

Synthesis of Novel α -keto Hydroxamic Acids

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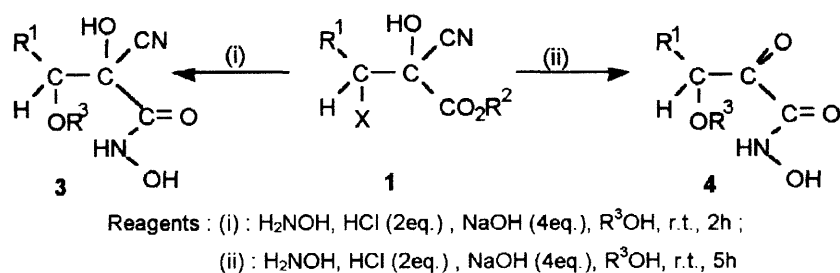
Abstract : Simple conditions are described to afford modified α -keto hydroxamic acids by reaction of halohydrins with hydroxylamine hydrochloride. © 1998 Published by Elsevier Science Ltd. All rights reserved.

In recent years hydroxamic acid derivatives have received increasing attention due to their biological activity especially as enzyme inhibitors,¹ and metal chelators.² Moreover, the hydroxamic acids constitute an important class of siderophores, which play a major role in iron-solubilisation and transport.³ Some of these compounds have already found applications as therapeutic agents, and the possibility of using them in drug delivery systems has been recently discussed.⁴ Although the synthetic methods of hydroxamic acids are well documented, the methods for the synthesis of α -keto and α -cyano- α -hydroxy hydroxamic acids are limited.

In connection with a research program aimed at the synthesis of new hydroxamic acids, we discovered a simple and general route for the preparation of novel α -keto and α -cyano- α -hydroxy hydroxamic acids starting from the easily accessible halohydrins **1**.⁵

In a typical experiment, α -cyano- β -halo- α -hydroxy esters **1** in alcohol (R^3OH) were treated with an excess of hydroxylamine hydrochloride (2 equivalents) and sodium hydroxide (4 equivalents) in water. After stirring for 2h at room temperature, the solution was washed with water, extracted with diethyl ether and evaporated. The crude product was chromatographed over silica-gel (hexane/ ethyl acetate 4/1 as eluent) to afford the pure α -cyano- α -hydroxy hydroxamic acids **3** (scheme 1) in the yields indicated in table 1 (entries a-c). Similarly, the halohydrin **1** yielded, under same conditions but for 5h, α -keto hydroxamic acid **4** (scheme 1) which was recrystallized from benzene or chromatographed over silica-gel (hexane/ ethyl acetate 4/1 as eluent). Various synthesized hydroxamic acids are listed in Table 1(entries a-i).

The structures were confirmed by their intense red color with $FeCl_3$, and spectroscopic data.



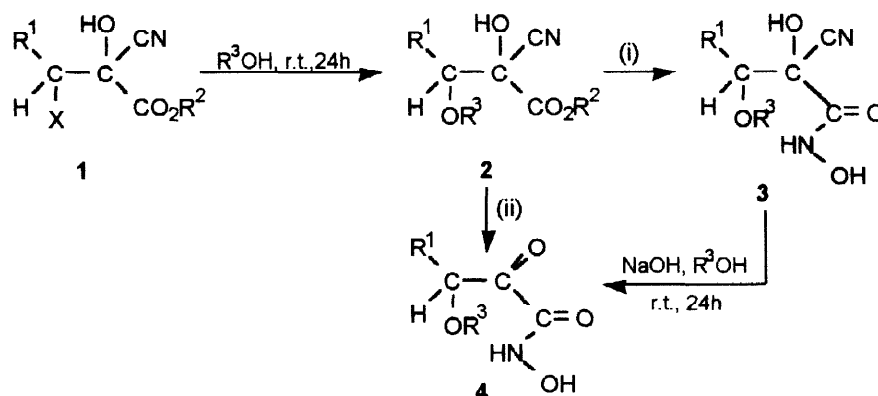
Scheme 1

The reaction was assumed to proceed by the regioselective substitution of the halohydrins **1** to the corresponding β -alkoxy esters **2** which then immediately react with hydroxylamine to yield the α -cyano- α -hydroxy hydroxamic acids **3** and subsequently α -keto hydroxamic acids **4** were obtained. Note that the halohydrins **1** react with alcohol in the presence of sodium hydroxide to give only β -alkoxy esters **2** in good yields (scheme 2).

Table : Reaction of halohydrins **1** with hydroxylamine hydrochloride.

Entry	Substrate	R ¹	R ²	X	R ³	Reaction time (h)	Products (yield, mp °C)
a	1a	4-MeC ₆ H ₄	Et	Cl	Et	2	3a (68, oil)
b	1b	4-ClC ₆ H ₄	Et	Cl	Et	2	3b (68, oil)
c	1f	4-MeC ₆ H ₄	Et	Cl	Me	2	3c (67, oil)
d	1a	4-MeC ₆ H ₄	Et	Cl	Et	5	4a (70, 110-1)
e	1b	4-ClC ₆ H ₄	Et	Cl	Et	5	4b (72, 125-6)
f	1c	Et	Et	Cl	Me	5	4c (65, oil)
g	1d	4-MeC ₆ H ₄	Et	Cl	Me	5	4d (67, 104-5)
h	1e	4-MeC ₆ H ₄	Me	Cl	Et	5	4a (74, 110-1)
i	1f	4-MeC ₆ H ₄	Me	Br	Et	5	4a (70, 110-1)

In order to confirm the mechanism, we subjected β -alkoxy esters **2** as the substrate to the same reaction under the same conditions. For this purpose, **2** (R¹ = 4-MeC₆H₄, R² = Me, R³ = Et) reacts with hydroxylamine to give the corresponding α -cyano- α -hydroxy hydroxamic acid **3** or α -keto hydroxamic acid **4** (scheme 2).



Reagents : (i) : H₂NOH, HCl (2eq.) , NaOH (4eq.) , R³OH, r.t., 2h ;

(ii) : H₂NOH, HCl (2eq.) , NaOH (4eq.) , R³OH, r.t., 5h

Scheme 2

We have also verified that the α -cyano- α -hydroxy hydroxamic acids **3** reacted with sodium hydroxide in alcohol at room temperature for 3h to give exclusively the α -keto hydroxamic acids **4**, after loss of hydrogen cyanide. The solvent plays an important role in these reactions; thus, when these latter are run in acetonitrile, the halohydrins **1** gave the corresponding epoxides, and the derivatives **2** were recovered unchanged.

In conclusion, we have presented a facile, simple and efficient method for the preparation of novel hydroxamic acids using α -cyano- β -halo- α -hydroxy esters. Further studies of these reactions are under investigation.

References and Notes

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