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Simple syntheses of hydroxamic acids and their conversion into α-hydroxy and α-amino acids

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Abstract

The nucleophilic ring opening of *gem*-dicyanoepoxides by LiBr or Li_2NiBr_4, in the presence of hydroxylamine derivatives leads to new α-halo hydroxamic acids. These compounds has been used in the synthesis of α-functionalized hydroxamic acids, α-hydroxy and α-amino acids in good yields.

Although α-halo hydroxamic acids are well-known compounds, prepared from α-halo acids chlorides and hydroxylamines,[1,2] most of them are in the alkyl series, only a few are known in the aryl series,[3] as the accessibility of α-halo acids chlorides is not as easy.[1,2] However, structurally diversified hydroxamic acids are of considerable interest due to their potential biological activity as antibiotic antagonists,[4] tumor inhibitors,[4] and metal chelators.[5]

We have shown that the reaction of epoxides **1** with hydrochlorides of hydroxylamines represents a direct route to a number of α-chloro hydroxamic acids.[6] Unfortunately, this method is useful only for α-chloro hydroxamic acids. We therefore tried to find a more general method for the synthesis of α-bromo hydroxamic acids. We report in this paper that α-bromo hydroxamic acids are less easily obtained from epoxides **1**, by using a lithium bromide.

Epoxides **1** (5 mmol) was dissolved in 15 mL of THF and 7.5 mmol of lithium bromide was added. While the mixture was refluxed during 1 h, a solution of hydroxylamine hydrochlorides (10 mmol) and triethylamine (10 mmol) in THF was added dropwise. After the addition was completed, refluxing was continued for 1 h. The solvent was partially removed under reduced pressure and the residue was extracted with dichloromethane. The combined extracts were dried (Na_2SO_4), filtered and evaporated to afford the residual α-bromo hydroxamic acids **2**[7] (Scheme 1, Table 1), which was chromatographed over silica gel (hexane:ethyl acetate 3:2 as eluent) or recrystallized from benzene. Compound **2** gives a positive red color test with ferric chloride.

The reaction was assumed to proceed by the association of the epoxides **1** with lithium bromide and regioselective ring opening by the nucleophile Br^- which always attacks the carbon β to the two nitrile

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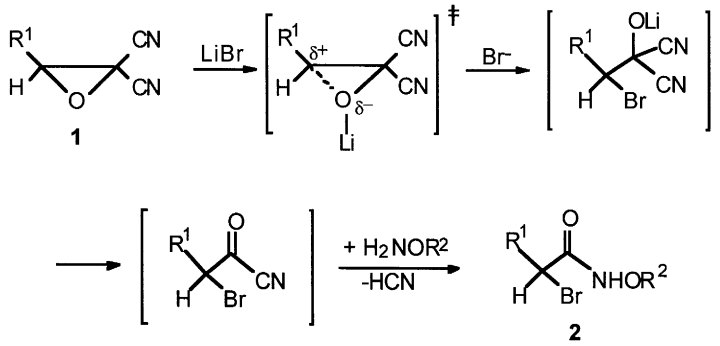


Scheme 1.

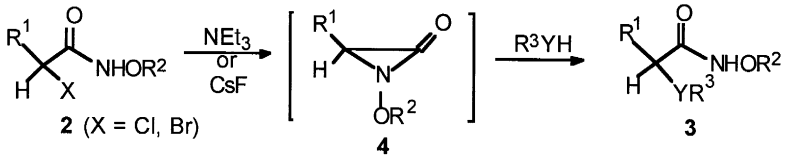
Table 1
Synthesis of α-bromo hydroxamic acids **2**

Entry	R^1	R^2	Products (Yield %, m. p °C)
a	4-$CH_3C_6H_4$	H	**2a** (84, oil)
b	4-ClC_6H_4	H	**2b** (86, oil)
c	C_6H_5	H	**2c** (85, oil)
d	4-$CH_3C_6H_4$	CH_3	**2d** (88, 142-3)
e	4-ClC_6H_4	CH_3	**2e** (86, 114-5)
f	C_6H_5	CH_3	**2f** (82, 90-1)
g	4-$NO_2C_6H_4$	CH_3	**2g** (76, 134-5)

groups. The unstable cyanohydrin loses lithium cyanide and the acyl cyanide intermediate reacts in situ with the hydroxylamine derivative to afford α-bromo hydroxamic acids **2**. When alcohols are used, the reaction of epoxides **1** with lithium bromide allows a convenient access to α-bromoesters.[8]

The particular structure of α-halo amide derivatives gives these compounds interesting properties which have been investigated.[9–11] Among these properties, we have studied their ability to undergo substitution reactions and the possibility to prepare α-lactams.[10] The results suggested that the reaction of α-halo hydroxamic acids **2** with nucleophiles might constitute a simple synthetic route to a number of new hydroxamic acids. We now report our studies on this new reaction which proved to be a convenient method of synthesis for α-functionalized hydroxamic acids **3** which, at the moment, is difficult to access.[12] In addition, a number of natural products have been isolated from bacterial cultures showing marked inhibition of aminopeptidases. These products such as phebestin[13] and probestin[14] contain α-hydroxy amide residues which are key units in their biological activity.

We have shown that α-alkoxy hydroxamic acids **3**[7] can be obtained from α-halo hydroxamic acids **2**, in a basic medium, not only alcohol but even water reacts as nucleophilic reagents so that α-hydroxy hydroxamic acids **3**[7] are also obtained according to this strategy (Scheme 2, Table 2, entries a–j).



Scheme 2.

We have shown that this reaction is not a direct nucleophilic substitution of the halogen but more likely proceeds through the formation of an aziridinone intermediate **4** which then undergoes nucleophilic ring

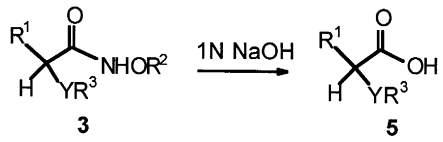
Table 2
Synthesis of α-alkoxy, α-hydroxy and α-amino hydroxamic acids **3**

Entry	R^1	R^2	YR^3	Conditions	Products (Yields %)[a]
a	4-$CH_3C_6H_4$	H	OEt	EtOH, 1h, reflux, NEt_3	**3a** (84)
b	4-ClC_6H_4				**3b** (86)
c	4-$CH_3C_6H_4$		OMe	MeOH, 1h, reflux, NEt_3	**3c** (85)
d	4-ClC_6H_4				**3d** (87)
e	4-$CH_3C_6H_4$	CH_3	OEt	EtOH, 1h, reflux, NEt_3	**3e** (80)
f	4-$CH_3C_6H_4$		OMe	MeOH, 1h, reflux, NEt_3	**3f** (81)
g	4-$CH_3C_6H_4$	H	OH	Dioxan-H_2O, 20h, r. t., CsF	**3g** (75)
h	4-ClC_6H_4				**3h** (76)
i	4-MeC_6H_4	CH_3			**3i** (80)
j	4-ClC_6H_4				**3j** (82)
k	4-$CH_3C_6H_4$	H	NHC_6H_5	CH_3CN, 3h, reflux	**3k** (75)
l	4-ClC_6H_4				**3l** (75)
m	4-$CH_3C_6H_4$		NHEt		**3m** (76)
n	4-ClC_6H_4				**3n** (74)
o	4-$CH_3C_6H_4$	CH_3	$N(Et)_2$		**3o** (73)
p	4-$CH_3C_6H_4$	H	NHMe		**3p** (72)
r	Et		NHC_6H_5		**3r** (75)

a- Isolated yields, after flash chromatography on silica gel hexane / ethyl acetate 3:2 as eluent.

opening. Such an aziridinone intermediate was also postulated in order to explain the formation of α-alkoxy hydrazides in the course of the reaction of α-halo hydrazides with alcohol in a basic medium.[4]

The same reaction was performed with amines as nucleophiles, at refluxing acetonitrile, to afford the α-amino hydroxamic acids **3**[7] in good to moderate yields (Table 2, entries k–r).



3 **5**

Scheme 3.

Table 3
Experimental conditions and physical data for α-hydroxy acids and α-amino acids **5**

Substrate	R^1	YR^3	Conditions	Product (Yields %)[a]	m. p °C
3g	4-$CH_3C_6H_4$	OH	CH_3CN, reflux, 3h	**5g** (85)	143-4 (Lit.[11] 145)
3h	4-ClC_6H_4			**5h** (86)	137-8
3k	4-$CH_3C_6H_4$	NHC_6H_5	dioxan, reflux, 24h	**5k** (80)	174-5 (Lit.[11] 174)
3l	4-ClC_6H_4			**5l** (82)	167-8

a- Yields of isolated, purified products. The solid compounds can be recrystallized from toluene.

Hydrolysis of α-amino hydroxamic acids **3** gave the corresponding α-amino acids **5** (Y=N), which are obtained in good yields when the reaction is run in a basic medium. This method was extended to the synthesis of α-hydroxy acids **5** (Y=O) from α-hydroxy hydroxamic acids **3**. In fact, employing 1N NaOH in CH_3CN or dioxan gave an essentially quantitative conversion of hydroxamic acids **3** into α-hydroxy acids **5** or α-amino acids **5** (Scheme 3). Table 3 lists the α-amino and α-hydroxy acids **5** which have been synthesized using this methodology.

In summary, we have described a new convenient one-pot synthesis of α-bromo hydroxamic acids. We have also shown that the α-halo hydroxamic acids react in basic media to give aziridinone intermediates

which can be trapped in the medium by nucleophiles present. The reaction opens a new route to α-alkoxy, α-amino and α-hydroxy hydroxamic acids, which can give α-amino and α-hydroxy acids.

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7. Spectral data are in full agreement with the proposed structures. For example: **2a**: IR (CCl_4): ν 1720 (CO) and 3150–3400 (NH, OH) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ ppm: 5.42 (s, 1H, CHBr); 7.65 (br s, 1H, OH); 7.31–7.47 (m, 5H, Ar, NH); 2.29 (s, 3H, CH_3). ^{13}C NMR: 170.8 (dd, ^2J=3.9 and 4.0 Hz, CO); 59.4 (d, ^1J=154.2 Hz, CHBr); 127.0, 128.5, 129.8, 134.8 (Ar-ring C); 21.2 (q, ^1J=126.2 Hz, CH_3). Compound **2d**: IR (Nujol): ν 1670 (CO) and 3120 (NH) cm^{-1}. ^1H NMR ($CDCl_3$+TFA, 250 MHz) δ ppm: 5.42 (s, 1H, CHBr); 7.30–7.40 (m, 4H, Ar); 3.78 (s, 3H, OCH_3); 2.30 (s, 3H, CH_3). ^{13}C NMR: 166.8 (dd, ^2J=4.0 and 4.4 Hz, CO); 58.8 (d, ^1J=153.2 Hz, CHBr); 127.2, 128.8, 132.8, 139.4 (Ar-ring C); 21.2 (q, ^1J=126.4 Hz, CH_3); 64.5 (q, ^1J=128.4 Hz, OCH_3). HMRS calcd for $C_{10}H_{12}NO_2Br$ ($M^{+\cdot}$): 259.0865, found: 259.083. Compound **2f**: IR (Nujol): ν 1690 (CO) and 3125 (NH) cm^{-1}. ^1H NMR ($CDCl_3$+TFA, 250 MHz) δ ppm: 5.44 (s, 1H, CHBr); 7.35–7.45 (m, 5H, Ar); 3.77 (s, 3H, OCH_3). ^{13}C NMR: 166.6 (dd, ^2J=4.1 and 4.2 Hz, CO); 58.4 (d, ^1J=153.4 Hz, CHBr); 127.2, 128.8, 130.2, 135.4 (Ar-ring C); 64.4 (q, ^1J=128.1 Hz, OCH_3). HMRS calcd for $C_9H_{10}NO_2Br$ ($M^{+\cdot}$): 244.9865, found: 244.984; calcd for ($M^+ - C_2H_4NO_2$): 170.9632; found: 170.961. Compound **3c**: IR (CCl_4): ν 1720 (CO) and 3200–3400 (NH, OH) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ ppm: 5.32 (s, 1H, CH); 7.61 (br s, 1H, OH); 7.31–7.41 (m, 5H, Ar, NH); 2.28 (s, 3H, CH_3), 3.40 (s, 3H, OCH_3). ^{13}C NMR: 171.6 (s, CO); 58.3 (d, ^1J=153.2 Hz, CH); 125.7, 128.5, 132.8, 138.4 (Ar-ring C); 20.2 (q, ^1J=126.7 Hz, CH_3), 57.3 (q, ^1J=127.5 Hz, OCH_3). Compound **3f**: IR (CCl_4): ν 1680 (CO) and 3120 (NH) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ ppm: 5.36 (s, 1H, CH); 7.30–7.42 (m, 5H, Ar, NH); 3.78 (s, 3H, $HNOCH_3$); 3.40 (s, 3H, OCH_3); 2.30 (s, 3H, CH_3). ^{13}C NMR: 166.6 (dd, ^2J=4.1 and 4.2 Hz, CO); 58.2 (d, ^1J=153.5 Hz, CH); 127.8, 129.2, 132.4, 139.7 (Ar-ring C); 21.2 (q, ^1J=126.4 Hz, CH_3); 57.4 (q, ^1J=128.5 Hz, OCH_3); 64.4 (q, ^1J=128.5 Hz, $HNOCH_3$). Compound **3g**: IR (CCl_4): ν 1720 (CO) and 3300–3400 (NH, OH) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ ppm: 5.35 (s, 1H, CH); 7.70 (br s,1H, OH); 7.31–7.41 (m, 5H, Ar, NH); 2.28 (s, 3H, CH_3); 4.20 (s, 1H, OH). Compound **3p**: IR (CCl_4): ν 1720 (CO) and 3210–3330 (NH, OH) cm^{-1}. ^1H NMR ($CDCl_3$, 250 MHz) δ ppm: 5.03 (s, 1H, CH); 7.61 (br s, 1H, OH); 7.31–7.42 (m, 5H, Ar, NH); 2.52 (d, 3H, NCH_3); 2.28 (s, 3H, CH_3). ^{13}C NMR: 169.5 (s, CO); 52.5 (d, ^1J=152.6 Hz, CH); 127.8, 129.2, 132.4, 139.7 (Ar-ring C); 20.2 (q, ^1J=126.7 Hz, CH_3); 51.3 (q, ^1J=126.5 Hz, NCH_3). HMRS calcd for $C_{10}H_{14}N_2O_2$ ($M^{+\cdot}$): 194.1055, found: 194.104. Compound **5g**: IR (Nujol): ν 1720 (CO) and 3400 (OH) cm^{-1}. ^1H NMR ($CDCl_3$+TFA, 250 MHz) δ ppm: 5.36 (s, 1H, CH); 7.22 (m, 4H, Ar); 2.30 (s, 3H, CH_3). HMRS calcd for $C_9H_{10}O_3$ ($M^{+\cdot}$): 166.0629, found: 166.062. Anal. calcd: C, 65.06; H, 6.02. Found: C, 64.94; H, 5.98. Compound **5k**: IR (Nujol): ν 15900 (CO), 2700 (NH) and 3060 (OH) cm^{-1}. ^1H NMR ($CDCl_3$+TFA, 250 MHz) δ ppm: 5.31 (s, 1H, CH); 7.25–7.40 (m, 9H, Ar); 2.30 (s, 3H, CH_3). ^{13}C NMR: 173.4 (s, CO); 58.9 (d, ^1J=153.5 Hz, CH); 127.8, 129.2, 132.4, 139.7 (Ar-ring C); 21.2 (q, ^1J=126.4 Hz, CH_3). HMRS calcd for $C_{15}H_{15}NO_2$ ($M^{+\cdot}$): 241.1103, found: 241.109. Anal. calcd: C, 74.69; H, 6.22; N, 5.81. Found: C, 74.37; H, 6.16; N, 5.77.
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