



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

Saïd Boukhris and Abdelaziz Souizi *

Laboratoire de Synthèse Organique et d'Agrochimie, Département de Chimie, Faculté des Sciences, Université Ibn Tofail,
B.P 133 Kénitra, Morocco

Received 23 January 2000; accepted 7 February 2000

Abstract

The nucleophilic ring opening of *gem*-dicyanoepoxides by LiBr or Li₂NiBr₄, in the presence of hydroxylamine derivatives leads to new α -halo hydroxamic acids. These compounds have been used in the synthesis of α -functionalized hydroxamic acids, α -hydroxy and α -amino acids in good yields. © 2000 Published by Elsevier Science Ltd. All rights reserved.

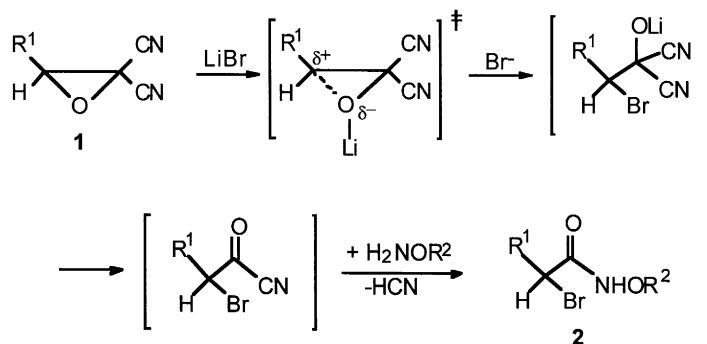
Although α -halo hydroxamic acids are well-known compounds, prepared from α -halo acids chlorides and hydroxylamines,^{1,2} most of them are in the alkyl series, only a few are known in the aryl series,³ as the accessibility of α -halo acids chlorides is not as easy.^{1,2} However, structurally diversified 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 (Na₂SO₄), 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

* Corresponding author.



Scheme 1.

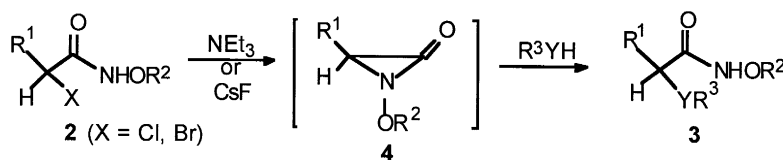
Table 1
Synthesis of α -bromo hydroxamic acids 2

Entry	R ¹	R ²	Products (Yield %, m. p °C)
a	4-CH ₃ C ₆ H ₄	H	2a (84, oil)
b	4-ClC ₆ H ₄	H	2b (86, oil)
c	C ₆ H ₅	H	2c (85, oil)
d	4-CH ₃ C ₆ H ₄	CH ₃	2d (88, 142-3)
e	4-ClC ₆ H ₄	CH ₃	2e (86, 114-5)
f	C ₆ H ₅	CH ₃	2f (82, 90-1)
g	4-NO ₂ C ₆ H 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 phebestin¹³ and probestin¹⁴ 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

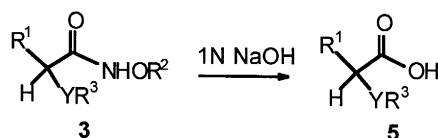
Table 2
Synthesis of α -alkoxy, α -hydroxy and α -amino hydroxamic acids **3**

Entry	R ¹	R ²	YR ³	Conditions	Products (Yields %) ^a
a	4-CH ₃ C ₆ H ₄	H	OEt	EtOH, 1h, reflux, NEt ₃	3a (84)
b	4-ClC ₆ H ₄				3b (86)
c	4-CH ₃ C ₆ H ₄		OMe	MeOH, 1h, reflux, NEt ₃	3c (85)
d	4-ClC ₆ H ₄				3d (87)
e	4-CH ₃ C ₆ H ₄	CH ₃	OEt	EtOH, 1h, reflux, NEt ₃	3e (80)
f	4-CH ₃ C ₆ H ₄		OMe	MeOH, 1h, reflux, NEt ₃	3f (81)
g	4-CH ₃ C ₆ H ₄	H	OH	Dioxan-H ₂ O, 20h, r. t., CsF	3g (75)
h	4-ClC ₆ H ₄				3h (76)
i	4-MeC ₆ H ₄	CH ₃			3i (80)
j	4-ClC ₆ H ₄				3j (82)
k	4-CH ₃ C ₆ H ₄	H	NHC ₆ H ₅	CH ₃ CN, 3h, reflux	3k (75)
l	4-ClC ₆ H ₄				3l (75)
m	4-CH ₃ C ₆ H ₄		NHEt		3m (76)
n	4-ClC ₆ H ₄				3n (74)
o	4-CH ₃ C ₆ H ₄	CH ₃	N(Et) ₂		3o (73)
p	4-CH ₃ C ₆ H ₄	H	NHMe		3p (72)
r	Et		NHC ₆ H 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).



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 ₃ C ₆ H ₄	OH	CH ₃ CN, reflux, 3h	5g (85)	143-4 (Lit. ¹¹ 145)
3h	4-ClC ₆ H ₄			5h (86)	137-8
3k	4-CH ₃ C ₆ H ₄	NHC ₆ H ₅	dioxan, reflux, 24h	5k (80)	174-5 (Lit. ¹¹ 174)
3l	4-ClC ₆ H 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 CH₃CN 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.

References

- Lai, J. T. *Tetrahedron Lett.* **1982**, 23, 595–598 and references cited therein.
- Ogata, Y.; Harade, T.; Mat Suyama, K.; Ikejiri, T. *J. Org. Chem.* **1975**, 40, 2960–2962.
- House, H. O. *Modern Synthetic Reactions*; Benjamin: Menlo Park, 1982; p. 301.
- (a) Neilands, J. B. *Science* **1967**, 156, 1443–1444. (b) Maehr, H. *Pure Appl. Chem.* **1971**, 28, 603–636.
- Karunartne, V.; Hoveyda, H. R.; Orvig, C. *Tetrahedron Lett.* **1992**, 33, 1827–1830.
- Boukhris, S.; Souizi, A.; Robert, A. *Tetrahedron Lett.* **1996**, 37, 179–182.
- Spectral data are in full agreement with the proposed structures. For example: **2a**: IR (CCl₄): ν 1720 (CO) and 3150–3400 (NH, OH) cm⁻¹. ¹H NMR (CDCl₃, 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, CH₃). ¹³C 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, CH₃). Compound **2d**: IR (Nujol): ν 1670 (CO) and 3120 (NH) cm⁻¹. ¹H NMR (CDCl₃+TFA, 250 MHz) δ ppm: 5.42 (s, 1H, CHBr); 7.30–7.40 (m, 4H, Ar); 3.78 (s, 3H, OCH₃); 2.30 (s, 3H, CH₃). ¹³C 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, CH₃); 64.5 (q, ¹J=128.4 Hz, OCH₃). HMRS calcd for C₁₀H₁₂NO₂Br (M⁺): 259.0865, found: 259.083. Compound **2f**: IR (Nujol): ν 1690 (CO) and 3125 (NH) cm⁻¹. ¹H NMR (CDCl₃+TFA, 250 MHz) δ ppm: 5.44 (s, 1H, CHBr); 7.35–7.45 (m, 5H, Ar); 3.77 (s, 3H, OCH₃). ¹³C 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, OCH₃). HMRS calcd for C₉H₁₀NO₂Br (M⁺): 244.9865, found: 244.984; calcd for (M⁺–C₂H₄NO₂): 170.9632; found: 170.961. Compound **3c**: IR (CCl₄): ν 1720 (CO) and 3200–3400 (NH, OH) cm⁻¹. ¹H NMR (CDCl₃, 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, CH₃), 3.40 (s, 3H, OCH₃). ¹³C 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, CH₃), 57.3 (q, ¹J=127.5 Hz, OCH₃). Compound **3f**: IR (CCl₄): ν 1680 (CO) and 3120 (NH) cm⁻¹. ¹H NMR (CDCl₃, 250 MHz) δ ppm: 5.36 (s, 1H, CH); 7.30–7.42 (m, 5H, Ar, NH); 3.78 (s, 3H, HNOCH₃); 3.40 (s, 3H, OCH₃); 2.30 (s, 3H, CH₃). ¹³C 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, CH₃); 57.4 (q, ¹J=128.5 Hz, OCH₃); 64.4 (q, ¹J=128.5 Hz, HNOCH₃). Compound **3g**: IR (CCl₄): ν 1720 (CO) and 3300–3400 (NH, OH) cm⁻¹. ¹H NMR (CDCl₃, 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, CH₃); 4.20 (s, 1H, OH). Compound **3p**: IR (CCl₄): ν 1720 (CO) and 3210–3330 (NH, OH) cm⁻¹. ¹H NMR (CDCl₃, 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, NCH₃); 2.28 (s, 3H, CH₃). ¹³C 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, CH₃); 51.3 (q, ¹J=126.5 Hz, NCH₃). HMRS calcd for C₁₀H₁₄N₂O₂ (M⁺): 194.1055, found: 194.104. Compound **5g**: IR (Nujol): ν 1720 (CO) and 3400 (OH) cm⁻¹. ¹H NMR (CDCl₃+TFA, 250 MHz) δ ppm: 5.36 (s, 1H, CH); 7.22 (m, 4H, Ar); 2.30 (s, 3H, CH₃). HMRS calcd for C₉H₁₀O₃ (M⁺): 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 (CDCl₃+TFA, 250 MHz) δ ppm: 5.31 (s, 1H, CH); 7.25–7.40 (m, 9H, Ar); 2.30 (s, 3H, CH₃). ¹³C 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, CH₃). HMRS calcd for C₁₅H₁₅NO₂ (M⁺): 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.
- Khamliche, L.; Robert, A. *Tetrahedron Lett.* **1986**, 27, 5491–5494.
- (a) Baumgarten, H. E. *J. Am. Chem. Soc.* **1962**, 84, 4975–4974. (b) L'Abbé, G. *Angew. Chem., Int. Ed. Engl.* **1980**, 19, 276–280. (c) Greenwald, R. B.; Taylor, E. C. *J. Am. Chem. Soc.* **1968**, 90, 5272–5274. (d) Taylor, E. C.; Haley, N. H.; Clemens, R. J. *J. Am. Chem. Soc.* **1981**, 103, 7743–7744.
- Scrimin, P.; D'Angeli, F.; Veronese, A. C. *Synthesis* **1982**, 586–587.
- Legrel, P.; Baudy-Floc'h, M.; Robert, A. *Tetrahedron* **1988**, 44, 4805–4814.
- (a) Robottom, G. M.; Marrero, R. *J. Org. Chem.* **1975**, 40, 3783–3785. (b) Moriarty, R. M.; Hu, H. *Tetrahedron Lett.* **1981**, 22, 2747–2750.
- Nagai, M.; Kojima, F.; Naganawa, H.; Hamada, M.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1997**, 50, 82–87.
- (a) Aoyagi, T.; Yoshida, S.; Nakamura, Y.; Shigihara, Y.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1990**, 43, 143–148. (b) Yoshida, S.; Nakamura, Y.; Naganawa, H.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1990**, 43, 149–154.