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Efficient Synthesis of N^{α},N-Disubstituted α-Aminocarbohydroxamic Acids

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The title compounds **3** can be prepared in good yields by the reaction of N-substituted α-chlorocarbohydroxamic acids **2** and primary amines in dimethylacetamide as solvent.

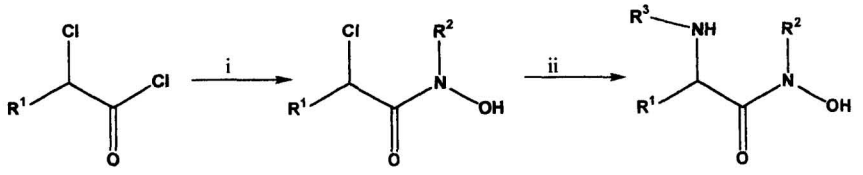
Keywords: N-substituted a-chlorocarbohydroxamic acids, primary amines, dimethylacetamide, N^{α},N-disubstituted α-aminocarbohydroxamic acids

Introduction

N-Unsubstituted α-aminocarbohydroxamic acids have attained growing interest in medicinal chemistry as building blocks for enzyme inhibitors [1,2]. Surprisingly, only little work has been devoted to N^{α},N-disubstituted α-aminocarbohydroxamic acids until now. Meier and Boche [3] investigated some N-aryl-N^{α}-benzylaminocarbohydroxamic acids and their rearrangement to the corresponding O-acyl derivatives which are suspected to be ultimate carcinogens of aromatic amines [4] and Ono and Itoh [5] described N^{α}-dimethylamino-N-methylacetohydroxamic acid as a reagent for selective cleavage of carboxylic esters under neutral conditions.

As a part of our research directed to bioactive molecules derived from bifunctional hydroxamic acids we needed a series of N^{α},N-disubstituted α-aminocarbohydroxamic acids **3** and found the target compounds to be readily available by reacting α-chlorocarbohydroxamic acids **2** with primary amines (Scheme 1).

Scheme 1



1a-c **2a-i** **3a-o**

i: R^2NHOH, $NaHCO_3$; ii: R^3NH_2, dimethylacetamide, 25°C; **1a**: R^1 =H, **1b**: R^1 = Me; **1c**: R^1 = Ph
2a: R^1 = H, R^2 = CH_2Ph; **2b**: R^1 = H, R^2 = $CH(Ph)_2$; **2c**: R^1 = H, R^2 = i-prop; **2d**: R^1 = H, R^2 = CH_2(2,4Cl)Ph;
2e: R^1 = CH_3, R^2 = $CH(Ph)_2$; **2f**: R^1 = Ph, R^2 = CH_3; **2g**: R^1 = Ph, R^2 = CH_2Ph; **2h**: R^1 = Ph, R^2 = 2F-Ph;
2i: R^1 = H, R^2 = CH_3

Results and Discussion

α-Chlorocarbohydroxamic acids **2** could easily be prepared according to Exner [6] in yields of 55-85% by dropping a solution of α-chlorocarboxylic acid chloride in diethyl ether into a heavily stirred two phase system of diethyl ether/water containing the appropriate N-substituted hydroxylamine.

Table 1:

3	R^1	R^2	R^3
a	H	Me	Ph
b	H	Me	CH_2(4-Cl)Ph
c	H	Me	CH_2(4-MeO)Ph
d	H	Me	$(CH_2)_2Ph$
e	H	$CH(Ph)_2$	Ph
f	H	CH_2Ph	Ph
g	H	$CH(Ph)_2$	CH_2Ph
h	H	CH_2(2,4-Cl)Ph	CH_2Ph
i	H	i-prop	Ph
j	Me	Me	CH_2Ph
k	Ph	Me	Ph
l	Ph	CH_2Ph	CH_2Ph
m	Ph	2F-Ph	CH_2Ph
n	Ph	2F-Ph	Ph
o	H	CH_2Ph	Ph

Initial aminolysis studies of **2** indicated a remarkable influence of the solvent on the formation of **3**: Yields were unsatisfactory when running the experiments in diethyl ether, ethyl acetate or acetonitrile. However, good results were obtained by reacting **2** in dimethylacetamide with a primary amine in a molar ratio of 1:3 at ambient temperature for 12-24h. Simply work-up of the reaction mixture by diluting with ice-cold water provided **3a-o** (Table 1) in 53-88% yields

as crystalline compounds, characterized by elemental analysis, IR and ^{1}H-NMR spectra (see experimental part) and a typical purple color reaction with ferric chloride in ethanol.

In conclusion, a simple synthetic approach to N$^{\alpha}$,N-substituted α-aminocarbohydroxamic acids **3** has been developed starting from commercially available α-chlorocarboxylic acid chlorides. Heterocyclizations of **3**, providing novel ring systems as well as biological activities of **3** and derivatives thereof will be reported in due course.

Experimental Part

Melting points (uncorrected) were taken in open capillary tubes using a Mettler FP 62 apparatus. ^{1}H-NMR spectra were recorded on a Bruker AMX 400 spectrometer with TMS as the internal standard. The IR spectra (KBr) were recorded on a ATI Mattson Genesis Series FTIR. Elemental analyses were performed on a Heraeus CHN-O-Rapid. For all compounds satisfactory microanalyses were obtained.

General Procedure for the Preparation of N-substituted α-chlorocarbohydroxamic acids 2a-i:

To a solution of sodium carbonate (10 mmol) in 10 ml H_2O was slowly added the corresponding N-substituted hydroxylamine (10 mmol) hydrochloride. After addition of 60 ml diethyl ether the mixture was cooled in an ice bath and a solution of α-chlorocarboxylic acid chloride (10 mmol) in 10 ml diethyl ether was added dropwise under vigorous stirring. After stirring the mixture at ambient temperature for 3 h the organic layer was separated and the aqueous solution extracted thrice with 10 ml diethyl ether. The combined organic layers were dried ($MgSO_4$) and evaporated. Oily residues crystallized from diethyl ether/petrolether within 24h on standing in the refrigerator. A single recrystallization of the crude products furnished pure **2a-h.**

N–Benzyl-α-chloroacetohydroxamic acid (2a)

Yield 92%; m.p 82° C ; IR: 3173 (OH), 1634 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 4.45 (s, 2H), 4.71 (s, 2H), 7.27-7.37 (m, 5 Ar-H), 10.17 (s, OH); $C_9H_{10}ClNO_2$ (199.6).

α-Chloro-N-(diphenylmethyl)acetohydroxamic acid (2b)

Yield 71%; m.p 128° C ; IR: 3153 (OH), 1630 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 4.52 (s, 2H), 6.75 (s, 1H), 7.20-7.40 (m, 10 Ar-H), 9.90 (s, OH); $C_{13}H_{14}ClNO_2$ (275.7).

α-Chloro-N-ispropylacetohydroxamic acid (2c)

Yield 48%; m.p 85° C ; IR: 3127 (OH), 1623 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 1.05 (d, J = 7.1 Hz, 6H), 4.36 (s, 2H), 4.50 (sept, J = 7.1 Hz, 1H), 9.64 (s, OH); $C_5H_{10}ClNO_2$ (151.6).

α-Chloro-N-(2,4-dichlorophenyl)acetohydroxamic acid (2d)

Yield 75%; m.p 131° C ; IR: 3187 (OH), 1635 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 4.49 (s, 2H), 4.80 (s, 2H), 7.36-7.65 (m, 3 Ar-H), 10.25 (s, OH); $C_9H_8ClNO_2$ (268.5).

α-Chloro-N-(diphenylmethyl)propiohydroxamic acid (2e)

Yield 58%; m.p 130° C ; IR: 3210 (OH), 1633 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 1.56 (d, J = 6.6 Hz, 3H), 5.12 (q, J = 6.6 Hz, 1H), 6.72 (s, 1H), 7.24-7.37 (m, 10 Ar-H), 9.97 (s, OH); $C_{16}H_{16}ClNO_2$ (289.8).

α-Chloro-N-methyl-phenylacetohydroxamic acid (2f)

Yield 78%; m.p 96° C ; IR: 3185 (OH), 1638 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.12 (s, 3H), 6.20 (s, 1H), 7.37-7.50 (m, 5 Ar-H), 10.32 (s, OH); $C_9H_{10}ClNO_2$ (199.6).

N–Benzyl-α-chlorophenylacetohydroxamic acid (2g)

Yield 82%; m.p 138° C ; IR: 3110 (OH), 1630 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 4.58 (q 2H), 6.20 (s, 1H), 7.15-7.52 (m, 10 Ar-H), 10.25 (s, OH); $C_{15}H_{14}ClNO_2$ (275.7)

α-Chloro-N-(2-fluorophenyl)phenylacetohydroxamic acid (2h)

Yield 73%; m.p 144° C ; IR: 3241 (OH), 1648 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 6.40 (s, 1H), 7.30-7.55 (m, 9 Ar-H), 11.13 (s, OH); $C_{14}H_{11}Cl_FNO_2$ (279.7)

α-Chloro-N-methyl-acetohydroxamic acid (2i) was prepared according to literature [6]

General Procedure for the Preparation of N^{α},N-substituted α-aminocarbohydroxamic acids 3a-o:

To a solution of **2** (10 mmol) in 20 ml dimethylacetamide was added the appropriate amine (30 mmol), the mixture was stirred at ambient temperature for 48h and finally poured on ice. The precipitate was separated and recrystallized from ethyl acetate furnishing pure **3a-o**.

N–Methyl-α-(phenylamino)acetohydroxamic acid (3a)

From **2i** [6] and aniline; yield 68%; m.p 126° C ; IR: 3386 NH), 3236 (br, OH), 1621 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.14 (s, 3H), 3.92 (s, 2H), 6.53-7.08 (m, 5 Ar-H), 9.99 (s, OH); $C_9H_{12}N_2O_2$ (180.2).

α-(4-Chlorobenzylamino)-N-methyl-acetohydroxamic acid (3b)

From **2i** and 4-chlorobenzylamine; yield 88%; m.p 166° C ; IR: 3271 (NH), 2461 (br, OH), 1637 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.09 (s, 3H), 3.30 (s, 2H), 3.68 (s, 2H), 7.29-7.44 (m, 4 Ar-H), 10.09 (s, OH); $C_{10}H_{13}ClN_2O_2$ (228.7).

α-(4-Methoxybenzylamino)-N-methyl-acetohydroxamic acid (3c)

From **2i** and 4-methoxybenzylamine; yield 85%; m.p 152° C ; IR: 3262 (NH), 2485 (br, OH), 1638 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.10 (s, 3H), 3.30 (s, 2H), 3,62 (s, 2H), 6.88 (d, 2 Ar-H), 7.23 (d, 2H), 10.09 (s, OH); $C_{11}H_{16}N_2O_3$ (224.3).

N-Methyl-α-(2-phenylethylamino)acetohydroxamic acid (3d)

From **2i** and 2-phenylethylamine; yield 64%; m.p 136° C ; IR: 3300 (NH), 2448 (br, OH), 1644 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 2.60-2.80 (m, 4H), 3.09 (s, 3H), 3.41 (s, 2H), 7.17-7.29; (m, 5 Ar-H); $C_{11}H_{16}N_2O_2$ (208.3).

N-(Diphenylmethyl)-α-(phenylamino)acetohydroxamic acid (3e)

From **2b** and aniline; yield 73%; m.p 145° C ; IR: 3409 (NH), 3263 (br, OH), 1639 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 4.10 (s, 2H), 3.91 (s, 2H), 6.55 (m, 3 Ar-H), 6.76 (s, 1H), 7.08 (m, 2Ar-H), 7.22-7.40 (m, 10 Ar-H), 9.80 (s, OH); $C_{21}H_{20}N_2O_2$ (332.4).

α-(Benzylamino)-N-methyl-acetohydroxamic acid (3f)

From **2i** and benzylamine; yield 79%; m.p 153° C ; IR: 3270 (NH), 2446 (br, OH), 1644 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.10 (s, 3H), 3.35 (s, 2H), 3.70 (s, 2H), 7.15-7.30 (m, 5 Ar-H), 10.09 (s, OH); $C_{10}H_{14}N_2O_2$ (194.2).

α-(Benzylamino)-N-(diphenylmethyl)acetohydroxamic acid (3g)

From **2b** and benzylamine; yield 73%; m.p 122° C ; IR: 3291 (NH), 2580 (br, OH), 1655 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.57 (s, 2H), 3.71 (s, 2H), 6.78 (s, 1H), 7.10-7.47 (m, 15 Ar-H), 9.60 (s, OH); $C_{22}H_{22}N_2O_2$ (346.4).

α-(Benzylamino)-N-(2,4-dichlorobenzyl)acetohydroxamic acid (3h)

From **2d** and 2,4-dichlorobenzylamine; yield 93%; m.p 152° C ; IR: 3274 (NH), 2498 (br, OH), 1644 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.49 (s, 2H), 3.72 (s, 2H), 4.79 (s, 2H), 7.18-7.66 (m, 8 Ar-H); $C_{16}H_{16}Cl_2N_2O_3$ (339.2).

N–Isopropyl-α-(phenylamino)acetohydroxamic acid (3i)

From **2c** and aniline; yield 65%; m.p 103° C ; IR: 3390 (NH), 3221 (OH), 1607 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 1.10 (d, J = 7.1 Hz, 6H), 3.90 (s, 2H), 4.55 (q, J = 7.1 Hz, 1H), 5.54 (s, 1H), 6.52-7.12 (m, 5 Ar-H), 9.49 (s, OH); $C_{11}H_{16}N_2O_2$ (208.3).

α-(Benzylamino)-N-methyl-propiohydroxamic acid (3j)

From **2e** and benzylamine; yield 53%; m.p 121° C ; IR: 3268 (NH), 2447 (br, OH), 1631 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 1.10 (d, 3H), 3.13 (s, 3H,), 3.55 (dd, 2H), 3.75 (q, 1H), 7.20-7.37 (m, 5 Ar-H), 9.88 (s, OH); $C_{11}H_{16}N_2O_2$ (208.3).

N-Methyl-α-(phenylamino)-phenylacetohydroxamic acid (3k)

From **2f** and aniline; yield 63%; m.p 146° C ; IR: 3398 (NH), 3265 (OH), 1625 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.11 (s, 3H), 5.66 (d, 1H), 6.03 (d, 1H), 6.52-7.48 (m 10 Ar-H), 10.19 (s, OH); $C_{15}H_{16}N_2O_2$ (256.3).

N-Benzyl-α-(benzylamino)phenylacetohydroxamic acid (3l)

From **2g** and benzylamine; yield 63%; m.p 102° C ; IR: 3260 (NH), 3040 (br, OH), 1630 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.62(d, 2H), 3.72 (d, 2H), 4.90 (s, 1H), 5.66 (d, 1H), 6.03 (d, 1H), 7.10-7.40 (m 15 Ar-H), 9.50 (s, OH); $C_{22}H_{22}N_2O_2$ (346.4)

α-(Benzylamino)-N-(2-fluorophenyl)phenylacetohydroxamic acid (3m)

From **2h** and benzylamine; yield 65%; m.p 135° C ; IR: 3306 (NH), 3156 (br, OH), 1627 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.55 (q, 2H), 5.06 (s, 1H), 7.18-7.48 (m 9 Ar-H), 10.76 (s, OH); $C_{21}H_{19}FN_2O_2$ (350.4).

N-(2-Fluorophenyl)-α-(phenylamino)phenylacetohydroxamic acid (3n)

From **2h** and aniline; yield 55%; m.p 141° C ; IR: 3398 (NH), 3258 (br, OH), 1632 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.55 (q, 2H), 5.90 (s, 1H), 7.18-7.54 (m 14 Ar-H), 11.00 (s, OH); $C_{20}H_{17}FN_2O_2$ (336.4).

N-Benzyl-α-(phenylamino)acetohydroxamic acid (3o)

From **2a** and aniline; yield 73%; m.p 141° C ; IR: 3273 (NH), 2780 (br, OH), 1646 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 4.01 (d, 2H), 4,75 (s, 2H), 5.15 (t, NH), 6.55-7.40 (m, 10 Ar-H),10.00 (s, OH); $C_{16}H_{19}N_2O_2$ (256.3).

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