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One-Pot Synthesis of α-Chloro Hydroxamic Acids using Gem-Dicyano Epoxides.

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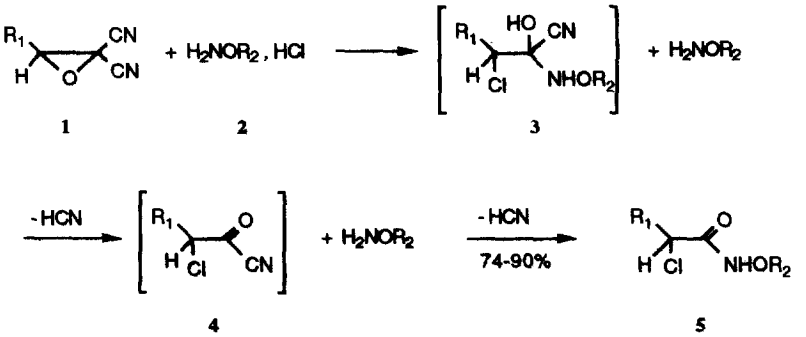
Abstract: Gem-dicyano epoxides **1**, when treated with hydrochlorides of hydroxylamines **2** in acetonitrile, at reflux, yield the α-chloro hydroxamic acids and derivatives **5** in good yields.

Hydroxamic acids are important biologically active compounds,[1] such as antibiotic antagonists,[1a] tumor inhibitors,[1a] cell-division factors,[1a] potent growth factors,[1b] antibiotics,[1c] or microbial iron transport compounds.[1d,e]

Although the synthetic methods for hydroxamic acids are well documented,[2] the methods for the synthesis of α-chloro hydroxamic acids are limited to two examples.[3-4] However, these compounds have synthetic value as they are interesting starting materials for the synthesis of intermediate aziridinones[5-7] used, in situ, as precursors to α-hydroxy acids[7] and α-amino acids.[7]

A general synthesis of α-haloesters, α-haloacids, and α-halohydrazides through the reaction of dicyano epoxides **1** with alcohols, water, and hydrazines in the presence of an halohydric acid[8-10] has been described. We would like to report here that the reaction of epoxides **1** with hydrochlorides of hydroxylamines represents a direct route to a number of new and higher hydroxamic acids.

Good yields of α-chloro hydroxamic acids and their derivatives **5a-5e**[11] have been obtained by reacting stoichiometric amounts of epoxide **1** with hydrochlorides of hydroxylamines **2** in acetonitrile (scheme 1, table 1: entry a-e). The structure of the hydroxamic acids **5a** and **5e** was further ascertained by comparison with authentic samples synthesized independently via the reaction of hydrochlorides of hydroxylamines with the corresponding ester by the method of Hauser and Renfrow.[2a]



1 2 3 4 5

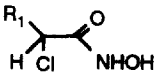
Scheme 1

Table 1: Reaction of epoxides 1 with hydrochlorides of hydroxylamines 2.

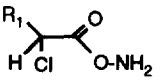
Entry	R_1	R_2	Solvent	Temperature (°C)	Reaction time (h)	Products (Yields %, mp °C)
a	4-MeC_6H_4	H	MeCN	78	2	**5a** (75, oil)[a]
b	4-ClC_6H_4	H	MeCN	78	2	**5b** (74, oil)[a]
c	C_6H_5	H	MeCN	78	2	**5c** (75, oil)[a]
d	4-MeC_6H_4	Me	MeCN	78	1.5	**5d** (90, 137-8)[b]
e	4-ClC_6H_4	Me	MeCN	78	1.5	**5e** (84, 99-100)[b]
f	4-MeC_6H_4	H	MeCN-H_2O	25	16	**5a** (50, oil)[a] + **6f** (35, 150-2)[b]
g	4-ClC_6H_4	H	MeCN-H_2O	25	16	**5b** (52, oil)[a] + **6g** (30, 173-4)[b]

a. Isolated yields after flash chromatography on silica gel hexane / ethyl acetate 7:3 as eluent.
b. Yields of isolated, purified products. The solid compounds **5d-e**, **6f-g** can be recrystallized from benzene.

When the protic nucleophile is hydroxylamine (entry a-c), two compounds **5** and **6** might be expected. However, only **5** is obtained as demonstrated by ^{13}C nmr where the carbonyl carbon in compound **5b** (R_1= 4-ClC_6H_4, R_2= H) appears in the ^{13}C NMR spectrum as doublet of doublet (^2J = 3.9 and 4.2 Hz). Moreover, as been expected, **5** gives a positive red color test with ferric chloride.[2b]



5a-5c



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The formation of **5** is consistent with the observation of Prabhakar et al. who observed O-arylated products when they reacted bulky hydroxylamines with aryl cyanides while hydroxamic acids were obtained from less hindered hydroxylamines.[12]

The opening of the epoxides by hydrogen chloride showed an original feature due to the double selectivity of the reaction. First a selective opening of the epoxides by hydrogen chloride giving the intermediates **3** and subsequently **4**, was always observed. Then a selective substitution of the cyano group of **4** by the hydroxylamine gave with very good yields, the α-chloro hydroxamic acids **5**.

The solvent and the temperature all have an important influence on the outcome of the reaction. Thus, when the epoxide **1** was reacted with hydroxylamine hydrochloride in non-stoichiometric ratio, at room temperature in the presence of water, a mixture of **5** and **6**[13] was obtained (table 1, entry f, g). **5** and **6** were separated by crystallisation from ether-petroleum ether 1:1 (**6** does not give a positive ferric chloride test). The reaction realized under these conditions, at reflux, gave complex mixtures of products which were not analyzed.

As gem-dicyano epoxides **1** are easily available starting materials,[14] and as the reaction is highly regio- and chemoselective and is a one-pot procedure, our new route to α-chloro hydroxamic acids and their derivatives **5**, using epoxides **1** as a synthetic equivalent of R_1HC^+--C^+=O synthons, seems of interest to us and compares favorably with the existing methods.[3-4]

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11. Spectral data are in full agreement with the proposed structures. ^{13}C spectra were recorded at 75 MHz, ^{1}H spectra at 300 MHz and IR spectra refer to nujol suspensions (ν cm^{-1}).
5a: IR ν: 3200-3400 (NH, OH) and 1715 (CO).
^{1}H NMR ($CDCl_3$) δ: 7.31-7.47 (m, 5H: Ar, NH); 5.30 (s, CHCl); 7.62 (br s, 1H, OH); 2.28 (s, CH_3).
^{13}C NMR δ: 171.5 (broad s, CO); 58.2 (d, ^{1}J=153.2 Hz, CHCl); 125.7, 127.5, 134.9, 138.4 (Ar-ring C); 20.2 (q, ^{1}J=126.7 Hz, CH_3).
Mass spectrum m/e: cal: 199.638 ($M^{+\cdot}$); found: 199.61 ($M^{+\cdot}$).
5b: IR ν: 3160-3400 (broad, NH, OH) and 1720 (CO).
^{1}H NMR ($CDCl_3$) δ: 7.29-7.45 (m,5H: Ar, NH); 5.27 (s,CHCl); 7.87 (br s, 1H, OH).
^{13}C NMR δ: 170.5 (dd, ^{2}J= 3.9 and 4.2 Hz, CO); 57.9 (d, ^{2}J=154.2 Hz, CHCl); 127.0, 130.6, 133.1, 143.2 (Ar-ring C).
Mass spectrum m/e cal: 220.0564 ($M^{+\cdot}$); found: 220.048 ($M^{+\cdot}$).
5c: IR ν: 3160-3350 (broad, NH,OH) and 1700(CO).
^{1}H NMR ($CDCl_3$) δ: 7.30-7.45 (m, 6H: Ar, NH); 5.35 (s, CHCl); 7.57 (br s, 1H, OH).
^{13}C NMR δ: 170.4 (broad s, CO); 58.7 (d, ^{1}J=153.5 Hz, CHCl); 125.7, 127.4, 130.8, 135.1 (Ar-ring C).
5d : IR ν: 3120 (NH) and 1660 (CO).
^{1}H NMR ($CDCl_3$ + TFA) δ: 7.30-7.40 (m, 4H Ar); 5.35 (s, CHCl); 3.78 (s, OCH_3); 2.48 (s, CH_3).
^{13}C NMR δ: 166.5 (dd, ^{2}J= 4.1 and 4.2 Hz, CO); 58.3 (d,^{1}J= 153.5 Hz, CHCl); 64.5 (q, ^{1}J= 145.77 Hz, OCH_3); 22.2 (q, ^{1}J=126.45 Hz, CH_3); 127.8, 129.7, 132.6, 139.7 (Ar-ring C).
Mass spectrum m/e: cal: 213.0556 ($M^{+\cdot}$), 139.0314 (M - $C_2H_4NO_2$)$^{+}$; found: 213.054 ($M^{+\cdot}$), 139.031 (M - $C_2H_4NO_2$)$^{+}$.
Anal. cal: C, 56.42; H, 5.72; N, 6.69; Cl, 16.41; found : C, 56.32; H, 5.67; N, 6.57; Cl, 16.41.

5e : IR ν: 3110 (NH) and 1665 (CO).
^{1}H NMR ($CDCl_3$ + TFA) δ: 7.35-7.45 (m, 4H Ar); 5.36 (s, CHCl); 3.80 (s, OCH_3).
^{13}C NMR δ: 165.5 (broad s, CO); 57.2 (d, ^1J= 154.59 Hz, CHCl); 64.3 (q, ^1J=145.2 Hz, OCH_3); 129.0, 129.3, 134.4, 135.4 (Ar-ringC).
Anal. cal: C, 45.62; H, 3.87; N, 6.42; Cl, 30.51; found : C, 45.69; H, 3.93; N, 6.42; Cl, 30.31.

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13. **6f**: IR ν: 2900-3100 (2 NH) and 1690 (CO).
^{1}H NMR (DMSO-d_6) δ: 7.10-7.40 (m, 4H, Ar); 5.26 (s, CHCl); 6.0 (s, 2H, NH_2); 2.50 (s, CH_3).
^{13}C NMR δ: 155.0 (d, ^2J=4 Hz, CO); 61.5 (d, ^1J=152.5 Hz, CHCl); 128.5, 129.7, 130.5, 139.0 (Ar-ring C); 21.5 (q, ^1J= 126.5 Hz, CH_3).
Mass spectrum m/e: cal: 199.638 ($M^{+\cdot}$); found: 199.080 ($M^{+\cdot}$).
Anal. cal: C, 53.78; H, 4.98; N, 6.97; Cl, 17.67; found : C, 53.82; H, 5.02; N, 7.37; Cl, 17.97.
6g: IR ν: 2900-3150 (2 NH) and 1700 (CO).
^{1}H NMR (DMSO-d_6) δ: 7.15-7.35 (m, 4H, Ar); 5.20 (s, CHCl); 6.10 (s, 2H, NH_2).
^{13}C NMR δ: 156.5 (d, ^2J=4.4 Hz, CO); 62.0 (d, ^1J=153.5 Hz, CHCl); 127.5, 130.6, 133.1, 143.2 (Ar-ring C).

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