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Short Communication

Synthesis of Cyclic Hydroxamic Acids by Oxidation of Secondary Amines with Dimethyldioxirane

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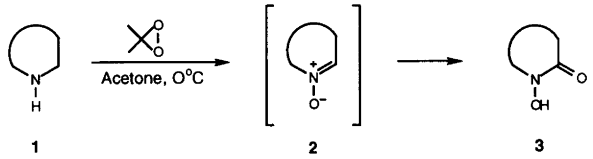
Work on α-functionalization of cyclic amines has led us to study synthetic routes to cyclic hydroxamic acids. Hydroxamic acids are important compounds which show a wide range of biological activities,[1] e.g., antiinflammatory and analgesic activities,[1b,e,f] enzyme inhibitory activities[1c,d] and interference with microbial iron transport.[1g]

Although several methods are available for the synthesis of aliphatic hydroxamic acids,[2] the preparation of cyclic hydroxamic acids has received little attention. Cyclic hydroxamic acids are usually made by condensation reactions[3] or reductive cyclisation reactions.[1f,4] Recently a tungstate-catalyzed oxidation of 1,2,3,4-tetrahydroquinolines to the corresponding hydroxamic acids has been published.[2] We have found that a number of cyclic secondary amines can be oxidized to the corresponding hydroxamic acid by dimethyldioxirane (DMD) (Scheme 1 and Table 1).



1 2 3

Scheme 1.

The method is simple since any excess of oxidant is destroyed/removed upon evaporation of the solvent (acetone).

DMD has been used in a number of oxidations,[5] and secondary amines have been oxidized to the corresponding hydroxylamines[5a] and nitrones.[6] Excess DMD in the oxidation of secondary amines leads to further oxidations, but the structure of the more highly oxidized products has not been discussed.[6]

We found that six-membered cyclic secondary amines such as piperidine and morpholine are readily oxidized to

Table 1. Oxidation of cyclic secondary amines **1** to hydroxamic acids **3** with dimethyldioxirane.

No.	Product	Yield (%)[a]
3a		27[b]
3b		71
3c		67
3d		89
3e		67
3f		85
3g		54
3h		83
3i		0[c]

[a] Isolated. [b] With 3.3 equiv. DMD a mixture of **3a** and the corresponding nitrone was formed. [c] With 3.3 equiv. DMD a mixture of **3i**, the corresponding nitrone and other oxidation products was formed; with 2.0 equiv. DMD the nitrone was isolated in 48% yield.

the corresponding hydroxamic acid at 0°C in acetone by DMD (Table 1, **3b** and **3c**). The reaction proceeds by way of the corresponding nitrone (**2**). Pyrrolidine, on the other hand, gave a mixture of the corresponding hydroxamic acid (Table 1, **3a**) and the corresponding nitrone. When the five-membered ring is fused to an aromatic ring, the hydroxamic acid is isolated in good yield (Table 1, **3g**). Piperazines with an electron-withdrawing substituent on one of the nitrogens are also easily oxidized chemoselectively to the hydroxamic acids **3d**, **3e** and **3f**, respectively (Table 1). 4-Methylpiperazine, however, gave a complex mixture of oxidation products resulting from oxidative reactions at both nitrogens.

The dimethyldioxirane reagent is compatible with a number of easily oxidized functional groups, as seen in the oxidations of *N*-formylpiperazine (Table 1, **3d**) where the secondary amine function is chemoselectively oxidized. The selectivity arises because of rapid consumption of the oxidizing agent in the hydroxamic acid formation. The oxidation of formyl groups by DMD is a much slower reaction.[7]

The water that is produced in the reaction does not seem to interfere with the oxidation, since addition of molecular sieves (4 Å) did not improve the yield of compound **3c**.

Fused cyclic secondary amines react readily to form the corresponding hydroxamic acids (Table 1, **3g** and **3h**), as long as there is no benzylic hydrogen *alpha* to the nitrogen atom. With 1,2,3,4-tetrahydroisoquinoline, which has benzylic hydrogens *alpha* to the nitrogens atoms, oxidation with three equivalents of DMD gave a mixture of the nitrone **2h** and the hydroxamic acid **3h** together with unidentified oxidation products. With two equivalents, however, a clean reaction to the nitrone **2i** is observed.

Experimental

Mass spectra were recorded under electron impact conditions at 70 eV (EI). Methane was used for chemical ionization (CI). The spectra are presented as *m/z* (% rel. int.). The ^{1}H NMR spectra were recorded at 200 or 300 MHz and the ^{13}C NMR spectra at 50 MHz. The amines were distilled from aluminium hydride prior to use. The acetone solution of dimethyldioxirane (DMD) was prepared by reaction of potassium monoperoxysulfate with acetone as described.[8] The concentration of DMD was determined by oxidation of methyl phenyl sulfide to its sulfoxide and the relationship between them quantified by ^{1}H NMR spectroscopy ($CDCl_3$; methyl signals).[8]

General procedure for the oxidation of cyclic secondary amines with dimethyldioxirane (DMD). An acetone solution of DMD (4.48–4.89 mmol) was added to an ice/water-cooled (0°C) solution of the required amine (1.40 mmol) in acetone (5 ml). The reaction mixture was stirred at 0°C for 20–30 min before the acetone was removed under reduced pressure. The crude product was purified either by recrystallization or by flash chromatography.

1-Hydroxy-2-pyrrolidone (**3a**).[9]

1-Hydroxy-2-piperidone (**3b**).[10] The eluent was methanol–acetonitrile 1:2; m.p. (sublimed once) 44–45°C.[1] ^{1}H NMR ($CDCl_3$): δ 1.73–1.84 (H-4, m), 1.88–2.00 (H-5, m), 2.45 (H-3, t, $J_{3,4}$ 6.4 Hz), 3.64 (H-6, t, $J_{6,5}$ 5.9 Hz), 9.8 (N–OH, br s). ^{13}C NMR ($CDCl_3$): δ 20.5, 23.0, 30.8 (C-3), 49.1 (C-6), 163.1 (C=O). MS (EI): 116 (2, *M*), 115 (12), 100 (15), 99 (100). IR (KBr): 3500–3000 (OH), 1620 (C=O) cm^{-1}.

4-Hydroxymorpholin-3-one (**3c**).[11] M.p. (sublimed once) 128–129°C. ^{1}H NMR ($CDCl_3$): δ 3.73 (H-5/H-6, t, *J* 5.1 Hz), 3.96 (H-5/H-6, t, *J* 5.1 Hz), 4.22 (H-2, s), 10.1 (N–OH, br s). ^{13}C NMR ($CDCl_3$): δ 49.0, 63.6, 67.1, 161.4 (C=O). MS (EI): 117 (20, *M*), 101 (100), 89 (15), 71 (48), 59 (25). IR (KBr): 3200–3000, 1665, 1640 (sh) cm^{-1}.

4-Hydroxy-3-oxopiperazine-1-carbaldehyde (**3d**). M.p. 140–141°C (ethanol). Anal. $C_5H_8N_2O_3$: C, H. ^{1}H NMR (DMSO-d_6, approx. 21°C, 300 MHz): δ 3.45 (t, *J* 5.7 Hz), 3.54 (t, *J* 5.5 Hz), 3.71 (t, *J* 5.4 Hz), 3.73 (t, *J* 5.4 Hz), 3.98 (s), 4.08 (s), 8.05 (N–OH, s), 9.92 (s), 9.95 (s). ^{1}H NMR (DMSO-d_6, approx. 52°C, 300 MHz): δ 3.48 (t, *J* 5.7 Hz), 3.56 (t, *J* 5.5 Hz), 3.72 (t, *J* 5.7 Hz), 3.74 (t, *J* 5.5 Hz), 3.99 (s), 4.08 (s), 8.06 (N–OH, s), 9.78 (formyl, s), 9.81 (formyl, s). ^{1}H NMR (DMSO-d_6, approx. 140°C, 300 MHz): δ 3.55, 3.74 (t, *J* 5.5 Hz), 4.02 (s), 8.07 (N–OH, s), 9.4 (formyl, br s). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.72 (t, *J* 5.6 Hz), 3.78 (s), 3.95 (t, *J* 5.6 Hz), 4.14 (s), 4.29 (s), 8.10 (formyl, s), 8.11 (formyl, s). ^{13}C NMR (DMSO-d_6): δ 36.4, 41.5, 43.4, 48.0, 49.5, 50.6, 159.4, 160.1. MS (EI): 145 (1, *M* + 1), 144 (10, *M*), 128 (11). IR (KBr): 3500–3350, 3200–3000, 1650 (hydroxamic C=O) cm^{-1}.

Benzyl 4-hydroxy-3-oxopiperazine-1-carboxylate (**3e**). M.p. 131–132°C (acetone). Anal. $C_{12}H_{14}N_2O_4$: C, H. ^{1}H NMR ($CDCl_3$): δ 3.69 (H-5/H-6, t, *J* 5.1 Hz), 3.82 (H-5/H-6, t, *J* 5.1 Hz), 4.20 (H-3, s), 5.14 (CH_2Ph, s), 7.34 (ArH, m), 8.44 (N–OH, br s). ^{13}C NMR ($CDCl_3$): δ 40.4, 46.4, 48.5, 67.2 (CH_2Ph), 126.6, 126.9, 127.1, 134.2 (CH_2–*C* in Ph), 152.5 (CO_2), 159.5 (N–C=O). MS (CI): 251 (7, *M* + 1), 250 (1, M), 91 (100, CH_2Ph). IR (KBr): 3500–3350, 3200–3000, 1705 (formyl C=O), 1650 (hydroxamic C=O), 1620 cm^{-1}.

4-(4-Acetylphenyl)-1-hydroxypiperazin-2-one (**3f**). M.p. 173–174°C (decomp.) Anal. $C_{12}H_{14}N_2O_3$: C, H. ^{1}H NMR (DMSO-d_6): δ 2.47 ($COCH_3$, s), 3.62 (H-6, d, *J* 5.4 Hz), 3.78 (H-5, t, *J* 5.4 Hz), 7.01 (ArH, d, *J* 8.9 Hz), 7.83 (ArH, d, *J* 8.9 Hz), 9.95 (N–OH, s). ^{13}C NMR (DMSO-d_6): δ 26.1 (CH_3), 44.1, 49.1, 51.2, 112.6, 126.7, 129.5, 151.0, 160.5 (NC=O), 194.2 (acetyl C=O). MS (EI): 235 (9, *M* + 1), 234 (53, *M*), 218 (57), 217 (86). IR (KBr): 3250–3000, 1660, 1600 cm^{-1}.

1,3-Dihydro-1-hydroxyindol-2-one (**3g**).[12] M.p. 197–198°C (THF and CH_2Cl_2, decomp.) ^{1}H NMR (DMSO-d_6): δ 3.54 (H-3, s), 6.88–7.02 (ArH, m), 7.21–7.30 (ArH, m), 10.64 (N–OH, s). ^{13}C NMR (DMSO-d_6): δ 33.4, 106.2, 120.5, 121.2, 123.7, 126.9, 142.8, 168.3. MS (EI): 150 (2, $M+1$), 149 (17, M), 133 (100), 105 (42), 104 (71). IR (KBr): 3200–3030, 1670, 1610 cm^{-1}.

1-Hydroxy-3,4-dihydroquinolin-2(1H)-one (**3h**).[2] M.p. 128–129°C (pentane–CH_2Cl_2).

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