Efficient Conversions of Carboxylic Acids into *O*-Alkyl, *N*-Alkyl and *O,N*-Dialkylhydroxamic Acids

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Abstract: Carboxylic acids were conveniently converted into unsubstituted, *N*-alkyl-, *O*-alkyl-, and *O,N*-dialkylhydroxamic acids via acylbenzotriazole intermediates. The ready availability of the reagents, mild conditions, and easy handling of the intermediates are advantageous.

Key words: hydroxamic acid, Weinreb amide, carboxylic acids, regioselectivity, nucleophilic

Hydroxamic acids are important biologically active compounds with a broad spectrum of applications. They possess matrix metalloproteinase inhibition properties[1] and antibiotic activity.[2] The therapeutic potential of hydroxamic acids and the synthesis of hydroxamic acid based siderophores have been summarized.[3] Preparative methods for hydroxamic acids and their applications have been investigated for 150 years.[4]

As starting materials, hydroxamic acids provide access to many compounds of biological and synthetic interest, such as α,α-difluoro-β-hydroxy ketones,[5] 1,2-benzisoxazolin-3-ones,[6] protected amino aldehydes,[7] α-amino and α-hydroxy acids,[8] β-amino acids,[9] α-fluoroalkyl ketones,[10] and 1-benzyloxyphenyl-3-phenylacetones.[11]

Recent reports on the synthesis of hydroxamic acids include preparations from (i) esters with *O*-benzylhydroxylamine in the presence of trimethylaluminum in refluxing toluene[12] or when prone to enolization, with *N*-(*tert*-butoxycarbonyl)-*O*-(2-pyridylsulfonyl)hydroxylamine;[13] (ii) hydroxamoyl chlorides with olefins in the presence of base;[14] (iii) *N*-acyloxazolidinones[15a] and 2-acyloxypyridines[15b] with *N*- and/or *O*-substituted hydroxylamines; and (iv) from mixed anhydrides in neutral conditions.[16]

Weinreb amides are hydroxamic acid derivatives which play a special role as building blocks for the synthesis of ketones and aldehydes[17] including α-amino derivatives.[18] Synthetic approaches to Weinreb amides include reactions of *O,N*-dimethylhydroxylamine with (i) carboxylic acids in the presence of a) [bis(2-methoxyethyl)amino]sulfur trifluoride (Deoxo-Fluor reagent);[19] b) tributylphosphine, triethylamine and (2-pyridine *N*-oxide)disulfide;[20] c) pivaloyl chloride via an intermediate mixed anhydride;[21] d) 2-chloro-4,6-dimethoxy-1,3,5-triazine and *N*-methylmorpholine;[22] e) tetrafluoroborate or hexafluorophosphate thiouronium salts derived from 2-mercaptopyridone *N*-oxide and tetramethylurea or *N,N'*-dimethylpropyleneurea;[23] and f) after conversion to mixed anhydrides[24] or esters;[11] (ii) lactones or esters in the presence of dimethylaluminum chloride;[25] (iii) esters in the presence of isopropyl magnesium chloride,[26a] and (iv) acylbenzotriazoles.[26b]

The conversion of carboxylic acids into amides, esters and derivatives of hydroxamic acid in the presence of carbonyl diimidazole (CDI) described by Staab et al.[27] is a general method which has found wide application. The use of CDI recently has been reported for the synthesis of hydroxamic acids[28] and Weinreb amides.[29]

Acylbenzotriazoles are neutral acylating agents,[30] successfully used for the preparation of primary, secondary and tertiary amides[30a] and cinnamoyl hydrazides,[31] formamides,[32] trifluoroacetylamides,[33] and oxamides.[34] Recently, various acylbenzotriazoles were used for the preparation of Weinreb amides.[26b] We now report further investigations on the use of acylbenzotriazoles for the preparation of diverse *O*-alkyl, *N*-alkyl and *O,N*-dialkyl hydroxamic acids.

The acylbenzotriazoles **2a**–**d** were conveniently prepared from carboxylic acids by reaction with 1-methanesulfonyl-1*H*-benzotriazole as reported previously.[30] Reaction of 1-benzoyl-1*H*-benzotriazole (**2a**) with hydroxylamine hydrochloride in the presence of potassium *tert*-butoxide in THF at 20 °C gave the desired hydroxamic acid **3a** in only 17% yield with benzotriazole and benzoic acid as by-products. Similar reaction with *O*-ethylhydroxylamine gave the corresponding *O*-ethylhydroxamic acid **3b** (isolated yield 24%) along with benzotriazole, *O*-unsubstituted benzoylhydroxamic acid and benzoic acid. However, changing the base to triethylamine improved the yield of *O*-ethylbenzoylhydroxamic acid up to 61%, with benzotriazole as the only by-product, which was easily removed by washing with aqueous sodium carbonate to give *O*-ethyl benzoylhydroxamic acid (**3b**) as pure compound. The yield of benzoylhydroxamic acid (**3a**) was 91% with the use of triethylamine; the purification required column chromatography. *O*-Benzylhydroxylamine gave *O*-benzylbenzoylhydroxamic acid (**3c**) in 87% yield after washing the reaction mixture with aqueous sodium carbonate. We extended the preparation of hydroxamic acid derivatives using hydroxylamine, *O*-ethyl- and *O*-benzylhydroxylamine, *N*-methylhydroxylamine and *N,O*-

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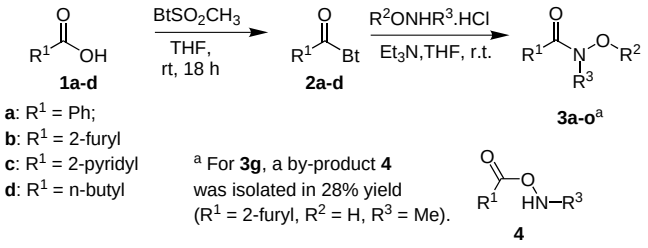
dimethylhydroxylamine hydrochlorides with a variety of acylbenzotriazoles (Scheme 1). The results are given in Table 1.

Independently of the substituent in both *N*-acylbenzotriazole and hydroxylamine, the desired *O*-alkyl, *N*-alkyl and *O*,*N*-dialkyl hydroxamic acids were obtained as sole products as a result of nucleophilic displacement of the benzotriazolyl moiety by the hydroxylamine nitrogen. Exceptionally, in the reaction of 2-furoylbenzotriazole (**2b**) with *N*-methylhydroxylamine hydrochloride, the desired *N*-hydroxy-*N*-methyl-2-furamide (**3g**) (Table 1, Entry 7) was obtained along with 28% of the isomeric product *N*-[(2-furylcarbonyl)oxy]methanamine (**4**), which is a result of nucleophilic attack by oxygen. Similar reaction of *N*-methylhydroxylamine with 1*H*-benzotriazol-1-yl(2-pyridinyl)methanone (**2c**) gave only the desired *N*-hydroxy-*N*-methyl-2-pyridinecarboxamide (**3k**). No product of type **4** was detected in the reaction mixture.



Scheme 1

Table 1 Preparation of *O*,*N*-Alkylated Hydroxamic Acids **3a**–**o**

Entry	Product	R^1	R^2	R^3	Yield (%)
1	**3a**	Ph	H	H	91
2	**3b**	Ph	Et	H	61
3	**3c**	Ph	Bn	H	87
4	**3d**	2-furyl	H	H	84
5	**3e**	2-furyl	Et	H	78
6	**3f**	2-furyl	Bn	H	80
7	**3g**	2-furyl	H	Me	64
8	**3h**	2-pyridyl	H	H	89
9	**3i**	2-pyridyl	Et	H	64
10	**3j**	2-pyridyl	Bn	H	91
11	**3k**	2-pyridyl	H	Me	92
12	**3l**	*n*-Bu	H	H	80
13	**3m**	*n*-Bu	Et	H	79
14	**3n**	*n*-Bu	Bn	H	94
15	**3o**	*n*-Bu	Me	Me	65

We have developed a practical and convenient method for the preparation of *O*-alkyl, *N*-alkyl and *O*,*N*-dialkyl hydroxamic acids. The simplicity of the reagents, mild conditions, the easy handling of the starting materials and intermediates are advantageous. Acylbenzotriazoles were shown to be efficient reagents for the preparation of a full variety of hydroxamic acids in neutral conditions whereas conversion of esters are limited to substituted hydroxylamines or required reaction media with pH > 10[16] or strong base for activation.[4,26a] Other published procedures to hydroxamic acids from esters provide high yields, but utilize environmentally challenged pyridine as a solvent.[4] *N*-Acyloxazolidinones in the presence of $Sm(OTf)_3$ give moderate to good yields of final compounds and require removal of oxazolidinone as by-product by chromatography.[15a] Our method avoids the use of dangerous compounds and large quantities of solvents; environmentally safe benzotriazole, the only by-product, can be easily removed. The use of trimethylaluminum was limited only to *N*-benzylhydroxylamine;[12] use of hydroxamoyl chlorides with olefins affords only *N*-vinylhydroxamates[14] lacking an *O*-substituent.

Melting points were determined using a capillary melting point apparatus equipped with a digital thermometer and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz NMR spectrometer (300 and 75 MHz, respectively) using $CDCl_3$ or acetone-d_6 as stated, with tetramethylsilane as an internal standard. Column chromatography was conducted with silica gel 230–400 mesh. All other reagents were of reagent grade and were used without purification. Acylbenzotriazoles **2a**–**d** were prepared as described.[30]

O-Alkyl, *N*-Alkyl and *O*,*N*-Dialkylhydroxamic Acids 3a–o; General Procedure

Acylbenzotriazole **2a**–**d** (1.5 mmol) was dissolved in anhyd THF (10 mL) followed by the addition of the hydroxylamine hydrochloride of choice (1.65 mmol) and Et_3N (0.23 mL, 1.65 mmol). The mixture was stirred vigorously for 16 h at r.t. and filtered through Celite to remove the hydrochloric salt of Et_3N. For **3b**,**i**,**m**, after rotary evaporation of THF, the crude product was dissolved in CH_2Cl_2 and washed with aq Na_2CO_3; no additional purification was required. Compounds **3c**,**f**,**j** were purified by recrystallization. Compounds **3a**,**d**,**e**,**g**,**h**,**k**,**l**,**n**,**o** were purified by column chromatography.

N-Hydroxybenzamide (3a)

Off-white microcrystals after gradient column chromatography with EtOAc–hexanes (from 1:3 to 1:1); mp 126–128 °C (Lit.[35] mp 125–128 °C).

^{1}H NMR (acetone-d_6): δ = 7.43–7.57 (m, 3 H), 7.84–7.87 (m, 2 H), 8.92 (br s, 1 H), 10.93 (br s, 1 H).

^{13}C NMR (acetone-d_6): δ = 127.9, 129.4, 132.4, 133.1, 166.3.

N-Ethoxybenzamide (3b)

White microcrystals were obtained after the removal of benzotriazole by washing with aq Na_2CO_3; mp 60–61 °C (Lit.[36] mp 58–59 °C).

^{1}H NMR ($CDCl_3$): δ = 1.26 (t, *J* = 7.0 Hz, 3 H), 4.04 (q, *J* = 7.0 Hz, 2 H), 7.34–7.40 (m, 2 H), 7.45–7.50 (m, 1 H), 7.75–7.79 (m, 2 H), 9.88 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 13.3, 71.8, 127.1, 128.3, 131.6, 131.8, 166.1.

***N*-(Benzyloxy)benzamide (3c)**
Recrystallized from benzene to give white flakes; mp 103–104 °C (Lit.[37] mp 100–102 °C).

^{1}H NMR ($CDCl_3$): δ = 5.02 (s, 2 H), 7.35–7.45 (m, 7 H), 7.46–7.52 (m, 1 H), 7.66 (d, *J* = 7.3 Hz, 2 H), 8.81 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 78.3, 127.0, 128.6, 128.6, 128.8, 129.3, 131.9, 132.0, 135.2, 166.4.

***N*-Hydroxy-2-furamide (3d)**
White microcrystals were obtained after column chromatography with EtOAc–hexanes (1:1); mp 124–125 °C (Lit.[38] mp 121–122 °C).

^{1}H NMR (acetone-d_6): δ = 6.59 (dd, *J* = 3.4, 1.8 Hz, 1 H), 7.09 (d, *J* = 3.4 Hz, 1 H), 7.68 (dd, *J* = 1.8, 0.8 Hz, 1 H), 8.71 (br s, 1 H), 10.65 (br s, 1 H).

^{13}C NMR (acetone-d_6): δ = 112.5, 114.7, 145.7, 147.4, 157.9.

***N*-Ethoxy-2-furamide (3e)**
White microcrystals were obtained after gradient column chromatography with EtOAc–hexanes (1:2→1:1); mp 81–82 °C.

^{1}H NMR ($CDCl_3$): δ = 1.31 (t, *J* = 7.0 Hz, 3 H), 4.08 (q, *J* = 7.0 Hz, 2 H), 6.50 (dd, *J* = 3.5, 1.8 Hz, 1 H), 7.20 (d, *J* = 3.5 Hz, 1 H), 7.44–7.45 (m, 1 H), 9.61 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 13.3, 72.5, 111.8, 115.2, 144.4, 145.7, 157.2.

Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 53.94; H, 5.92; N, 8.82.

***N*-(Benzyloxy)-2-furamide (3f)**
Recrystallized from $CHCl_3$–hexanes to give white needles; mp 100–101 °C.

^{1}H NMR ($CDCl_3$): δ = 5.02 (s, 2 H), 6.49 (dd, *J* = 3.4, 1.8 Hz, 1 H), 7.19 (d, *J* = 3.4 Hz, 1 H), 7.36–7.46 (m, 6 H), 8.89 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 78.8, 112.0, 115.7, 128.6, 128.8, 129.2, 135.0, 144.4, 145.6, 157.0.

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.52; H, 5.33; N, 6.76.

***N*-Hydroxy-*N*-methyl-2-furamide (3g)**
White microcrystals were obtained after gradient column chromatography with EtOAc–hexanes (1:6→1:1); mp 103–104 °C (Lit.[39] mp 103–105 °C).

^{1}H NMR ($CDCl_3$): δ = 3.34 (s, 3 H), 6.57 (dd, *J* = 3.4, 1.8 Hz, 1 H), 7.22 (dd, *J* = 3.4, 0.7 Hz, 1 H), 7.71 (dd, *J* = 1.8, 0.7 Hz, 1 H), 9.35 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 37.2, 112.2, 117.9, 145.9, 147.2, 159.7.

***N*-[(2-Furylcarbonyl)oxy]methanamine (4)**
Colorless oil was separated from compound **3g**.

^{1}H NMR ($CDCl_3$): δ = 2.95 (s, 3 H), 6.54 (dd, *J* = 3.4, 1.8 Hz, 1 H), 7.24 (d, *J* = 3.4 Hz, 1 H), 7.61–7.63 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 39.9, 11.9, 118.5, 142.8, 146.7, 159.0.

Anal. Calcd for $C_6H_7NO_3$: C, 51.06; H, 5.00; N, 9.92. Found: C, 51.41; H, 5.11; N, 9.71.

***N*-Hydroxy-2-pyridinecarboxamide (3h)**
White microcrystals were obtained after column chromatography with EtOAc–hexanes (1:1); mp 119–120 °C (Lit.[40] mp 120 °C).

^{1}H NMR (acetone-d_6): δ = 7.54–7.59 (m, 1 H), 7.99 (td, *J* = 7.7, 1.6 Hz, 1 H), 8.08 (d, *J* = 7.7 Hz, 1 H), 8.58 (d, *J* = 4.7 Hz, 1 H), 8.85 (br s, 1 H), 11.08 (br s, 1 H).

^{13}C NMR (acetone-d_6): δ = 122.8, 127.4, 138.5, 149.5, 150.5, 162.6.

***N*-Ethoxy-2-pyridinecarboxamide (3i)**
Light brown oil was obtained after the removal of benzotriazole by washing with aq Na_2CO_3.

^{1}H NMR ($CDCl_3$): δ = 1.36 (t, *J* = 7.0 Hz, 3 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 7.43–7.48 (m, 1 H), 7.84–7.90 (m, 1 H), 8.19 (d, *J* = 7.7 Hz, 1 H), 8.51–8.54 (m, 1 H), 10.34 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 13.5, 72.4, 122.3, 126.6, 137.4, 148.1, 149.0, 161.9.

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.57; H, 6.19; N, 16.74.

***N*-(Benzyloxy)-2-pyridinecarboxamide (3j)**
Recrystallized from $CHCl_3$–hexanes to give white needles; mp 95–96 °C.

^{1}H NMR ($CDCl_3$): δ = 5.06 (s, 2 H), 7.37–7.49 (m, 6 H), 7.85 (td, *J* = 7.7, 1.6 Hz, 1 H), 8.18 (d, *J* = 7.7 Hz, 1 H), 8.45–8.47 (m, 1 H), 10.23 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 78.5, 122.3, 126.7, 128.6, 128.7, 129.2, 135.2, 137.4, 148.2, 149.0, 161.9.

Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.68; H, 5.40; N, 12.22.

***N*-Hydroxy-*N*-methyl-2-pyridinecarboxamide (3k)**
Off-white microcrystals were obtained after gradient column chromatography with EtOAc–hexanes (1:2→1:1), mp 80–81 °C.

^{1}H NMR ($CDCl_3$): δ = 3.50 (s, 3 H), 7.50–7.55 (m, 1 H), 7.99 (td, *J* = 7.7, 1.6 Hz, 1 H), 8.30 (d, *J* = 7.7 Hz, 1 H), 8.51–8.53 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 35.9, 125.3, 126.1, 138.6, 145.4, 151.8, 157.4.

Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.43; H, 5.29; N, 18.40.

***N*-Hydroxypentanamide (3l)**
White microcrystals were obtained after column chromatography with EtOAc–hexanes (1:1); mp 53– 54 °C (Lit.[41] mp 50–51 °C).

^{1}H NMR ($CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, 3 H), 1.27–1.39 (m, 2 H), 1.55–1.65 (m, 2 H), 2.16 (t, 7.3 Hz, 2 H), 9.31 (br s, 2 H).

^{13}C NMR ($CDCl_3$): δ = 13.7, 22.2, 27.5, 32.7, 172.1.

***N*-Ethoxypentanamide (3m)**
Colorless oil was obtained after the removal of benzotriazole by washing with aq Na_2CO_3.

^{1}H NMR ($CDCl_3$): δ = 0.91 (t, *J* = 7.3 Hz, 3 H), 1.25 (t, *J* = 7.0 Hz, 3 H), 1.31–1.39 (m, 2 H), 1.57–1.68 (m, 2 H), 2.14 (t, *J* = 7.0 Hz, 2 H), 3.95 (q, *J* = 7.0 Hz, 2 H), 9.92 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 13.2, 13.6, 22.2, 27.5, 32.8, 71.7, 171.2.

Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.30; H, 10.81; N, 9.77.

***N*-(Benzyloxy)pentanamide (3n)**
Colorless oil was obtained after gradient column chromatography with elution from $CHCl_3$→$CHCl_3$–MeOH (20:1).

^{1}H NMR ($CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3 H), 1.25–1.38 (m, 2 H), 1.53–1.64 (m, 2 H), 2.00–2.10 (m, 2 H), 4.80–4.90 (m, 2 H), 7.36–7.39 (m, 5 H), 8.56 (br s, 1 H).

^{13}C NMR ($CDCl_3$): δ = 13.6, 22.2, 27.4, 33.0, 78.0, 128.5, 128.6, 129.2, 135.4, 171.1.

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.28; H, 8.52; N, 7.06.

***N*-Methoxy-*N*-methylpentanamide (3o)**

Yellow oil was obtained after gradient column chromatography with EtOAc–hexanes (1:6→1:1).

^{1}H NMR ($CDCl_3$): δ = 0.96 (t, *J* = 7.3 Hz, 3 H), 1.30–1.44 (m, 2 H), 1.56–1.67 (m, 2 H), 2.42 (t, *J* = 7.3 Hz, 2 H), 3.18 (s, 3 H), 3.69 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 13.7, 22.4, 26.7, 31.5, 32.1, 61.1, 174.7.

Anal. Calcd for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.65. Found: C, 58.08; H, 10.87; N, 9.56.

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