A facile and rapid preparation of hydroxamic acids by hydroxylaminolysis using DBU as base

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Graphical Abstract

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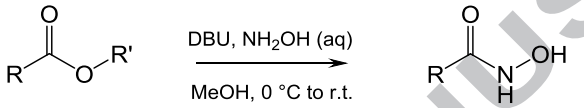

R' = Me, Et, i-Pr, Bn

18 Examples
Yields 40-80%

Pergamon

TETRAHEDRON
LETTERS

A facile and rapid preparation of hydroxamic acids by hydroxylaminolysis using DBU as base

Audrey Beillard, Yushma Bhurruth-Alcor, Claire Bouix-Peter, Karinne Bouquet, Sandrine Chambon, Laurence Clary, Craig S. Harris,* Corrine Millois, Grégoire Mouis, Gilles Ouvry, Romain Pierre, Arnaud Reitz, Loic Tomas

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Abstract— While there are many protocols for the preparation of hydroxamic acids from their corresponding carboxylic acid or carboxylic ester precursors, most use strong mineral bases that can lead to carboxylic acid impurities that can be difficult to remove using standard chromatographic techniques. This problem is exacerbated when the carbonyl group is hindered. Herein, we communicate a robust hydroxylaminolysis protocol for the preparation of hydroxamic acids in high yield and purity.

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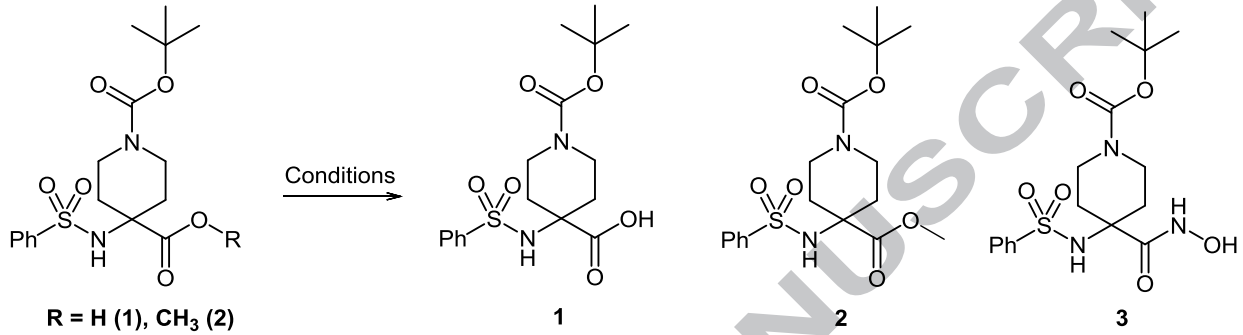
Keywords: hydroxylaminolysis, hydroxamic acid formation, DBU

During a recent program, we became interested in preparing hydroxamic acids for an undisclosed target. The hydroxamic acid group has consistently been used as a core binding group for the development of notably metalloenzyme inhibitors.[1] While there are many protocols published to prepare hydroxamic acids either from the corresponding carboxylic acid precursors in the presence of a suitable dehydrating agent and hydroxylamine or *O*-protected hydroxylamine derivatives,[2-6] or through direct hydroxylaminolysis from methyl ester substrates,[7-10] we were disappointed by the overall ineffectiveness of these processes when complex hindered carbonyl precursors (eg., **1** or **2**) were employed for library synthesis (Table 1).

Table 1. A selection of the conditions screened for the preparation of **3**.[a] Product distribution determined by LCMS.



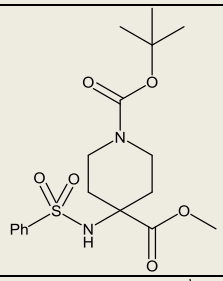
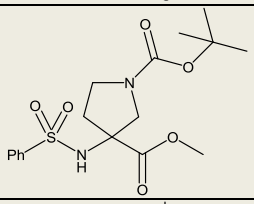
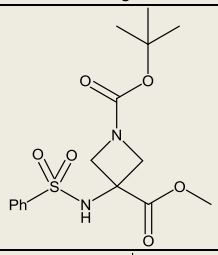
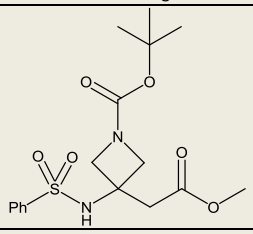
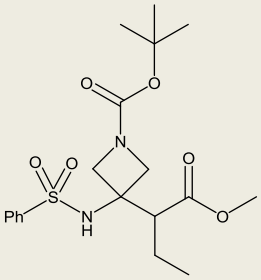
Entry	R	Conditions*	% 1[a]	% 2[a]	% 3[a]	Yield (%)
1	H	IBCF, NMM followed by $NH_2OH.HCl$, DIPEA, 0 °C – r.t., 24 h	89	-	11	-
2	H	T3P, $NH_2OH.HCl$, TEA, MeCN, 0 °C to r.t. , 24 h	95	-	4	-
3	H	Pfp-OH, EDCI, DMF followed by $NH_2OH.HCl$, DIPEA, DMF, r.t., 24 h	55	-	45	23
4	H	NBSoxy, DMAP, $NH_2OH.HCl$, DIPEA, DMF, r.t., 24 h	65	-	35	19
5	Me	7 eq $NH_2OH.HCl$, KOH, MeOH, r.t., 24 h	35	22	43	20
6	Me	7 eq $NH_2OH.HCl$, NaOMe, MeOH, r.t., 24 h	45	10	45	19
7	Me	10-50 eq NH_2OH (50% aq), MeOH, r.t., 24 h	1	99	0	-
8	Me	10 eq NH_2OH (50% aq), MeOH, 60 °C, 24 h	78	20	2	-
9	Me	20 eq NH_2OH (50% aq), KCN, THF-MeOH, r.t., 72 h	12	76	12	-
10	Me	10 eq NH_2OH (50% aq), 3 eq DBU, MeOH, r.t., 48 h	30	0	70	59
11	Me	10 eq NH_2OH (50% aq), 3 eq DBU, MeOH, 40 °C, 16 h	45	6	49	-
12	Me	10 eq NH_2OH (50% aq), 3 eq DBU, MeOH, 60 °C, 16 h	70	0	30	-

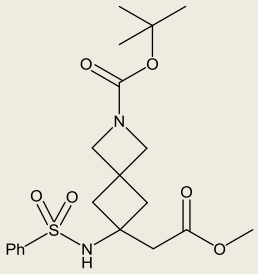
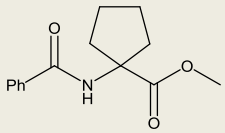
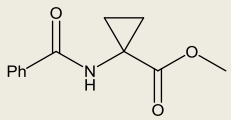
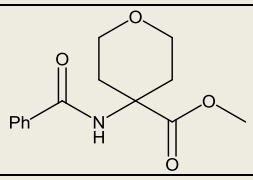
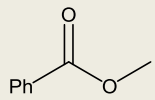
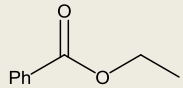
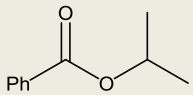
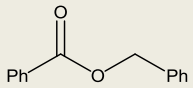
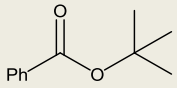
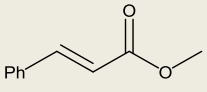
* IBCF = isobutylchloroformate; T3P = propylphosphonic anhydride; NMM = *N*-methylmorpholine; DIPEA = *N*,*N*-diisopropylethylamine; Pfp-OH = pentalfluorophenol; NBSoxy = ethyl 2-cyano-2-(4-nitrophenylsulfonyloxyimino)acetate; DMAP = N,N-dimethylaminopyridine

Table 1 shows selected results from screening several conditions to form the desired hydroxamic acid product **3** from either the carboxylic acid precursor **1** (entries 1-4) or the methyl ester precursor **2** (entries 5-12). In the case of the acid precursor **2**, only two sets of conditions (entries 3-4) afforded an acceptable conversion to **3** albeit with poor overall isolated yields. Direct hydroxylaminolysis of the methyl ester precursor (entries 5-6) using "dry hydroxylamine" afforded a reasonable conversion towards the hydroxamic acid product **3** but with an almost equal quantity of the carboxylic acid impurity **1** that was difficult to remove by chromatography. Attempts to obtain a complete reaction by using a large excess of hydroxylamine in the absence of a strong base failed at room temperature and heating the reaction mixture afforded practically only the carboxylic acid impurity **1** (entries 7 & 8). From previous experience in the team, we found that the addition of KCN as the catalyst, as disclosed by Cho and co-workers at Merck's Laboratories,[9] did dramatically increase the ratio of hydroxamic acid product over carboxylic acid impurity in the case of non-hindered esters (*eg.*, entry 4, condition C, Table 2). However, application of these conditions to the more hindered precursor **2** afforded little conversion (entry 9). Attempts to increase the conversion by heating or adding more KCN only increased the level of carboxylic acid impurity. Finally, we postulated that employment of a nucleophilic superbase[11] such as DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)[12] could be an interesting alternative to strong mineral bases such, as KOH or NaOMe, in order to reduce *in situ* saponification of the ester during the reaction. To our delight, the reaction proceeded very smoothly affording the final compound in acceptable isolated yield after chromatography (entry 10). Attempts to decrease reaction times by heating the reaction mixture only led to poorer conversions to the desired hydroxamic acid product and an increase in the carboxylic acid impurity (entries 11, 12).

With this knowledge in hand, we decided to retain DBU as the base and evaluate the scope of the reaction conditions with other ester substrates. In certain cases, these conditions were compared to conditions previously used by the team during this research programme to determine what influence they had on product distribution with respect to structural variation (Table 2).

Table 2. A selection of comparative results using the DBU process. Conditions A: NH_2OH (50% aq) (10 eq), DBU (3 eq), MeOH (4 vol), r.t.; conditions B: NH_2OH (50% aq) (10 eq), MeOH (4 vol), r.t.; conditions C: NH_2OH (50% aq) (20 eq), KCN (5 mol%), MeOH-THF (1:1, 10 vol), r.t.

Entry	Substrate	Conditions	Time	Carboxylic acid (%)[a]	Ester (%)[a]	Hydroxamic acid (%)[a]	Isolated yield (%)[b]
1		A	48 h	30	0	70	59
2		A	12 h	5	0	95	76
3		A	2 h	2	0	98	77
4		A	20 min.	1	0	99	82
		B	24 h	3	82	15	-
		C	24 h	4	0	96	78
5		A	72 h	32	0	68	47
		C	96 h	4	95	1	-

6		A	30 min	0	1	99	82
7		A	24 h	10	0	90	75
		C	96 h	15	75	12	-
8		A	1 h	1	0	99	81
9		A	32 h	24	0	76	61
10		A	5 min	3	0	97	76
		B	1 h	5	0	95	-
11		A	15 min	5	0	95	-
		B	3 h	9	0	91	-
12		A	6 h	2	0	98	-
		B	6 h	4	83	13	-
13		A	3 h	5	0	95	-
14		A	5 h	5	95	-	-
15		A	1 h	1	0	99	91

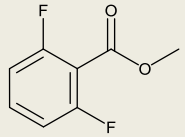
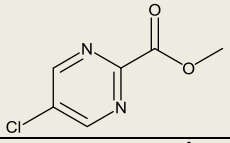
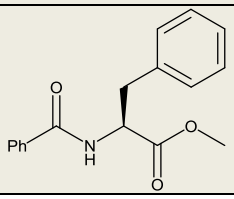
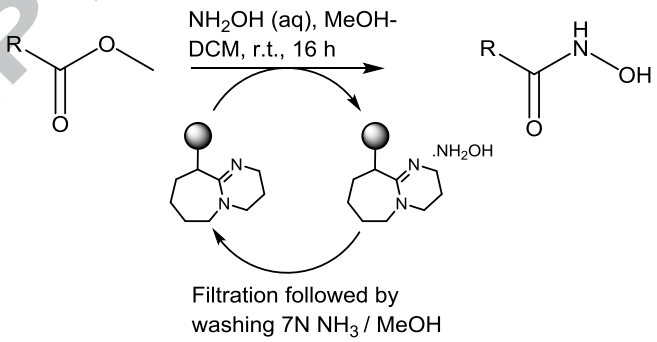
16		A	1 h	10	0	90	54
17		A	1 h	4	0	96	64
18		A	1 h	3	0	97	86 *(e.r. = >99:1)*

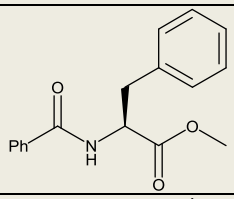
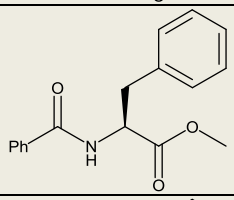
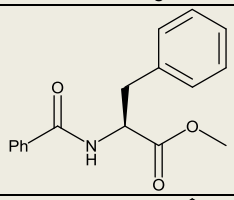
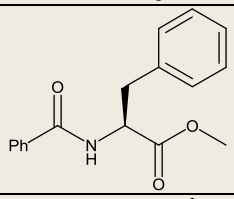
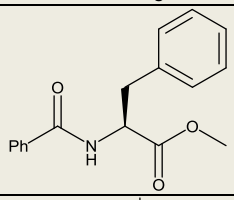
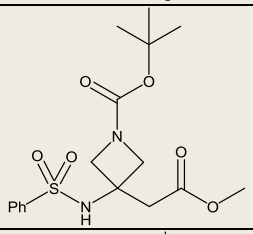
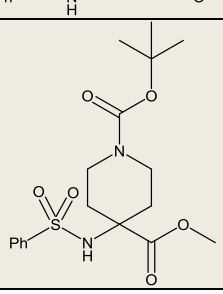
Table 2 shows the results of a small library of hydroxamic acids prepared using this process in order to give the reader an idea of substrate scope. It is clear that steric hindrance affects the ratio hydroxamic acid to carboxylic acid whereby yields of hydroxamic acid product increased on reducing the ring size and reaction times reduced dramatically (entries 1-3 & 7-8). Decreasing further steric hindrance by adding an additional methylene group between the core and the ester group (entry 3 vs 4 & 6) decreased reactions times down from 4 hours to a remarkable 30 minutes with a ratio of hydroxamic acid / carboxylic acid of >99:1. We also compared the conditions head-to-head with the KCN catalyzed process (entry 4 & entry 5) and found not only was the reaction much faster (20 min. compared to 24 h) but there was a cleaner crude reaction profile with <1% of carboxylic acid impurity. As a control reaction, we carried out the reaction in the absence of a catalyst and observed very little conversion (entry 4, condition B). Increased hindrance around the methyl ester moiety led to more carboxylic acid (entry 4 v entry 5). Next we turned our attention to more reactive benzoate esters (entries 10-14). In general, the effect of adding DBU became dominant where the carbonyl was the most sterically congested. In all cases where DBU was present, the reaction was much faster than in the absence of DBU (entries 10-13) and even *i*-Pr esters were efficiently converted to hydroxamic acids in high purity where the control reaction failed (entry 12). As expected, no reaction took place using *tert*-butyl esters (entry 14) as substrates. These conditions were also efficient in the presence of other electrophilic functionality (entries 15-17) whereby unsaturated esters and heteroaromatic substrates gave excellent conversions to hydroxamic acid products. Finally, we also show that no erosion of the chiral center was observed when using *L*-phenyl alanine methyl ester as a model substrate under these conditions (entry 18).



Scheme 1. Application of PS-DBU for the formation of hydroxamic acids

Finally, we successfully evaluated the effects of employing immobilized DBU (PS-DBU) in this process with the aim of developing a process that would afford hydroxamic acid products without the need for chromatography. As expected, the reaction rates were greatly compromised whereby complete conversion to hydroxamic acid products required 16 h compared to 1 h using free DBU using unhindered esters as the substrates (Table 3, entry 1 v 2). Base washing with methanolic ammonia was also necessary to regenerate the polymer supported DBU free base for successive use without comprising reaction rates (entry 3 v 4 and 5). Unfortunately, the conditions were impractical when hindered ester substrates were employed (*eg.*, entry 6 v 7) that we believe is due to the poor swelling of the polystyrene support in the polar medium.

Table 3. Application of PS-DBU for this hydroxylaminolysis process. N/A = not analysed

Entry	Substrate	Conditions	Time	Conversion (%)	Enantiomeric ratio
1		DBU (3 eq), 50% NH_2OH (aq) (10 eq), MeOH (4 vol)	1 h	97	99:1
2		Cycle 1: PS-DBU, 50% NH_2OH (aq) (10 eq), DCM-MeOH (1:1, 4 vol)	16 h	95	99:1
3		Cycle 2: Un-treated PS-DBU, 50% NH_2OH (aq) (10 eq), DCM-MeOH (1:1, 4 vol)	16 h	65	N/A
4		Cycle 2: Pre-treatment of PS-DBU (NH_3/MeOH 7N) , 50% NH_2OH (aq) (10 eq), DCM-MeOH (1:1, 4 vol)	16 h	96	99:1
5		After 5 cycles of pre-treatment of PS-DBU (NH_3/MeOH 7N) , 50% NH_2OH (aq) (10 eq), DCM-MeOH (1:1, 4 vol)	16 h	93	99:1
6		PS-DBU, 50% NH_2OH (aq) (10 eq), DCM-MeOH (1:1, 4 vol)	16 h	99	-
7		PS-DBU, 50% NH_2OH (aq) (10 eq), DCM-MeOH (1:1, 4 vol)	16 h	8	-

In conclusion, we have discovered a very efficient and robust hydroxylaminolysis process, using both DBU in solution and immobilized on a solid support, to prepare libraries of hydroxamic acids and demonstrated its potential on a wide range of complex ester substrates with good to excellent results. Work is ongoing to further optimise the reaction conditions.[14]

Acknowledgements
The authors would like to acknowledge Spirochem AG for supplying a selection of the starting materials to prepare the substrates cited in the tables.

Supplementary data

Full experimental procedures and supporting LCMS, ^{1}H- and ^{13}C-NMR characterisation data are available for a selection of compounds described in this letter is available at no extra charge *via* the on-line version.

References and notes

1. a) Muri, E. M. F.; Nieto, M.J.; Sindelar, R. D.; Williamson, J. S. *Curr. Med. Chem.* **2002**, *9*, 1631-1653; b) Kontogiorgis, C. A.; Papaioannou, P.; Hadjipavlou-Litina, D. J. *Curr. Med. Chem.* **2005**, *12*, 339-355.
2. Lombart, H.-G.; Feyfant, E.; Joseph-McCarthy, D.; Huang, A.; Lovering, F.; Sun, Lin H.; Zhu, Y.; Zeng, C.; Zhang, Y.; Levin, J. *Bioorg. Med. Chem. Lett.* **2007** *17*, 4333-4337.
3. Vasanthaa, B.; Hemantha, H. P. ; Sureshbabu, V. V. *Synthesis* **2010**, 2990-2996.
4. Brookings, D. C.; Davis, J. M.; Langham, B. J. *PCT Int. Appl.*, 2004000846.
5. Krchnak, V. *Mini-Rev. Med. Chem.* **2006**, *6*, 27-36.
6. Kishore T.; Srinivasa R. M.; Dharm D., Bhubaneswar M. *J. Org. Chem.* **2014**, *79*, 3765–3775 and referenced cited therein.
7. Duan, J.; King, B. W.; Decicco, C.; Maduskuie, T. P.; Voss, M. E; Gilmore, J. L.; King, B. W.; Harris, C.; Maduskuie, T.; Mercer, S. E.; Liu, R-Q.; Covington, M. B.; Qian, M.; Ribadeneria, M. D.; Vaddi, K.; Trzaskos, J. M.; Newton, R. C.; Decicco, C. P.; Duan, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2699-2704.
8. Levin, J. I.; Chen, J. M.; Cole, D. C.; Du, M. T.; Laakso, L. M. **2001**, *US 622531*.
9. Ho, C.Y.; Strobel, E.; Ralbovsky, J.; Galemmo, R. A. Jr. *J. Org. Chem*. **2005**, *70*, 4873–4875.
10. Gediya, L.K.; Chopra, P.; Purushottamachar, P.; Maheshwari, N.; Njar, V.C. *J. Med. Chem.* **2005**, *48*, 5047-5051.
11. a) Ishikawa, T.; Harwood L. M. *Synlett* **2013**, *24*, 2507-2509; b) Ishikawa, T. *Superbases for Organic Chemistry* **2009**, John Wiley & Sons; c) Leito, I.; Koppel, I. A.; Koppel, I.; Kaupmees, K.; Tshepelevitsh, S.; Saame, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 9262 –9265.
12. For recent references showing DBU as a nucleophilic catalyst, please consult: a) Shieh,W-C; Dell, S; Repič, O. *J. Org. Chem.* **2002**, *67*, 2188–2191; b) Horn, H. W.; Jones G. O.; Wei, D. S.; Fukushima, K.; Lecuyer, J. M.; Coady, Daniel J.; Hedrick, J. L.; Rice, J. E. *J. Phys. Chem. A* **2012,** *116*, 12389–12398.
13. Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev.* **2003**, *103*, 3401–3430.
14. Typical procedure: To a stirred solution of the methyl ester (1 eq) in MeOH (4 volumes), was added DBU (3 eq) and 50% v/v aqueous solution NH_2OH (aq) (10 eq) at 0 °C to room temperature. The reaction mixture was stirred for 20 minutes to 48 h (depending on the steric hindrance around the ester) and then purified directly by mass-triggered preparative LCMS Waters X-Terra reverse-phase column (C-18, 5 microns silica, 19 mm diameter, 100 mm length, flow rate of 40 ml / minute) and decreasingly polar mixtures of water (containing 0.1% formic acid) and acetonitrile as eluent. The fractions containing the desired compound were evaporated to dryness to afford the final compounds usually as a crystalline solid.

- An efficient process to prepare hindered hydroxamic acids from esters is proposed.
- Quickest reaction times and best yields were observed when using DBU as the base.
- A chromatography-free process using recyclable PS-DBU is also disclosed.
- No epimerisation occured when using L-phenylalanine methyl ester as the substrate.