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Short and Efficient Synthesis of new α-Oximino Esters

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Abstract: α-Cyano α-alkoxy carbonyl epoxides **1** react, in refluxing alcohol, with hydroxylamine hydrochloride **2** in a direct ring opening reaction to give β-alkoxy α-oximino esters **4** in good yields. We have shown that this reaction proceeds through the formation of chlorohydrins **3**. Copyright © 1996 Published by Elsevier Science Ltd

Structurally diversified oximino esters are of considerable interest due to their potentiel biological activity, as bactericide,[1] antimalarial[2] and pesticides.[3] In addition, the α-oximino esters are highly versatile class of intermediates for the synthesis of compounds exhibiting strong biological activity[4-5] and synthetic utility[6-7] such as N-hydroxy amino acids[8-10] and α-amino acids.[11-13]

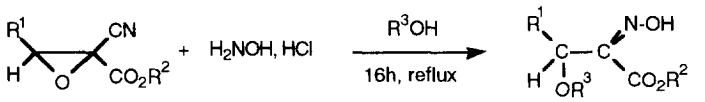
The classical methods for the synthesis of α-oximino esters are nitrosyl chloride addition to olefins,[14] nitrosation at a carbon bearing an active hydrogen,[15] addition of Grignard reagents to the conjugate bases of nitro compounds,[16] or, in some cases, a direct condensation reaction of the corresponding α-keto esters with hydroxylamine hydrochloride.[11,17]

These methods, however, have the following disadvantages: for the nitroso-chloro addition, nitrosation reaction or addition of Grignard reagents, the resulting yields are moderate, and undesirable byproducts are also produced. In the case of the condensation reaction, although this method affords the desired product in a very satisfactory yield, it suffers from poor accessibility of the various reagents, rendering a large scale exploitation difficult.

In order to overcome these disadvantages, it is of interest to examine the possibility of synthesis of α-oximino esters from epoxides . Indeed, α,α-dicyano oxiranes and α-cyano α-alkoxy carbonyl oxiranes are easily accessible,[18] and are important synthetic intermediates in organic chemistry.[19-23] Recently, we have described a direct and easy method of preparation of α-chloro hydroxamic acids, using α,α-dicyano oxiranes.[24] In theses reactions, the two carbons of cyano epoxides act as potentiel electrophilic centers.

We report here a general preparation of β-alkoxy α-oximino esters **4a-g** starting from epoxides **1**.

More explicitly, in a typical experiment, α-cyano α-alkoxy carbonyl epoxides **1** were treated with an excess of hydroxylamine hydrochloride **2** in refluxing alcohol (R^3OH) during 16 hours (scheme 1). After evaporation of the solvent, the oximes were extracted with a 5% NaOH solution. The aqueous layer was acidified to pH 2 with 1N HCl and extracted with diethyl ether. The purification by flash chromatography (hexane/ ethyl acetate 7:3 as eluent) afforded the protected β-alkoxy α-oximino esters **4a-g**, as oily products, in the yields indicated in table 1 (entries a-g).



1a-g **2** **4a-g**

Scheme 1

Table 1: Synthesis of β-alkoxy α-oximino esters 4a-g.

Entry	Substrate	R^1	R^2	Alcohol (R^3OH)	Temp. °C	Products (yield)[a]	(Z/E) ratio[b]
a	**1a**	4-MeC_6H_4	Et	EtOH	82	**4a** (75)	75/25
b	**1b**	4-ClC_6H_4	Et	EtOH	82	**4b** (73)	80/20
c	**1c**	C_6H_5	Et	EtOH	82	**4c** (70)	78/22
d	**1d**	4-MeC_6H_4	Me	EtOH	82	**4d** (75)	78/22
e	**1e**	4-ClC_6H_4	Me	EtOH	82	**4e** (74)	80/20
f	**1f**	4-MeC_6H_4	Me	MeOH	65	**4f** (74)	67/33
g	**1g**	4-ClC_6H_4	Me	MeOH	65	**4g** (73)	70/30
h	**3a**	4-MeC_6H_4	Et	EtOH	82	**4a** (87)	75/25
i	**3b**	4-ClC_6H_4	Et	EtOH	82	**4b** (83)	80/20
j	**3c**	C_6H_5	Et	EtOH	82	**4c** (75)	78/22
k	**3d**	4-MeC_6H_4	Me	EtOH	82	**4d** (84)	78/22
l	**3e**	4-ClC_6H_4	Me	EtOH	82	**4e** (82)	80/20
m	**3d**	4-MeC_6H_4	Me	MeOH	65	**4f** (82)	75/25

a. All the yields refer to isolated chromatographically pure compounds and the assigned structures have been confirmed by IR, NMR (^1H and ^{13}C), and MS data. b. The determination of the ratio is based on ^1H NMR analysis of the crude reaction mixture.

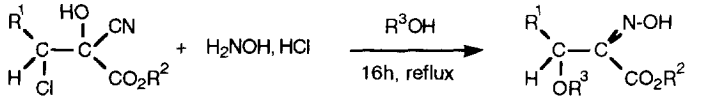
The reaction always gives a mixture of two diastereoisomers E and Z, with the latter as the major product (made possible probably by a hydrogen connection) which we did not manage to isolate by column chromatography.

The determination of the configuration of major product (Z) was also confirmed in agreement with ^{13}C NMR in accord with the results published by Roberts[25] and Nelson.[26]

The reaction was assumed to proceed by the regioselective opening of the oxirane to the corresponding chlorohydrin **3** which then immediately reacts with hydroxylamine to yield the β-alkoxy α-oximino esters **4**. Note that the gem-dicyano epoxides reacts with alcohols in the presence of halohydric acid to give only α-haloesters in good yields.[27, 23]

In order to confirm the mechanism, we subjected methyl or ethyl 3-aryl-3-chloro-2-cyano-2-hydroxy propanoates **3**[28] as the substrate to the same reaction under the same conditions. For this purpose, **3a-e** reacts with hydroxylamine hydrochloride **2** to give β-alkoxy α-oximino esters **4a-f** in good yields (scheme 2, table 1: entries h-m).

The solvent plays an important role in these reactions; thus, when these latter are realized in refluxing acetonitrile, the chlorohydrin **3** and hydroxylamine hydrochloride **2** were recovered unchanged.



3a-e **2** **4a-f**

Scheme 2

The possible mechanism of unexpected substitution of halogen by an alkoxy group is a direct substitution nucleophilic reaction. Indeed, in order to ascertain this hypothesis, we have verified that the methyl 3-chloro-3-(4-methylphenyl)-2-cyano-2-hydroxypropanoate **3d** reacted with ethanol at room temperature for 24h or at reflux for 3h to give exclusively the substitution product methyl 3-ethoxy-3-(4-methylphenyl)-2-cyano-2-hydroxypropanoate **5d**.[29]

In conclusion, the reaction described here appears to be an efficient, simple and mild method for the synthesis of β-alkoxy α-oximino esters **4a-g**. The analysis of the mechanism shows that the reaction proceeds through the formation of chlorohydrin **3**. This method for preparing the α-oximino esters **4** constitutes an excellent complement to existing procedures. We are presently attempting to develop this method to synthesize amino acids.

Spectral data[30] of selected compounds:

Ethyl 3-ethoxy-3-(4-methylphenyl)-2-hydroxyiminopropanoate **4a**:
Oil; two isomers (E/Z): IR (CCl_4) ν : 3300 (OH); 1600 (C=N) and 1720 (CO).
^1H NMR ($CDCl_3$) δ: 7.12-7.43 (m, 4H, Ar); 2.32 (s, 3H, CH_3); 1.24 (t, 3H, $CO_2CH_2\underline{CH_3}$); 4.22 (q, 2H, $CO_2\underline{CH_2}CH_3$); 9.9 (s, 1H, OH); 1.24 (t, 3H, $OCH_2\underline{CH_3}$); 3.58 (q, 2H, $O\underline{CH_2}CH_3$); 5.96 (s, 1H, CH, isomer Z); 5.15 (s, 1H, CH, isomer E).
^{13}C NMR: isomer Z δ: 125.5, 128.9, 134.7, 137.5 (Ar-ring C); 20.2 (q, ^1J= 126.3, CH_3); 61.75 (t, ^1J= 148.4, $CO_2\underline{CH_2}CH_3$); 13.98 (q, ^1J= 127.4, $CO_2CH_2\underline{CH_3}$); 79.7 (d, ^1J= 146.6, CH); 151.6 (d, ^2J= 4, C=N); 162.2 (s, CO); 65.8 (t, ^1J= 141.6, $O\underline{CH_2}CH_3$); 15.18 (q, ^1J= 126.4, $OCH_2\underline{CH_3}$). Isomer E δ: 127.2, 129.1, 134.2, 138.0 (Ar-ring C); 20.2 (q, ^1J= 126.3, CH_3); 61.69 (t, ^1J= 148.4, $CO_2\underline{CH_2}CH_3$); 13.96 (q, ^1J= 127.4, $CO_2CH_2\underline{CH_3}$); 74.0 (d, ^1J= 144.9, CH); 152.0 (d, ^2J= 4, C=N); 162.4 (s, CO); 65.08 (t, ^1J= 141.6, $O\underline{CH_2}CH_3$); 15.05 (q, ^1J= 126.4, $OCH_2\underline{CH_3}$). HRMS calc. for $C_{14}H_{19}NO_4$: 265,1314; found: 265,131.

Ethyl 3-ethoxy-3-phenyl-2-hydroxyiminopropanoate **4c**:
Oil; two isomers (E/Z): IR (CCl_4) ν : 3415 (OH); 1610 (C=N) and 1740 (CO).
^1H NMR ($CDCl_3$) δ: 7.29-7.49 (m, 5H, Ar); 1.23 (t, 3H, $CO_2CH_2\underline{CH_3}$); 4.21 (q, 2H, $CO_2\underline{CH_2}CH_3$); 9.92 (s, 1H, OH); 1.23 (t, 3H, $OCH_2\underline{CH_3}$); 3.61 (q, 2H, $O\underline{CH_2}CH_3$); 5.99 (s, 1H, CH, isomer Z); 5.20 (s, 1H, CH, isomer E).
^{13}C NMR: isomer Z δ: 126.5, 127.7, 128.2, 137.8 (Ar-ring C); 61.7 (t, ^1J= 148.4, $CO_2\underline{CH_2}CH_3$); 13.88 (q, ^1J= 127.4, $CO_2CH_2\underline{CH_3}$); 79.76 (d, ^1J= 148.4, CH); 151.54 (d, ^2J= 4.15, C=N); 162.2 (s, CO); 65.84 (t, ^1J= 141.8, $O\underline{CH_2}CH_3$); 15.15 (q, ^1J= 126.4, $OCH_2\underline{CH_3}$). Isomer E δ: 127.1, 128.4, 128.8, 137.2 (Ar-ring C); 61.7 (t, ^1J= 148.4, $CO_2\underline{CH_2}CH_3$); 13.88 (q, ^1J= 127.4, $CO_2CH_2\underline{CH_3}$); 73.65 (d, ^1J= 146.7, CH); 151.98 (d, ^2J= 4.2, C=N); 162.34 (s, CO); 65.12 (t, ^1J= 141.8, $O\underline{CH_2}CH_3$); 14.99 (q, ^1J= 126.4, $OCH_2\underline{CH_3}$). HRMS calc. for $C_{13}H_{16}NO_3$ $(M - OH\cdot)^+$: 234,1157; found: 234.114

Methyl 3-ethoxy-3-(4-methylphenyl)-2-hydroxyiminopropanoate **4d**:
Oil; two isomers (E/Z): IR (CCl_4) ν : 3420 (OH); 1615 (C=N) and 1740 (CO).
^1H NMR ($CDCl_3$) δ: 7.12-7.40 (m, 5H, Ar); 2.32 (s, 3H, CH_3); 3.74 (s, 3H, CO_2CH_3); 9.85 (s, 1H, OH); 1.24 (t, 3H, $OCH_2\underline{CH_3}$); 3.59 (q, 2H, $O\underline{CH_2}CH_3$); 5.93 (s, 1H, CH, isomer Z); 5.17 (s, 1H, CH, isomer E).
^{13}C NMR: isomer Z δ: 126.6, 129.0, 134.6, 137.6 (Ar-ring C); 21.2 (q, ^1J= 126.6, CH_3); 52.58 (q, ^1J= 147.8, CO_2CH_3); 79.69 (d, ^1J= 146.6, CH); 151.6 (d, ^2J= 3.9, C=N); 162.7 (s, CO); 65.94 (t, ^1J= 141.7, $O\underline{CH_2}CH_3$); 15.0 (q, ^1J= 126.4, $OCH_2\underline{CH_3}$). Isomer E δ: 127.2, 129.1, 134.2, 138.0 (Ar-ring C); 21.2 (q, ^1J= 126.6, CH_3); 52.35 (q, ^1J= 147.8, CO_2CH_3); 74.20 (d, ^1J=144.7, CH); 151.91 (d, ^2J= 3.9, C=N); 162.87 (s, CO); 65.15 (t, ^1J= 141.7, $O\underline{CH_2}CH_3$); 14.97 (q, ^1J= 126.4, $OCH_2\underline{CH_3}$). HRMS calc. for $C_{13}H_{16}NO_3$ $(M - OH\cdot)^+$: 234,1157; found: 234.115

Methyl 3-ethoxy-3-(4-chlorophenyl)-2-hydroxyiminopropanoate **4e**:
Oil; two isomers (E/Z): IR ν : 3420 (OH); 1610 (C=N) and 1740 (CO).
^1H NMR ($CDCl_3$) δ: 7.26-7.43 (m, 4H, Ar); 3.74 (s, 3H, CO_2CH_3); 9.87 (s, 1H, OH); 1.23 (t, 3H, $OCH_2\underline{CH_3}$); 3.58 (q, 2H, $O\underline{CH_2}CH_3$); 5.92 (s, 1H, CH, isomer Z); 5.15 (s, 1H, CH, isomer E).
^{13}C NMR: isomer Z δ: 127.9, 128.5, 133.5, 136.3 (Ar-ring C); 52.63 (q, ^1J= 148.0, CO_2CH_3); 79.10 (d, ^1J= 147.0, CH); 151.16 (d, ^2J= 4.1, C=N); 162.5 (s, CO); 66.0 (t, ^1J= 141.8, $O\underline{CH_2}CH_3$); 15.14 (q, ^1J= 126.4, $OCH_2\underline{CH_3}$). Isomer E δ: 128.0, 128.6, 134.2, 135.2 (Ar-ring C); 52.43 (q, ^1J= 148.0, CO_2CH_3); 72.97 (d, ^1J= 145.7, CH); 151.66 (d, ^2J= 4.1, C=N); 162.6 (s, CO); 65.38 (t, ^1J= 141.8, $O\underline{CH_2}CH_3$); 14.38 (q, ^1J= 126.4, $OCH_2\underline{CH_3}$). HRMS calc. for $C_{12}H_{14}NO_4Cl$: 271,0611; found: 271,0615.

Ethyl 3-chloro-3-(4-methylphenyl)-2-cyano-2-hydroxypropanoate **3a**:
Oil; IR (CCl_4) ν : 1740 (CO); 3430 (OH); 2250 (CN).
^1H NMR ($CDCl_3$) δ: 7.50-7.60 (m, 4H, Ar); 4.5 (s, 1H, OH); 1.20 (t, 3H, $OCH_2\underline{CH_3}$); 4.40 (q, 2H, $O\underline{CH_2}CH_3$); 5.50 (s, 1H, CH); 2.40 (s, 3H, CH_3), 76.4 (sd, ^2J= 3.7, $\underline{C}$-CN).
^{13}C NMR: δ: 128.5, 128.9, 130.9, 139.0 (Ar-ring C); 62.7 (d, ^1J= 155.5, CH); 116.3 (s, CN); 166.0 (s, CO); 61.90 (t, ^1J= 144.5, $O\underline{CH_2}CH_3$); 13.5 (q, ^1J= 120.0, $OCH_2\underline{CH_3}$); 20.6 (q, ^1J= 126.1, CH_3).

Methyl 3-chloro-3-(4-chlorophenyl)-2-cyano-2-hydroxypropanoate **3e**:
Mp= 115 °C (CCl_4) (lit.[31] mp = 113°C); IR (KBr) ν : 1755 (CO); 3360 (OH); 2250 (CN).
^1H NMR (DMSO-d_6) δ: 7.50-7.60 (m, 4H, Ar); 4.25 (s, 1H, OH); 3.80 (s, 3H, OCH_3); 5.50 (s, 1H, CH).
^{13}C NMR: δ: 128.4, 130.8, 132.9, 134.3 (Ar-ring C); 61.5 (d, ^1J= 159.7, CH); 116.3 (s, CN); 166.0 (s, CO); 53.9 (q, ^1J= 149.4, OCH_3); 76.6 (sd, ^2J= 3.7, $\underline{C}$-CN).

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28. The compounds **3** are prepared by reacting the epoxides **1** with hydrochloric acid in ether, at room temperature for 5h. We believe that this new approch to chlorohydrins compares favorably with existing methods, and shows interesting and promising results for further development. The chlorohydrins products are obtained with good to excellent chemical yields and regioselectivity, as well as trans- stereoselectivity. The structure of chlorohydrin **3** was confirmed by comparaison with authentic samples.[31]
29. Methyl 3-ethoxy-3-(4-methylphenyl)-2-cyano-2-hydroxypropanoate **5d**: Yield 90 %; IR (CCl_4, ν cm^{-1}): 1740 (CO); 2250 (CN); 3400 (OH). ^1H NMR (60MHz, $CDCl_3$) δ: 3.82 (s, 3H, CH_3); 4.25 (s, 1H, OH); 5.25 (s, 1H, CH); 7.25-7.45 (m, 4H, Ar); 3.85 (q, 2H, $O\underline{CH_2}CH_3$); 1.13 (t, 3H, $OCH_2\underline{CH_3}$).
30. ^1H NMR spectra were recorded at 300 MHz on a WP 300 BRUKER spectrometer and ^{13}C NMR spectra were at 75 MHz on a AM 300 BRUKER spectrometer. ^1H and ^{13}C chemical shifts (δ) are given in ppm relative to TMS as internal standard. Coupling constants (J) are given in hertz. ν are given in cm^{-1}. The major isomer is expected on the basis of steric hindrance and hydrogen connection to have the OH syn to the carbonyl carbon. With this assumption, and with the aid of the results published by Roberts and Nelson, the individual resonances can be assigned to particular carbons of all of these oximes.
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