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Synthesis of β-chloro-α-cyano-α-hydroxyesters

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Summary — Regioselective ring opening of 3-aryl-2-cyano 2-(methoxy and ethoxycarbonyl) oxiranes **1** with chlorhydric acids gave halohydrins **3** with OH, CN and CO_2Me or CO_2Et on the same carbon atom.

oxirane / β-chloro-α-cyano-α-hydroxyester / ketoester / regio-stereoselectivity

Résumé — Synthèse de β-chloro-α-hydroxyesters. L'ouverture régiosélective des 3-aryl-2-cyano-2-(méthoxy et éthoxycarbonyl)époxydes **1** par l'acide chlorhydrique, conduit à des chlorocyanhydrines **3** substituées par OH, CN et CO_2Me ou CO_2Et sur le même atome de carbone.

époxyde / β-chloro-α-cyano-α-hydroxyester / cétoester / régio-stéréosélectivité

Introduction

Halohydrins have attained considerable importance in organic synthesis [1]. They can be utilized for some useful synthetic transformations [2], and are also key intermediates in the synthesis of halogenated marine natural products [3]. Halohydrins with OH and CN on the same carbon atom have synthetic value because they are interesting starting materials for the synthesis of β-halo-α-amino acids [4]. Recently, special attention has been paid to the preparation of halohydrins as a method for introducing a halogen atom into organic compounds [5].

The syntheses of halohydrins from the ring-opening reaction of epoxides by hydrogen fluoride [6], pyridine polyhydrofluoride [7, 8], and silica-gel-supported metal halides (copper(II) bromide, zinc bromide and ferric chloride) [9] have been widely investigated.

Cyano epoxides are known to undergo regiospecific ring opening. The reaction of *gem*-dicyano epoxides with halohydric acids generates an α-halocyanoformyl intermediate, which can be trapped with a nucleophile [10–12]. α-Bromoketones are obtained via Li_2NiBr_4 [13] or bromohydric acid [10] ring opening of cyano epoxides. Mesoionic dithioles have been prepared by ring opening of *gem*-dicyano epoxides with piperidinium dithiocarbamates [14].

In this communication, we focus on the preparation of halohydrins **3** with OH, CN and CO_2R on the same carbon atom by reaction of cyano ester oxiranes **1**, with particular emphasis on the regio- and chemoselective control of the ring opening.

Both the solvent and the temperature have an important influence on the outcome of the reaction. Thus, when ether is used, the synthesis of chlorohydrins is performed by reacting 3-aryl-2-cyano-2-(methoxy- and ethoxycarbonyl)oxiranes **1** with chlorohydric acid at room temperature.

Table I gives the prepared functionalized halohydrins **3a–f**. Because the medium is acidic, the formation of halohydrins **3** with the hydroxy, cyano and ester groups on the same carbon atom cannot be explained without assuming the existence of a benzylic epoxonium carbocation intermediate **2**. Furthermore, the reaction regioselectivity indicates that the anion Cl^- reacts on the benzylic epoxonium intermediate as shown above.

The ring opening of 3-aryl-2-cyano-2-(methoxy- and ethoxycarbonyl)oxiranes **1a,b** in refluxing acetonitrile for 3 h gave mixtures of halohydrins **3a,b** and the ketoesters corresponding **4a,b** (scheme 1; table I, entries g and h).

When this reaction used the chlorohydrin **3a,b** as the substrate under these conditions for 18 h in the presence of silica gel, it was converted into the ketoester corresponding to **4a,b** (scheme 1; table I: entries i and j), after loss of hydrogen cyanide. A similar elimination of hydrogen cyanide has been observed during the regioselective ring opening of the *gem*-dicyano epoxide [12, 13, 16].

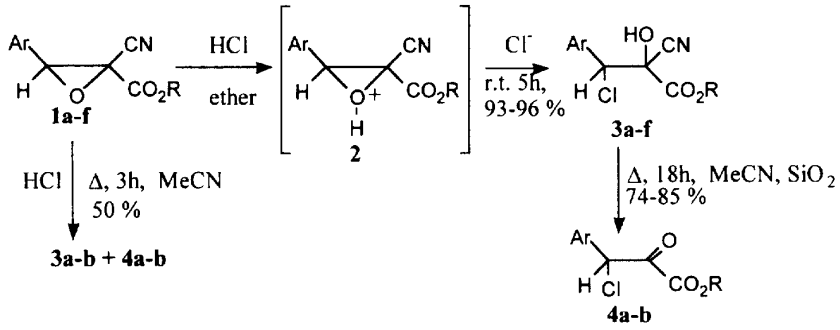
In order to confirm the structure of the chlorohydrin **3** and to ascertain that its formation is in accordance with the postulated benzylic epoxonium **2**, we verified that when the chlorohydrin **3a** was treated with Na_2CO_3 at room temperature for 2 h it gave the corresponding epoxide **1a** (scheme 2; table I: entry k).

* Correspondence and reprints

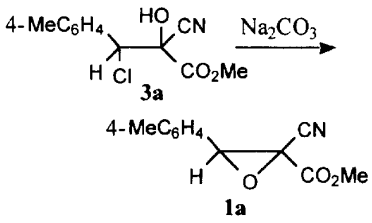
Table I. Experimental details and physical data for halohydrins **3** and α-ketoesters **4**.

Entry	*Substrate*	*Ar*	*R*	*Conditions*	*Product (yield %)*	*mp °C (Lit)*
a	**1a**	4-MeC_6H_4	Me	Et_2O, rt, 5 h	**3a** (93)[a]	101–102
b	**1b**	4-ClC_6H_4	Et	Et_2O, rt, 5 h	**3b** (97)[b]	Oil
c	**1c**	C_6H_5	Me	Et_2O, rt, 5 h	**3c** (90)[a]	98 (97 [9])
d	**1d**	4-ClC_6H_4	Me	Et_2O, rt, 5 h	**3d** (95)[a]	115 (113 [9])
e	**1e**	4-MeC_6H_4	Et	Et_2O, rt, 5 h	**3e** (96)[b]	Oil
f	**1f**	C_6H_5	Et	Et_2O, rt, 5 h	**3f** (93)[b]	Oil
g	**1a**	4-MeC_6H_4	Me	MeCN, reflux, 3 h	**3a** (50)[c] + **4a** (50)[c]	Oil
h	**1b**	4-ClC_6H_4	Et	MeCN, reflux, 3 h	**3b** (50)[c] + **4b** (50)[c]	Oil
i	**3a**	4-MeC_6H_4	Me	MeCN, reflux, SiO_2, 18 h	**4a** (85)[b]	Oil
j	**3b**	4-ClC_6H_4	Et	MeCN, reflux, SiO_2, 18 h	**4b** (74)[a]	175–176
k	**3a**	4-MeC_6H_4	Me	MeCN, rt, Na_2CO_3, 2 h	**1a** (86)	93 (93 [15])

[a] Yields of isolated, purified product. The solid compounds **3a, 3c, 3d** and **4d** can be recrystallized from carbon tetrachloride. [b] Isolated yields after flash chromatography on silica gel hexane/ethyl acetate 3:2 as eluent. [c] The determination of the ratio is based on ^1H NMR analysis of the crude reaction mixture.



Scheme 1



Scheme 2

Conclusion

In conclusion, the method described here appears to be an efficient, mild and simple method for the synthesis of β-chloro-α-cyano-α-hydroxyesters. In addition, the advantages of high regio- and stereoselectivity, high yields and relatively short reaction times make this method a useful addition to the present methodologies in organic synthesis.

Experimental section

^1H NMR spectra were at 300 MHz on a WP 300 Bruker spectrometer and ^{13}C NMR spectra 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. IR spectra were determined with a Perkin Elmer 1600 Series FTIR spectrometer. Melting points were taken with a Kofler hot stage apparatus and are uncorrected.

β-Chloro-α-cyano-α-hydroxyesters **3**. *General procedure*

To a solution of chlorhydric acid (14 mL) in diethyl ether (10 mL), *gem*-cyano ester oxiranes **1** (10 mmol) dissolved in Et_2O (10 mL) were added dropwise at 25 °C. The reaction mixture was stirred at this temperature for 5 h. The mixture was shaken with cold water (50 mL) and extracted. The combined organic extracts were washed with water and finally dried over Na_2SO_4. After evaporation of the solvent, the β-chloro-α-cyano-α-hydroxyesters **3** were recrystallized or purified by flash chromatography.

- *Methyl 3-chloro-2-cyano-2-hydroxy-3-(4-methylphenyl)propanoate* **3a**

IR (KBr): ν = 1 745 (CO), 2 240 (CN), 3 375 (OH) cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.8 (s, 3H, OCH_3), 4.25 (s, 1H, OH), 5.5 (s, 1H, CH), 7.40–7.5 (m, 4H, Ar), 2.30 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 53.9 (q, ^1J = 149.1, OCH_3), 62.5 (d, ^1J = 158.7, CH), 76.8 (d, ^2J = 3.7, *C*CN), 116.5 (s, CN), 128.5, 128.9, 130.9, 139.0 (Ar-ring C), 166.3 (s, CO), 20.6 (q, ^1J = 126.1, CH_3).

- *Ethyl 3-chloro-3-(4-chlorophenyl)-2-cyano-2-hydroxypropanoate* **3b**

IR (KBr): ν = 1 745 (CO), 3 430 (OH), 2 250 (CN) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.3 (t, 3H, OCH_2CH_3), 4.5 (q, 2H, OCH_2CH_3), 5.9 (s, 1H, OH), 5.5 (s, 1H, CH), 7.5–7.6 (m, 4H, Ar).

^{13}C NMR ($CDCl_3$): δ = 13.5 (q, ^1J = 127.2, OCH_2CH_3), 61.9 (t, ^1J = 144.55, OCH_2CH_3), 62.6 (d, ^1J = 156.3, CH), 76.4 (d, ^2J = 3.7, *C*CN), 166.0 (s, CO), 128.5, 129.1, 130.4, 133.4 (Ar-ring C), 116.3 (s, CN).

HRMS: calc for $C_{11}H_{10}O_3Cl_2$ $[M - HCN]^{+\cdot}$: 260.0007, found 260.001.

• *Methyl 3-chloro-2-cyano-2-hydroxy-3-phenylpropanoate* **3c**

IR ($CHCl_3$): ν = 1 750 (CO), 2 260 (CN), 3 400 (OH) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 3H, OCH_3), 4.30 (s, 1H, OH), 5.5 (s, 1H, CH), 7.40 (s, 5H, Ar).

^{13}C NMR ($CDCl_3$): δ = 53.9 (q, ^1J = 149.2, OCH_3), 62.4 (d, ^1J = 158.7, CH), 76.7 (d, ^2J = 3.6, *C*CN), 116.4 (s, CN), 128.5, 129.1, 130.4, 133.4 (Ar-ring C), 166.4 (s, CO).

HRMS: calc for $C_{11}H_{10}NO_3Cl$ $[M]^{+\cdot}$: 239.034, found 239.032.

• *Methyl 3-chloro-3-(4-chlorophenyl)-2-cyano-2-hydroxypropanoate* **3d**

IR (KBr): ν = 1 755 (CO), 2 250 (CN), 3 360 (OH) cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.8 (s, 3H, OCH_3), 4.25 (s, 1H, OH), 5.5 (s, 1H, CH), 7.5–7.6 (m, 4H, Ar).

^{13}C NMR (DMSO-d_6): δ = 53.9 (q, ^1J = 149.4, OCH_3), 61.5 (d, ^1J = 159.7, CH), 76.6 (d, ^2J = 3.7, *C*CN), 116.3 (s, CN), 128.4, 130.8, 132.9, 134.3 (Ar-ring C), 166.0 (s, CO).

• *Ethyl 3-chloro-2-cyano-2-hydroxy-3-(4-methylphenyl)propanoate* **3e**

IR ($CHCl_3$): ν = 1 760 (CO), 2 250 (CN), 3 350 (OH) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.2 (t, 3H, OCH_2CH_3), 4.4 (q, 2H, OCH_2CH_3), 4.5 (s, 1H, OH), 5.5 (s, 1H, CH), 7.5–7.6 (m, 4H, Ar), 2.4 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 13.5 (q, ^1J = 128.0, OCH_2CH_3), 61.9 (t, ^1J = 144.5, OCH_2CH_3), 116.3 (s, CN), 62.7 (d, ^1J = 155.5, CH), 76.6 (d, ^2J = 3.7, *C*CN), 166.0 (s, CO), 128.5, 128.9, 130.9, 139.0 (Ar-ring C), 20.6 (q, ^1J = 126.1, CH_3).

HRMS: calc for $C_{12}H_{13}O_3Cl$ $[M - HCN]^{+\cdot}$: 240.055; found 240.054.

• *Ethyl 3-chloro-2-cyano-2-hydroxy-3-phenylpropanoate* **3f**

IR ($CHCl_3$): ν = 1 750 (CO), 2 260 (CN), 3 500 (OH) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.28 (t, 3H, OCH_2CH_3), 4.35 (q, 2H, OCH_2CH_3), 4.30 (s, 1H, OH), 5.5 (s, 1H, CH), 7.35 (s, 5H, Ar).

^{13}C NMR ($CDCl_3$): δ = 13.6 (q, ^1J = 127.5, OCH_2CH_3), 61.8 (t, ^1J = 145.0, OCH_2CH_3), 62.6 (d, ^1J = 157.8, CH), 76.5 (d, ^2J = 3.5, *C*CN), 116.4 (s, CN), 129.0, 129.5, 131.5, 132.6 (Ar-ring C), 166.0 (s, CO).

HRMS: calc for $C_{11}H_{11}O_3Cl$ $[M - HCN]^{+\cdot}$: 226.039; found 226.039.

α-Ketoesters **4**. *General procedure*

A solution of β-chloro-α-cyano-α-hydroxyesters **3** (0.24 mmol) in acetonitrile (10 mL) was added to silica gel (1 g). The mixture was heated at 78 °C for 18 h. The silica gel was filtered off. Removal of acetonitrile gave α-ketoesters **4**.

• *Methyl 3-chloro-3-(4-methylphenyl)-2-oxopropanoate* **4a**

IR ($CHCl_3$): ν = 1 735, 1 740 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 3.8 (s, 3H, OCH_3), 6.4 (s, 1H, CH), 7.5–7.7 (m, 4H, Ar), 2.3 (s, 3H, CH_3).

This structure was ascertained by comparison with an authentic sample [9].

• *Ethyl 3-chloro-3-(4-chlorophenyl)-2-oxopropanoate* **4b**

IR (KBr): ν = 1 730, 1 740 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 3.96 (q, 2H, OCH_2CH_3), 1.13 (t, 3H, OCH_2CH_3), 6.35 (s, 1H, CH), 7.34–7.54 (m, 4H, Ar).

^{13}C NMR (DMSO-d_6), δ = 13.54 (q, ^1J = 127.2, OCH_2CH_3), 61.90 (t, ^1J = 144.62, OCH_2CH_3), 62.69 (d, ^1J = 156.3, CH), 167.82 (t, ^3J = 3.2, $CO_2CH_2CH_3$), 168.81 (s, CO), 128.5, 129.1, 130.4, 133.4 (Ar-ring C).

References

1 Bartlett PA, In *Asymmetric Synthesis* (Norrison JD, Ed), Academic, Orlando, FL, 1984, 3, 411

2 For a selection of transformation see:
a) Tarasow TM, *J Org Chem* (1989) 54, 4966
b) Corey EJ, *Tetrahedron Lett* (1982) 23, 4217
c) Ueda Y, Maynard SC, ibid (1988) 29, 5197
d) Nace HR, Crosby GA, *J Org Chem* (1979) 44, 3105
e) Sisti AG, Vitalr AC, ibid (1972) 37, 4090, and references therein

3 For reviews see:
a) Moore RE, In *Marine Natural Products* (Scheuer PJ, Ed), Academic, New York (1978) 1, chap 2
b) Fenical W, ibid (1980) 2, 174
c) Barrow KD, ibid (1983) 5, 51
d) Erickson KL, ibid (1983) 5, 131
e) Faulkner DJ, *Nat Prod Rep* (1984) 251 (1986) 1

4 Ayi AI, Remli M, Guedj R, *Tetrahedron Lett* (1981) 16, 1505-1508

5 Bonini C, Righi G, *Synthesis* (1994) 3, 225-238

6 Farges G, Kergomrd A, *Bull Soc Chim Fr* (1963) 51

7 a) Olah GA, Meidor A, *Israel J Chem* (1978) 17, 148
b) Ayi AI, Remli M, Condom R, Guedj R, *J Fluorine Chem* (1981) 17, 565

8 Amadi F, Chaabouni MM, Amri H, Baklouti *Synth Commun* (1993) 23, 17, 2389-2395

9 Brine N, Foucaud A, *Bull Soc Chim Fr* (1993) 130, 620-624

10 Robert A, Jaguelin S, Guinamant JL, *Tetrahedron* (1986) 42, 2275

11 LeGrel P, Baudy-Floc'h M, Robert A, *Synthesis* (1987) 306

12 Florac C, LeGrel P, Baudy-Floc'h M, Robert A, *Synthesis* (1991) 741

13 Khamliche L, Ariès-Gautron I, Guerro M, Robert A, *Tetrahedron* (1992) 48, 1585

14 Souizi A, Robert A, *CR Acad Sci Fr* (1982) 295 (II), 571

15 Baudy M, Robert A, Foucaud A, *J Org Chem* (1978) 43, 3742

16 a) Guinamant JL, Robert A, *Tetrahedron* (1986) 42, 1169
b) Khamliche L, Robert A, *Tetrahedron* (1988) 44, 2503
c) Khamliche L, Robert A, *J Chem Soc, Chem Commun* (1987) 1869