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SYNTHESIS OF α,β-EPOXY DIAZOMETHYL KETONES

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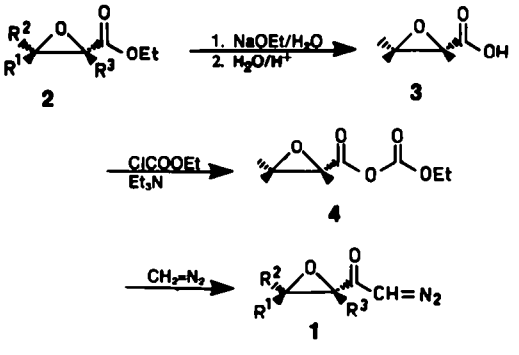
Abstract—The preparation of eighteen epoxy diazomethyl ketones 1 is described. Two general methods were developed. Firstly, treatment of the mixed anhydrides of glycidic acids and carbonic acid ester with diazomethane led to the title compounds in yields ranging from 17–74%. Secondly, glycidyl chlorides which were obtained from sodium glycidates and oxalyl chloride, gave the desired products upon treatment with diazomethane (yields 60–74%). The required α,β-epoxy carboxylic esters were prepared by Darzens condensation and epoxidation of α,β-unsaturated esters, but in some cases also by reaction of α-oxo carboxylic esters with diazomethane.

α,β-Epoxy diazomethyl ketones 1 represent a class of compounds containing two reactive functional groups. These substrates are of interest as they enable us to study the chemospecific behaviour of reagents that are reactive towards both epoxides and diazoketones.[1,2]

In design α,β-epoxy diazomethyl ketones 1 can be synthesised by introduction of a diazo group into a molecule already containing an epoxide function and alternatively, by formation of an epoxide with reagents possessing the diazomethyl ketone moiety. The latter approach was used by Woolsey and Khalil[3] who performed a Darzens condensation of non-enolisable aldehydes with 1 - chloro - 3 - diazopropanone. This paper deals with the preparation of α,β-epoxy diazomethyl ketones starting from epoxide containing compounds, viz. glycidic acid derivatives.[4]

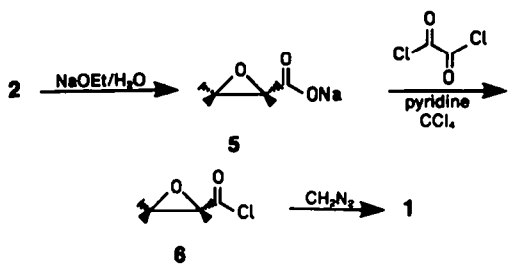
The first sequence of reactions used is depicted in Scheme 1. Claisen saponification[5] of glycidic esters 2



Scheme 1.

afforded sodium glycidates which, after careful acidification, were converted into glycidic carbonic anhydrides 4 by treatment with ethyl chloroformate in the presence of triethylamine. Without being isolated these mixed anhydrides were treated with slightly more than two molar equivalents of diazomethane. With a few exceptions the desired epoxy diazomethyl ketones were isolated by crystallisation or by chromatography in quite acceptable yields (Table 1). When attack of diazomethane takes place at the carbonic CO group in the mixed anhydrides an unwanted side reaction occurs, namely the formation of methyl glycidates and ethyl diazoacetate (only the former was isolated in some cases). This side reaction could partly be suppressed by the use of a bulkier alkyl group in the chloroformate such as the isobutyl substituent.

The second method used is shown in Scheme 2.



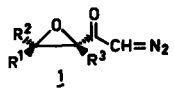
Scheme 2.

Treatment of well-dried sodium glycidates 5, suspended in benzene or preferably in carbon tetrachloride, with oxalyl chloride gave the acid chlorides 6 almost quantitatively, subsequent reaction with excess of diazomethane resulted in the diazo ketones 1 in good yields (Table 1). Glycidyl chlorides were prepared by Speciale and Frazier[6] in essentially the same manner during their synthesis of glycidamides. In our case it turned out to be of crucial importance that the sodium glycidates do not contain any adherent water. Conversion of glycidic acids 3 into the corresponding chlorides 6 could also be accomplished by using oxalyl chloride,[7] however, for our purpose the results were generally less satisfactory.

The required glycidic esters were prepared either by a Darzens condensation or by epoxidation of unsaturated esters (Experimental). α-Aryl substituted glycidates could be obtained via the Darzens condensation in a limited number of cases only (type 2c, g and h). However, 3,3 - dimethyl - 2 - aryl acrylic esters could be obtained in a sequence of reactions from methyl oxalate as described by Micetich.[8] Subsequent epoxidation then led to the epoxy esters 2 (n, o, p) in good yields (Scheme 3).

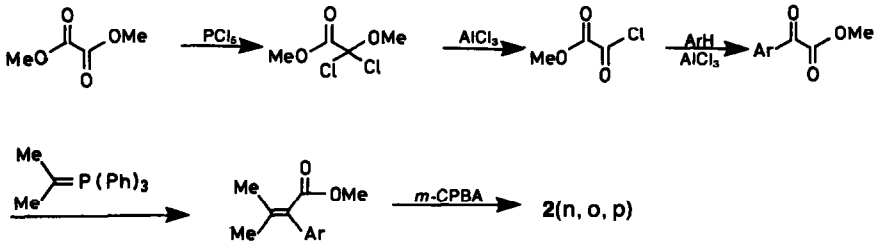
Glycidic esters that are unsubstituted at the β-C atom could be obtained as depicted in Scheme 4. Treatment of the α-oxo esters 7 with excess of diazomethane resulted

Table 1.

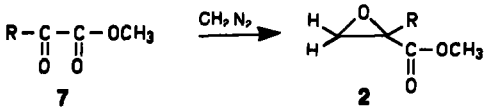


1

no.	R^1	R^2	R^3	m.p. °C	Yield (%) via anhydride	Yield (%) via acid chloride
a	Ph	H	H	89.5-92.5	43	
b	Ph	Ph	H	72-74	55	65
c	Ph	H	Ph	90-93	51	76
d	H	Ph	Ph	130.5-132.0	62	
e	Ph	Me	H	73-75	42	71
f	Ph	Me	Me	61-63.5	26	71
g	Tol	H	Ph	>125 (dec)	74	74
h	Ph	H	Tol	86-87	55	
i			H	66-68	60	60
j			H	oil	23	
k			H	91-92.5	56	
l			Me	92-93.5	17	
m	Me	Me	Me	oil		64
n	Me	Me	Ph	72-80	68	
o	Me	Me	p-CH_3-Ph	100-105	60	
p	Me	Me	p-CH_3O-Ph	123-126	63	
q	H	H	Ph	42-43	18	
r	H	H	Ph_2CH	130-140 (dec)	51	



Scheme 3.



2q: R = Ph
2r: R = Ph_2CH
2s: R = α-Thienyl,

Scheme 4.

in the epoxy esters 2 (q, s). This reaction failed when the aryl substituent is mesityl or *p*-methoxyphenyl. In one case this method was used to introduce a diazo- and epoxide function simultaneously. Saponification of α-oxo ester 2r, subsequent treatment with ethyl chloroformate and triethylamine, followed by reaction with excess of diazomethane gave epoxy diazo ketone 1r in a one pot procedure.

The chemistry of epoxy diazomethyl ketones will be described in forthcoming papers.

EXPERIMENTAL

All b.ps and m.ps are uncorrected. M.ps were measured on a Reichert m.p. microscope. IR spectra were taken on a Perkin-Elmer 257 grating spectrometer. NMR spectra were recorded on a Varian EM 390 instrument, using TMS as internal standard. All crystalline epoxy diazomethyl ketones showed a correct elemental analysis. The glycidic esters 2a, b, c, e, f, g, h, i, j, k, l were all prepared through a Darzens condensation of the corresponding carbonyl compound with the appropriate α-chloro ester.[9-12] Glycidic ester 2d was prepared by oxidation of ethyl *cis*-α-phenyl cinnamate[13] with mCPBA in refluxing benzene. Glycidic ester 2m was prepared according to Darzens.[14] Esters 2n, o and p were synthesised according to the procedure[8] outlined in Scheme 3.

Preparation of 1 *via mixed anhydrides (general procedure).* A small excess of 4N HCl was added to a cooled (ice) soln of Na or K glycidate (15 mmoles) in water (50 ml) (sometimes some MeOH is needed also). In most cases the acids 3 precipitated. After extraction with ether and drying of the ether soln over $MgSO_4$ at 4°, slight excess of Et_3N (16 mmoles) was added and then, with stirring, one equivalent of ethyl chloroformate in ether. The soln of mixed anhydride obtained after filtration of

Et_3N·HCl, was added to an excess of ethereal diazomethane (40 mmoles) at −20°. After standing for 2 days at room temp and filtration of some solid and oily material, excess of diazomethane was removed by flushing with air. Removal of the solvent gave the crude 1 which was crystallised from petroleum ether–benzene or EtOH. In cases the crude product is oily, crystals could be obtained by trituration with ether–pentane. Yields and m.p. are compiled in Table 1, spectral data are given below.

Preparation of 1 *via acid chlorides* 6 (*general procedure*). A suspension of 20 mmoles of carefully dried Na glycidate in 75 ml CCl_4 (or benzene) containing 4–5 drops pyridine was treated with a soln of oxalyl chloride (25 mmoles) in CCl_4 (10 ml), while stirring and cooling with an ice–salt bath. The suspension gradually dissolved (0.5 h). Solvent and excess of oxalyl chloride were removed *in vacuo* at a temp < 10°. After addition of ether and subsequent filtration, excess of diazomethane in ether (50 mmoles) was added. After standing overnight excess of diazomethane and ether was removed by flushing with N_2, giving crude 1. Crystallisation from an appropriate solvent gave pure 1, yields and m.p. see Table 1, spectral data are listed below.

IR and NMR data of the epoxy diazomethyl ketones. IR (νC=N_2, νC=O). ^{1}H-NMR (diazo proton, epoxide protons, remaining protons). **1a**: IR (KBr): 2100, 1630 cm^{-1}; NMR ($CDCl_3$): δ 5.50 (s, 1H), 3.25 (d, 1H, J = 1.2 Hz), 3.80 (d, 1H, J = 1.2 Hz), 7.25 (br.s, 5H). **1b**: IR (KBr): 2105, 1618 cm^{-1}; NMR ($CDCl_3$): δ 5.05 (s, 1H), 3.80 (s, 1H), 7.25 (m, 10H). **1c**: IR (KBr): 2110, 1632 cm^{-1}; NMR ($CDCl_3$): δ 5.67 (s, 1H), 4.37 (s, 1H), 6.7–7.4 (m, 10H). **1d**: IR (KBr): 2100, 1628 cm^{-1}; NMR ($CDCl_3$): δ 5.65 (s, 1H), 4.17 (s, 1H), 7.2–7.8 (m, 10H). **1e**: IR (KBr): 2105, 1642 cm^{-1}; NMR (CCl_4): δ 5.02 (s, 1H), 3.51 (s, 1H), 1.68 (s, 3H), 7.32 (m, 5H). **1f**: IR (KBr): 2120, 1630 cm^{-1}; NMR (CCl_4): δ 5.77 (s, 1H), 1.10 (s, 3H), 1.65 (s, 3H), 7.37 (m, 5H). **1g**: IR (KBr): 2115, 1639 cm^{-1}; NMR (CD_3COCD_3): δ 6.00 (s, 1H), 4.44 (s, 1H), 2.19 (s, 3H), 6.96 (s, 4H), 7.1–7.4 (m, 5H). **1h**: IR (KBr): 2105, 1629 cm^{-1}; NMR (CCl_4): δ 5.60 (s, 1H), 4.24 (s, 1H), 2.21 (s, 3H), 6.75–7.25 (m, 9H). **1i**: IR (KBr): 2120, 1630 cm^{-1}; NMR (CCl_4): δ 5.49 (s, 1H), 3.13 (s, 1H), 1.62 (m, 10H). **1j**: IR (neat): 2105, 1620 cm^{-1}; NMR (CCl_4): δ 5.62 (s, 1H), 3.42 (s, 1H), 1.3–2.4 (m, 8H). **1k**: (KBr): 2105, 1626 cm^{-1}; NMR ($CDCl_3$): δ 5.60 (s, 1H), 3.35 (s, 1H), 1.1–2.3 (m, 14H). **1l**: IR (KBr): 2115, 1614 cm^{-1}; NMR (CCl_4): δ 5.60 (s, 1H), 1.44 (s, 3H), 1.62 (m, 10H). **1m**: IR (neat): 2100, 1625 cm^{-1}; NMR (CCl_4): δ 5.55 (s, 1H), 1.30 (s, 3H), 1.33 (s, 3H), 1.40 (s, 3H). **1n**: IR (KBr): 2100, 1615 cm^{-1}; NMR ($CDCl_3$): δ 5.76 (s, 1H), 1.06 (s, 3H), 1.50 (s, 3H), 7.15–7.80 (m, 5H). **1o**: IR (KBr): 2095, 1615 cm^{-1}; NMR ($CDCl_3$): δ 5.72 (s, 1H), 1.04 (s, 3H), 1.46 (s, 3H), 2.32 (s, 3H), 7.0–7.5 (ABq, 4H). **1p**: IR (KBr): 2095, 1620 cm^{-1}; NMR ($CDCl_3$): δ 5.75 (s, 1H), 1.05 (s, 3H), 1.46 (s, 3H), 3.76 (s, 3H), 6.80–7.55 (ABq, 4H). **1q**: IR (KBr): 2095, 1630 cm^{-1}; NMR (CCl_4): δ 5.57 (s, 1H), 2.84 (d, 1H, J = 6 Hz), 3.06 (d, 1H, J = 6 Hz), 7.2–7.7 (m, 5H). **1r**: IR (KBr): 2100, 1620 cm^{-1}; NMR ($CDCl_3$): δ 5.65 (s, 1H), 2.20 (d, 1H, J = 5 Hz), 2.53 (d, 1H, J = 5 Hz), 5.11 (s, 1H), 6.8–7.7 (m, 10H).

Methyl 2-*phenyl*-2,3-*epoxy-propionate* **2q**. Methyl phenylglyoxylate[8] (1.64 g, 10 mmoles) dissolved in ether was treated with diazomethane (20 mmoles) in ether at 20°. After standing for 2 days at 20° excess of diazomethane and solvent were evaporated and the residue distilled *in vacuo*, yield: 1.11 g (68%), b.p. 80–86°/0.3 mm Hg; IR (neat): ν(C=O) 1740 cm^{-1}; NMR (CCl_4): δ 2.78 + 3.30 (ABq, 2H, 6 Hz), 3.56 (s, 3H), 7.0–7.5 (m, 5H).

Methyl 2-*diphenylmethyl*-2,3-*epoxy-propionate* **2r**. β,β-Diphenyl-α-oxo-propionic acid (see prep of 1r) (1.0 g) dissolved in ether was treated with an excess of ethereal diazomethane. After standing overnight, filtration and removal of solvent, **2r** was obtained in a quantitative yield. IR: ν(CO) 1735 cm^{-1}; NMR (CCl_4): δ 2.41 + 2.77 (ABq, 2H, J = 5 Hz), 3.48 (s, 3H), 4.95 (s, 1H), 7.0–7.5 (m, 10H).

Methyl 2-(2′-*thienyl*)-2,3-*epoxy-propionate* **2s**. Methyl α-thienylglyoxylate[8] was treated twice with an excess of diazomethane as described for **2q**, yield: 68%; b.p. 86–94°/0.5 mm Hg; IR (neat): ν(C=O) 1740 cm^{-1}; NMR (CCl_4): 2.94 + 3.32 (ABq, 2H, J = 6 Hz), 3.72 (s, 3H), 6.76–7.27 (m, 3H).

1-*Diazo*-3-*diphenylmethyl*-3,4-*epoxy-butane*-2-*one* **1r**. To an ice-cold soln of Na-β,β-diphenyl-2-oxopropionate[10] (2.62 g, 10 mmoles) in water (50 ml) one equiv of 4N HCl was added. The propionic acid was extracted with ether. The ethereal soln was dried over $MgSO_4$ (0°), filtered and treated with Et_3N (1.1 g, 11 mmoles) and ethyl chloroformate (1.08 g) in ether (10 ml) at 0°. After stirring for 1 h Et_3N·CHl was filtered off and the filtrate added to diazomethane (50 mmoles) in ether (150 ml) at −20°. After standing for 2 days excess of diazomethane was removed by flushing with air and the solvent evaporated. The residue was crystallized from petr.ether–benzene. Yield: 1.42 g (51%) of yellow crystalline **1r**, m.p. 130–140° (dec).

REFERENCES

[1]P. M. M. van Haard, L. Thijs and B. Zwanenburg, *Tetrahedron Letters* 803 (1975). For copper induced reactions and cyclopropanation reactions, see accompanying papers.
[2]A. C. Brouwer, L. Thijs and B. Zwanenburg, *Ibid.* 807 (1975).
[3]N. F. Woolsey and M. H. Khalil, *J. Org. Chem.* **38**, 4216 (1973); **40**, 3521 (1975).
[4]B. Zwanenburg and L. Thijs, *Tetrahedron Letters* 2459 (1974).
[5]L. Claisen, *Ber. Dtsch. Chem. Ges.* **38**, 693 (1905).
[6]A. J. Speciale and H. W. Frazier, *J. Org. Chem.* **26**, 3176 (1961).
[7]A. Padwa and N. C. Das, *Ibid.* **34**, 816 (1969).
[8]R. G. Micetich, *Org. Prep. and Proc.* **2**, 249 (1970); R. Raap, C. G. Chin and R. G. Micetich, *Can. J. Chem.* **49**, 2143 (1971).
[9]W. S. Johnson, J. S. Belew, L. J. Chinn and R. H. Hunt, *J. Am. Chem. Soc.* **75**, 4995 (1953).
[10]F. F. Blicke and J. A. Faust, *Ibid.* **76**, 3156 (1954).
[11]F. F. Blicke, J. A. Faust and H. Raffelson, *Ibid.* **76**, 3161 (1954).
[12]C. F. H. Allen and J. Van Allen, *Org. Synth.* **24**, 82 (1944).
[13]For Z-α-phenylcinnamic acid, see L. F. Fieser, *Organic Experiments* (2nd Ed.) p. 228; Heath and Comp., Lexington, Mass (1968). The compound which is designed as *trans* (m.p. 138°) has the Z-configuration.
[14]G. Darzens, *C. R. Acad. Sci., Paris* **141**, 766 (1905).