A Facile One-Pot Synthesis of α-Hydroxy Acids and Their Derivatives

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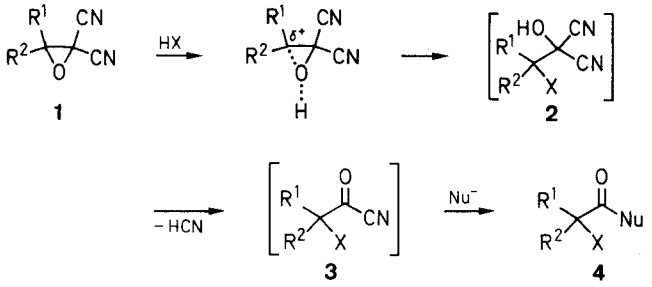
2-Substituted oxirane-1,1-dicarbonitriles react with water, alcohols or phenol to give 2-substituted 2-hydroxyacetic acids, alkyl 2-alkoxyacetates and phenyl 2-phenoxyacetates, respectively. Reaction of 2-substituted oxirane-1,1-dicarbonitrile with thiophenol and a nucleophile, typically water ethanol or urea, gave 2-(phenylthio)acetic acids, ethyl 2-(phenylthio)acetates and *N*-aminocarbonyl-2-(phenylthio)acetamides.

α-Hydroxy acids and their derivatives were conveniently synthesized in good yield using a one-pot procedure involving the simple reaction of water, alcohol, phenol or thiophenol with *gem*-dicyanoepoxides, which acted as an $R^1R^2C(Nu)-\overset{+}{C}=O$ synthetic equivalent. The opening of *gem*-dicyanoepoxides **1** by halohydric acids generates an α-halocyanoformyl intermediate **3** which rapidly reacts with nucleophilic reagents. As a consequence, epoxides **1** in the presence of halohydric acids are synthetic equivalents of the synthons $R^1R^2C(X)-\overset{+}{C}=O$ of particular interest in synthesis.[1-3]

The usefulness of this synthesis arise from its very high regioselectivity. It seems likely that the reaction, catalyzed by the halohydric acid (HX), presents a carbocationic transition state. As the positive charge will preferably be located on the carbon β to the two nitriles, the nucleophilic attack of X^- is exclusively orientated toward this positive center (Scheme **1**).

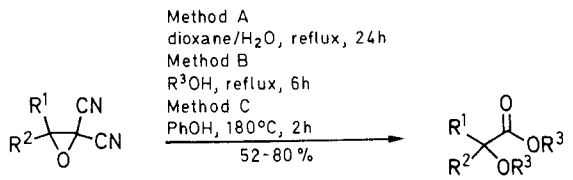


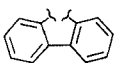
Scheme 1

In order to extend the scope of this synthetic strategy, it seemed to us of interest to see if it were possible to ring open the epoxides **1** with other protic nucleophiles NuH. Should an initial protonation of the epoxide by NuH be followed by the nucleophilic ring opening then the epoxides **1** will be synthetic equivalents of synthons $R^1R^2C(Nu)-\overset{+}{C}=O$.

We describe here the reaction of the *gem*-dicyanoepoxides (2-substituted oxirane-1,1-dicarbonitriles) **1** with water, alcohol, phenol and thiophenol. The *gem*-dicyanoepoxides **1** are converted into α-hydroxy acids **4** (R^2 = H) after 24 hours in refluxing dioxane/water (Scheme **2**).

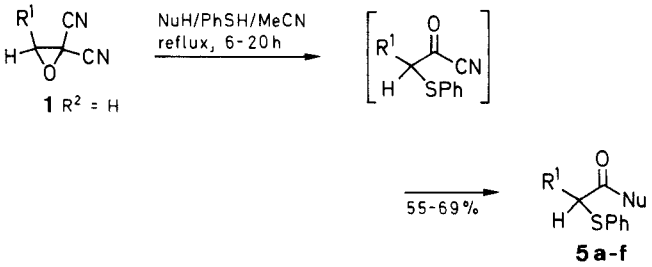
The α-alkoxy esters **4** (R^2 = alkyl) and the α-phenoxy esters **4** (R^2 = Ph) are prepared in a similar way by reacting the *gem*-dicyanoepoxides **1** in the appropriate alcohol or phenol at reflux for 6 and 2 hours, respectively (Scheme **2**).



4	R^1	R^2	R^3	4	R^1	R^2	R^3
a	4-ClC_6H_4	H	H	i	Ph	H	Et
b	4-MeC_6H_4	H	H	j	Ph	Ph	Et
c	4-$MeOC_6H_4$	H	H				
d	*n*-C_7H_{15}	H	H	k			Et
e	4-MeC_6H_4	H	Me				
f	4-MeC_6H_4	H	Et	l	4-MeC_6H_4	H	Ph
g	4-ClC_6H_4	H	Et				
h	4-$O_2NC_6H_4$	H	Me				

Scheme 2

We have also shown that when the protic nucleophile is thiophenol, it is possible to carry out the reaction in the presence of a second nucleophile (water, alcohol, urea). In these cases, the reaction is regio- and chemoselective: the epoxide **1** is ring opened by the thiophenol and the α-phenylthiocyanoformyl intermediate reacts mainly with the second nucleophile to give **5** with good yield (Scheme **3**).



5	R^1	Nu	5	R^1	Nu
a	4-MeC_6H_4	OH	d	Ph	OEt
b	4-MeC_6H_4	OEt	e	4-ClC_6H_4	$NHCONH_2$
c	4-ClC_6H_4	OEt	f	4-MeC_6H_4	$NHCONH_2$

Scheme 3

As *gem*-dicyanoepoxides **1** are easily available starting materials,[4] and as the reaction is highly regio- and chemoselective and is a one-pot procedure, our new route to α-hydroxy acids and their derivatives, using epoxides **1** as synthetic equivalents of $R^1R^2C(Nu)-\overset{+}{C}=O$ synthons seems us of interest and compares favorably with existing methods.[5-13]

^{1}H-NMR spectra were recorded at 80 MHz on a WP 80 Bruker Spectrometer and ^{13}C-NMR spectra at 75 MHz on a AM 300

Table 1. Compounds **4** Prepared

Product	Yield (%)	bp (°C)/2 Torr[a] or [mp (°C)]	Molecular Formula[b] or Lit. Data	IR (Nujol) (cm^{-1}) ν_{OH}	$\nu_{C=O}$	^{1}H-NMR (solvent[c]/TMS) δ
4a	60	[115]	105[12]	3410, 2500–3300	1715	5.21 (s, 1H), 5.81 (s, 2H), 7.45 (m, 4H)
4b	65	[145]	144[8]	3407, 2500–3400	1710	2.31 (s, 3H), 5.12 (s, 1H), 6.10 (s, 2H), 7.25 (m, 4H)
4c	68	[89]	108[8, d]	3510, 2500–3400	1710	3.75 (s, 3H), 5.22 (s, 1H), 7.15 (m, 4H), 7.62 (m, 2H)
4d	80	[58–60]	$C_9H_{18}O_3$ (174.2)	3440, 3380, 2500–3300	1710	0.90 (t, 2H), 1.31 (m, 8H), 1.75 (m, 2H), 4.28 (t, 1H), 7.55 (m, 2H)
4e	77	80	130/11 Torr[12]	–	1755 1740	2.35 (s, 3H), 3.40 (s, 3H), 3.67 (s, 3H), 4.77 (s, 1H), 7.22 (m, 4H)
4f	72	100	$C_{13}H_{18}O_3$[12] (222.1)	–	1750	1.17 (t, 3H), 1.29 (t, 3H), 2.32 (s, 3H), 3.52 (m, 2H), 4.12 (q, 2H), 4.83 (s, 1H), 7.21 (m, 4H)
4g	64	100	$C_{12}H_{15}ClO_3$[12] (242.1)	–	1735	1.27 (t, 3H), 1.35 (t, 3H), 3.61 (m, 2H), 4.21 (q, 2H), 4.87 (s, 1H), 7.40 (m, 4H)
4h	70	140	$C_{12}H_{15}NO_5$ (253.1)	–	1745 1734	1.25 (t, 3H), 1.27 (t, 3H), 3.60 (m, 2H), 4.22 (q, 2H), 5.05 (s, 1H), 7.95 (m, 4H)
4i	64	100	$C_{12}H_{16}O_3$ (208.1)	–	1746	1.18 (t, 3H), 1.26 (t, 3H), 3.57 (m, 2H), 4.15 (q, 2H), 4.86 (s, 1H), 7.40 (m, 5H)
4j	63	130	$C_{18}H_{18}O_3$ (282.1)	–	1730	1.20 (t, 6H), 3.30 (q, 2H), 4.20 (q, 2H), 7.50 (m, 10H)
4k	61	130	$C_{18}H_{18}O_3$ (282.1)	–	1735	1.00 (t, 3H), 1.23 (t, 3H), 3.02 (q, 2H), 4.05 (q, 2H), 7.50 (m, 8H)
4l	52	170	$C_{21}H_{18}O_3$ (318.1)	–	1775	2.41 (s, 3H), 5.82 (s, 1H), 7.25 (m, 14H)

[a] Bp here indicates bulb-to-bulb bath temperature.
[b] Satisfactory microanalyses obtained C ±0.35, H ±0.26; **4h** N −0.08; **4g** Cl −0.06.
[c] Solvent **4a–c**: acetone-d_6; **4d–l**: $CDCl_3$.
[d] Satisfactory microanalysis and HRMS (−0.0007 amu).

Table 2. Compounds **5** Prepared

Product	Yield (%)	bp (°C)/2 Torr[a] or [mp (°C)]	Molecular Formula[b]	IR (Nujol) (cm^{-1}) ν_{NH}	ν_{CO}	^{1}H-NMR ($CDCl_3$/TMS) δ
5a	55	[122]	$C_{15}H_{14}O_2S$ (258.1)	–	1710	2.33 (s, 3H), 4.87 (s, 1H), 7.20 (m, 9H)
5b	65	160	$C_{17}H_{18}O_2S$ (286.1)	–	1735	1.21 (t, 3H), 2.37 (s, 3H), 4.14 (q, 2H), 4.92 (s, 1H), 7.22 (m, 9H)
5c	61	130	$C_{16}H_{15}ClO_2S$ (306.1)	–	1730	1.11 (t, 3H), 4.08 (q, 2H), 4.81 (s, 1H), 7.30 (m, 9H)
5d	65	120	$C_{16}H_{16}O_2S$ (272.1)	–	1735	1.22 (t, 3H), 4.15 (q, 2H), 4.94 (s, 1H), 7.37 (m, 9H)
5e	64	[230]	$C_{15}H_{13}ClN_2O_2S$ (320.1)	3500–3200	1710, 1670	4.90 (s, 1H), 7.35 (m, 9H)[c]
5f	69	[238]	$C_{16}H_{16}N_2O_2S$ (300.1)	3500–3150	1709, 1660	2.30 (s, 3H), 4.90 (s, 1H), 7.25 (m, 9H)[c]

[a] Bp here indicates bulb-to-bulb bath temperature.
[b] Satisfactory microanalyses obtained: C ±0.27, H ±0.35, S ±0.27; **5c, e** Cl ±0.37; **5e, f** N ±0.12.
[c] Measured in $CDCl_3$ + TFA.

Bruker spectrometer. Mass spectra were determined with a Varian Mat 311 Spectrometer. IR spectra were determined with a Perkin-Elmer 225 or 1420 Spectrometer. Melting points were taken with a Kofler hot stage apparatus.

α-Hydroxy Acids 4a–d; General Procedure;
Method A: *gem*-dicyanoepoxide **1**[4] (10 mmol) are heated under reflux in dioxane (50 mL) and water (20 mL) for 24 h. After evaporation of dioxane, 1N NaOH is added to the mixture to obtain a basic solution. The aqueous phase is washed with Et_2O (2 × 30 mL) then acidified with 4N HCl and extracted with Et_2O (2 × 50 mL). The combined organic layers are washed with water, dried (Na_2SO_4) and evaporated to give the crude product which crystallizes on cooling. The α-hydroxy acids **4** are recrystallized from toluene (Table 1).

α-Alkoxy Esters 4e–k; General Procedure;
Method B: *gem*-dicyanoepoxide **1** (10 mmol) and the corresponding alcohol (20 mL) are heated under reflux for 6 h. The α-alkoxy esters **4** are obtained almost pure after evaporation of the alcohol. The compounds **4** are rectified by bulb-to-bulb distillation with a Buchi apparatus (Table 1).

Phenyl 2-(Phenoxy)-2-(*p*-tolyl)acetate (4l):
Method C: *gem*-dicyanoepoxide **1** (10 mmol) and phenol (60 mmol) are heated to 180 °C with an oil bath for 2 h. After cooling, the mixture is dissolved in Et_2O, washed by a solution of 1N NaOH, and by water. The organic layer is dried (Na_2SO_4) and evaporated affording **4l** which is rectified by bulb-to-bulb distillation with a Buchi apparatus (Table 1).

α-Phenylthio Acids and Esters 5; General Procedure:
gem-Dicyanoepoxides **1** (5 mmol), thiophenol (10 mmol) and the other nucleophilic reagent (water, alcohol, amide) (5 mmol) are heated in refluxing acetonitrile (20 mL) for 2 h. After evaporation of the solvent, the crude product **5**, which is purified either by recrystallisation or by column chromatography (silica gel, eluant: Et_2O/petroleum ether (bp 43–62 °C) 30:70) (Table 2), is obtained.

Received: 28 January 1991

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