

SYNTHESIS AND REACTIONS OF α,β -EPOXY DIAZOMETHYL KETONES

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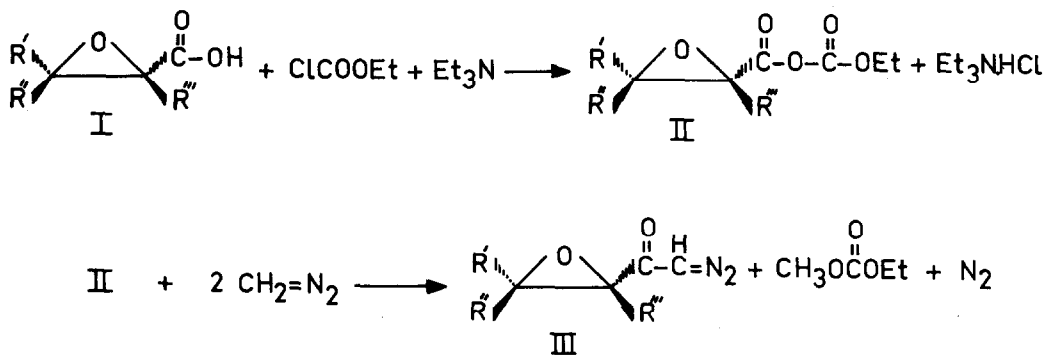
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Selective transformations in organic compounds containing two or more functional groups that show reactivity towards one and the same reagent are of fundamental interest for the strategy in organic synthesis. With this motive we decided to study compounds possessing a combination of an epoxide and a diazo function, *viz.* α,β -epoxy diazomethyl ketones. In this communication we describe our approach to the synthesis of these compounds (see Scheme 1).

The conventional procedure for the conversion of a carboxyl group into an acyldiazomethane by reaction of the corresponding acid chloride with diazomethane appeared not to be applicable, because glycidic acid chlorides are not accessible by the reaction of the glycidic acids (I) with phosphorous trichloride, thionylchloride or triphenylphosphine/carbon tetrachloride. This problem could be circumvented by converting the glycidic acids¹⁾ (I) into reactive mixed anhydrides by reaction with ethyl chloroformate in the presence of triethylamine. Without being isolated the glycidic carbonic anhydrides II were brought into reaction with a slight excess of diazomethane²⁾. The desired epoxydiazomethyl ketones III were isolated, by crystallization or by chromatography on florisil, in yields ranging from 40 to 60% (see Table).

S C H E M E 1

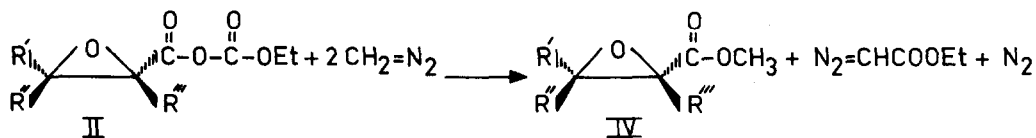


α,β -epoxydiazomethyl ketones III

	R'	R''	R'''	Yield	m.p.	$\nu_{C=O}$ (cm ⁻¹)	$\nu_{N=N}$ (cm ⁻¹)	$\delta_{C=N_2}^H$	λ_{max}	log ϵ
a	C ₆ H ₅	C ₆ H ₅	H	55%	72-74	1619	2100	5.14	243 285	4.04 4.02
b	H	C ₆ H ₅	C ₆ H ₅	51%	90-93	1632	2110	5.67	247 282	4.18 4.04
c	C ₆ H ₅	H	C ₆ H ₅	62%	130 ⁵ -132	1628	2100	5.65	248 279	sh 3.98
d	H	C ₆ H ₅	H	43%	89 ⁵ -92 ⁵	1630	2100	5.60	243 281	4.10 4.08
e			H	56%	91-92 ⁵	1626	2105	5.60	248 279	3.94 4.02

Attack of diazomethane at the ester carbonyl function in the anhydrides II gives rise to an undesired side reaction, *viz.* the formation of methyl glycidate IV and ethyl diazoacetate (only the former was isolated) (Scheme 2). This side reaction can partly be suppressed by the use of a bulkier ester group in the chloroformate, *viz.* by taking iso-propyl or iso-butyl instead of ethyl esters. In this respect, the use of mixed anhydrides of glycidic acids and pivalic acid appeared to be very attractive.

S C H E M E 2



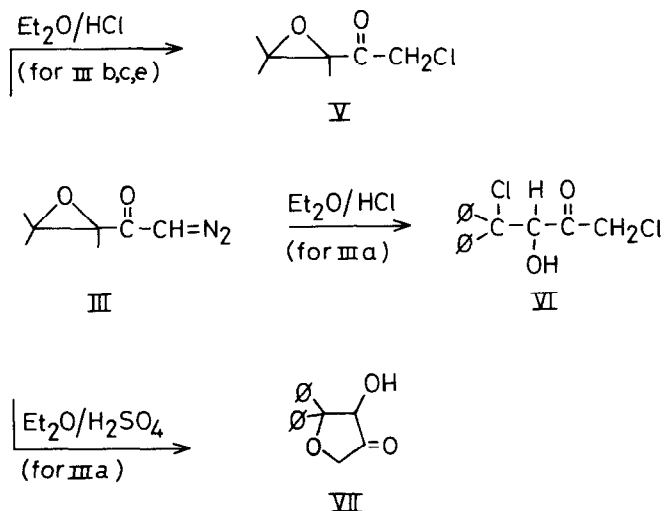
The structures of the yellow crystalline products III were established on basis of correct combustion analyses and the spectral characteristics, particularly, the carbonyl and diazo infra-red absorption, and the PMR signal of the diazomethine proton (see Table). The structure is supported by the formation of phosphazines upon treatment of the epoxydiazomethyl ketones with triphenylphosphine. These phosphazines can be reconverted into the diazo compounds III by reaction with methyl iodide.

Furthermore, the spectral data of the epoxydiazomethyl ketone IIIId are identical with those recently reported by Woolsey and Khalil³⁾, who elegantly prepared this compound by a Darzens condensation of 1-chloro-3-diazopropanone and benzaldehyde.

The diazo compounds III were treated with acidic reagents. Careful treatment of IIIb, IIIc and IIIe with an excess of hydrogen chloride in ether, gave only the conversion of the diazomethyl into the chloromethyl group (yield: 65-80%), while the epoxide function remained intact (Scheme 3). However, the β,β -diphenyl compound IIIa showed a concomitant reaction of the epoxide and diazo function to

give the product VI (Scheme 3). Evidently, the presence of two β -phenyl groups weakens the C β -O bond sufficiently to allow an acid-catalyzed nucleophilic epoxide opening under the conditions chosen.

S C H E M E 3

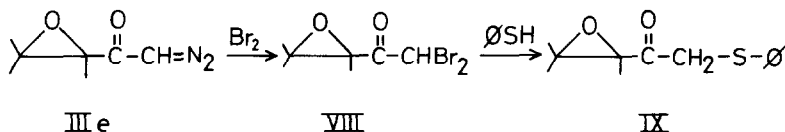


The structures of the new compounds V were deduced from the following spectral features: Vb (m.p. 82-83°), ν (C=O) 1730 cm^{-1} , δ (CH₂) 4.33 (s), δ (CH) 4.41 (s) ppm; Vc (m.p. 74-76°), ν (C=O) 1740 cm^{-1} , δ (CH₂) 3.89 (d), 4.18 (d) (AB qu, J 18 Hz), δ (CH) 4.25 (s) ppm; Ve (m.p. 90-94°), ν (C=O) 1710 cm^{-1} , δ (CH₂) 4.25 (s), δ (CH) 3.71 (s) ppm. Compound VI, yield 50%, m.p. 80-85 (dec.) (NMR: δ (CH₂) 3.62 (s), δ (CH) 5.33 (s), δ (OH) 3.50 (s) ppm), was treated with CH₃OH/CH₃ONa giving the displacement of one chlorine to: (C₆H₅)₂C(Cl)CHOHCOCH₂OCH₃, m.p. 108-109°, ν (OH) 3460, ν (C=O) 1720 cm^{-1} , δ (OCH₃) 3.13 (s), δ (CH₂) 4.61 (d), 4.19 (d) (AB qu, J 16 Hz), δ (OH) 3.62 (d), δ (CH) 5.42 (s) ppm. This product was compared with that obtained by acid-catalyzed methanolysis of IIIa, *viz.* (C₆H₅)₂C(OCH₃)CHOHCOCH₂OCH₃, yield 96%, oil, ν (OH) 3440, ν (C=O) 1715 cm^{-1} , δ (OCH₃) 3.18, δ (OCH₃) 3.34, δ (CH₂) 4.53 (d), 4.05 (d) (AB qu, J 18 Hz), δ (OH) 3.70, δ (CH) 5.22 ppm. (its crystalline benzoate melted at 78-81°).

When the acidic reagent does not contain a nucleophilic anion as for instance in ether/conc. H₂SO₄ an intramolecular reaction takes place with IIIa (Scheme 3). The formation of the observed five-membered ring product VII (m.p. 128-130°, yield 50%) can be explained by assuming that the initially formed hydroxymethyl compound alcoholyses the epoxide function intramolecularly. Alternatively, the product can be explained by a nucleophilic reaction of the epoxy function with the protonated diazomethyl group⁴). The structure of VII was deduced from the spectral data: ν (C=O) 1765, ν (OH) 3400 cm^{-1} , δ (CH₂) 4.08 (d), 4.45 (d) (AB qu, J 18 Hz),

δ (CH) 4.87 and δ (OH) 2.97 (s) ppm, and a positive acyloine test. From IIIb and THF/conc. H_2SO_4 a product similar to VII was isolated in 38% yield (m.p. 112-114 $^\circ$, ν (C=O) 1765, ν (OH) 3400 cm^{-1} , δ (CH₂) 4.18 (d), 4.60 (d) (AB qu, J 18 Hz), δ (CH) 5.09 (s), δ (OH) 3.21 (s) ppm).

S C H E M E 4



The reaction of diazomethyl ketone IIIe with the electrophilic reagent bromine in carbon tetrachloride resulted in the α',α' -dibromomethyl ketone VIII (Scheme 4) in which the epoxy function is still present according to the spectral data: ν (C=O) 1720 cm^{-1} , δ (CHBr₂) 5.85 (s), δ (OCH) 3.80 (s) ppm. This dibromide showed a curious reaction with thiophenol in benzene: only one bromine is displaced by the S-phenyl group, while the second halogen is exchanged by hydrogen. The product IX was obtained in a yield of 80%; m.p. 70-72 $^\circ$, ν (C=O) 1710 cm^{-1} , δ (CH₂) 3.91 (d), 3.35 (d) (AB qu, J 17 Hz). The latter exchange reaction most likely proceeds *via* a nucleophilic attack of thiophenol on bromine and subsequent protonation of the thus-formed α' -carbon ion.

References and Notes

- 1) Prepared by a Darzens condensation and subsequent saponification of the glycidic esters according to L. Claisen, *Chem. Ber.*, **38**, 693 (1905).
- 2) Compare: B. Penke, J. Czombos, L. Balaspiri, J. Petres and K. Kovacs, *Helv. Chim. Acta*, **53**, 1057 (1970); D.S. Tarbell and J.A. Price, *J. Org. Chem.*, **22**, 245 (1957).
- 3) N.F. Woolsey and M.H. Khalil, *J. Org. Chem.*, **38**, 4216 (1973).
- 4) Cf. N.A. Nelson, *J. Org. Chem.*, **38**, 3798 (1973).