T. H. *Tetrahedron Lett*. **1983**, *24*, 1569−1572. (b) Davidsen, S. K.; May, P. D.; Summers, J. B. *J. Org. Chem.* **1991**, *56*, 5482−5485. (c) Mathews, J. A. *J. Am. Chem. Soc*. **1898**, 20, 648–668. (d) Chemat, F. *Tetrahedron Lett*. **2002**, *43*, 5555–5557.
6. Hansen S. U.; Miller, G. J.; Baráth, M.; Broberg, K. R.; Avizienyte, E.; Jayson, G. C.; Gardiner, J. M. *J. Org. Chem.* **2012**, *77*, 7823-7843.
7. (a) Kuhne, M. E. *J. Am. Chem. Soc*. **1961**, *83*, 1492−1498. (b) Olah, G. A.; Olah, J. A. *J. Org. Chem.* **1965**, *30*, 2386−2387. (c) Woodward, R. B. *Pure Appl. Chem*. **1973**, *33*, 145−177. (d) Hurd, C. D.; Sowd, J. C. *J. Am. Chem. Soc.* **1938**, *60*, 235−237. (e) Sperber, N.; Papa, D.; Schwenk, E. *J. Am. Chem. Soc.* **1948**, *70*, 3091−3094. (f) Barton, D. H. R.; Geŕo, S. D.; Quiclet-Sire, B.; Samadi, M. *Tetrahedron: Asymmetry* **1994**, *5*, 2123−2136. (g) Adams, D. R.; Bailey, P. D.; Collier, I. D.; Heffernan, J. D.; Stokes, S. *Chem. Commun*. **1996**, *3*, 349-350.
8. **4-Hydroxybenzoic acid (10)**: 4-hydroxybenzamide (137 mg, 1.0 mmol) was dissolved in acetic acid (2.0 mL), and to this stirred solution was added amyl nitrite (0.40 mL, 3.0 mmol) under a N_2 atmosphere and heated to 80 °C for 21 hours, whereupon the reaction was deemed complete as adjudged by consumption of starting material by TLC. The solution was condensed, co-evaporated with toluene (2 x 5 mL) and then purified *via* preparatory plate TLC. Sections containing product and by-products were scraped, extracted into EtOAc and solvent removed *in vacuo*. This yielded two separate fractions. **A**: 95.8 mg of a light yellow powder which was an inseparable mixture of **10** (0.13 mmol) and **17** (0.43 mmol), as adjudged by ^{1}H NMR analysis; R_f = 0.68 (50% EtOAc in Hexane); For **10**: ^{1}H NMR (400 MHz; MeOD): δ 8.02 (d, *J* = 9.2 Hz, 2H), 6.79 (d, *J* = 9.2 Hz, 2H); **MS** *m/z* 138.0 (M^-, 100%); For **17**: ^{1}H NMR (400 MHz; MeOD): δ 8.58 (s, 1H), 8.09 (d, *J* = 7.1 Hz, 1H), 7.09 (d, *J* = 7.1 Hz, 1H); **MS** *m/z* 182.0 (M^-, 100%). **B**: 71.0 mg of a yellow powder **16** (0.39 mmol); R_f = 0.24 (50% EtOAc in Hexane); ^{1}H NMR (400 MHz; MeOD) δ 8.66 (d, *J* = 2.2 Hz, 1H), 8.12 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H); **MS** *m/z* 181.0 (M^-, 100%); **m.p.** 184-187 °C; **IR** (neat) ν_{max} 3289 (br, O-H stretch), 1662 (s, C=O stretch), 1627 (C=C), 1538 (nitro, asymmetric), 1326 (nitro, symmetric), 1258 (acyl C-O) cm^{-1}.
9. Koley, D.; Colón, O. C.; Savinov, S. N. *Org. Lett.* **2009**, *11*, 4172–4175.
10. Barrow, P.; Bullen, J. V.; Dent, A.; Murphy, T.; Ridd, J. H.; Sabe, O. *J. Chem. Soc. Chem. Commun*. **1986**, *22*, 1649-1650.