Tetrahedron. Vol. 28, pp. 3009 to 3013. Pergamon Press 1972. Printed in Great Britain

CHEMISTRY OF α-HALOMETALCOMPOUNDS

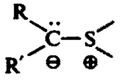
A GENERAL METHOD FOR OBTAINING EPOXIDES FROM ALDEHYDES AND KETONES

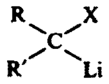
G. CAINELLI†, N. TANGARI and A. UMANI RONCHI†
Istituto di Chimica Organica Università Via Amendola 173 70126 Bari (Italy).

(*Received in the UK* 7 *December* 1971; *Accepted for publication* 28 *January* 1972)

Abstract—A general oxirane synthesis from a geminal dibromide and a carbonyl compound was studied. The reaction proceeds through an α-bromolithium species, most conveniently generated by reacting a geminal dihalogenide (e.g. ethylidene, isopropylidene. benzylidene bromide and ethyl dibromoacetate) and butyllitium or lithium suspended in THF. Aliphatic, alicyclic and aromatic aldehydes and ketones give rise to the corresponding epoxides, in good yields.

IN A PRECEDING PAPER[1] we have emphasized the analogy between sulphurylides (I) and α-halolithium derivatives (II) Both classes of compounds can be considered as carbanion-like species whose negative charge is stabilized to some extent by an adjacent electronegative element or group which also displays leaving group properties. This structural analogy suggests analogous chemical behaviour.


I

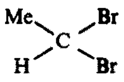

X = Cl, Br
R = R′ = H

II

We have previously shown that bromolithium and chlorolithium methane react in THF with aldehydes and ketones to give the corresponding oxiranes in similar manner to dimethyloxosulphonium and dimethylsulphonium methylide.[2]

The potential utility of the α-halolithium compounds as reagents for selective epoxidation of carbonyl compounds in organic synthesis prompted us to investigate the possibility of extending this reaction to substituted methylene groups.

We have chosen four representatives and readily accessible geminal dihalogenides: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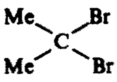
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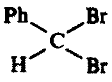
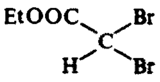

V


VI

ethylidene bromide (III), isopropylidene bromide (IV),[3] benzylidene bromide (V) and ethyl dibromoacetate (VI). We have been able to show that the reaction between carbonyl compounds and α-halolithium derivatives give oxiranes, through the formation of an intermediate halohydrin salt, as depicted in the scheme: Synthesis of the halometal

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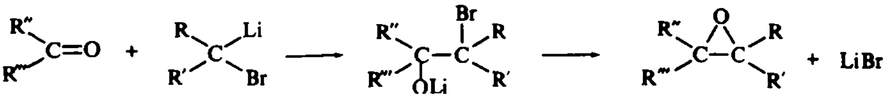
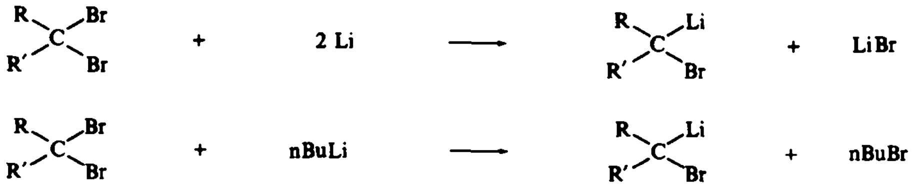
† Present Address Istituto Chimico, G. Ciamician Via Selmi 2, Bologna.



species from the starting dihalogenides has been achieved in THF by Br-Li interconversion, either by treatment with Li metal (Method A) or BuLi (Method B).[1,4]



Because of high instability of the generated α-halolithium species it is necessary to prepare the reagents in the presence of the carbonyl compound. The use of Li metal (A) although particularly simple, seems in general, to be less satisfactory than use of BuLi (B). This is probably due to the fact that BuLi can be used at very low temperatures where the half-life of the involved organometallic species is greater.

The general procedure for Method A involves addition at room temperature of a solution of the carbonyl compound and the geminal halogenide in THF to a suspension of Li metal in THF. After stirring for a few hours MeOH is added to destroy excess Li, the mixture poured into ice-water and the products isolated by ether extraction. The oxirane, if necessary, can be separated by chromatography on silica gel.

In Method B, a mole of BuLi in hexane is added under stirring at −78° to an equimolar amount of carbonyl compound and the geminal halogenide in THF. After one hour the mixture is allowed to reach room temperature and is worked up.

The BrLiCHCOOEt, having the partial negative charge on the carbon stabilized by the adjacent electron withdrawing carbonyl group, is more stable than the alkyl substituted halolithium species and it is possible to prepare the reagent by treatment with BuLi at −78° before adding the carbonyl compound.

The products were identified either by comparison with authentic samples or by spectroscopic, mass spectral and elemental analysis. As shown in Table 1, the reaction seems to have wide applicability, saturated aliphatic and aromatic aldehydes and ketones as well as steroids can be employed. Yields in the majority of cases studied are about 60–70%, remaining material being chiefly unreacted starting material.

The lower yield observed in the case of benzophenone is probably due to steric hindrance at the carbonyl centre.[8]

The reaction seems to lack stereospecificity since an approximately 1 : 1 mixture of *cis-trans* oxirane isomers (analysed by TLC, VPC and NMR) was isolated in all cases studies.

Since the epoxidation reaction is quite general, and gives high yields of oxiranes it can be of considerable practical value. Preparative interest in the reaction is increased by the fact that Corey's reaction[6] is less useful for substituted epoxides since sulphoniumalkylides are less stable than sulphonium methylide and can be generated efficiently only by careful selection of base, solvent and working conditions.[8]

Work is in progress in this laboratory, to further investigate the chemistry of this class of compounds.

TABLE 1. EPOXIDES OBTAINED FROM GEMINAL DIHALOGENIDES AND CARBONYL COMPOUNDS.

Carbonyl compound	epoxide obtained	Yield%[*]	
	from ethylidene bromide		
Octanal	2-methyl-3-heptyl-oxirane	80[a,c]	35[b,c]
Benzaldehyde	2-methyl-3-phenyl-oxirane[5,6]	75[a,c]	35[b,c]
Methylhexylketone	2-methyl-3-methyl-3-hexyl-oxirane	95[a,c]	50[b,c]
Acetophenone	2-methyl-3-methyl-3-phenyl-oxirane[7]	85[a,c]	25[b,c]
Benzophenone	2-methyl-3,3-Diphenyl-oxirane[6]	35[b]	
5 α-cholestan-3-one	3,3′-epoxy-3′-methyl-5 α-cholestane	65[b,c]	
	from isopropylidene bromide		
Cyclohexanone	2,2-dimethyl-3,3-pentamethylene-oxirane[8]	50[a]	
	from benzylidene bromide		
p-chloro-benzaldehyde	2-phenyl-3-*p*-chlorophenyl-oxirane[9a,b]	45[a,c]	
Cyclohexanone	2-phenyl-3,3-pentamethylene-oxirane	55[a]	
5 α-cholestan-3-one	3,3′-epoxy-3′-phenyl-5 α-cholestane	65[a,c]	
	from ethyl dibromoacetate		
Benzaldehyde	2-phenyl-3-carbethoxy-oxirane[10a,b,c]	50[a,c]	
Methylhexylketone	2-methyl-2-hexyl-3-carbethoxy-oxirane	50[a,c]	
5 α-cholestan-3-one	3,3′epoxy-3′-carbethoxy-5 α-cholestane	60[a,c]	

[*] The yield indicated refers to pure isolated compounds

[a] Method B (with BuLi)

[b] Method A (with Li dispersion)

[c] Mixture of isomers as demonstrated by NMR, VPC and TLC

EXPERIMENTAL

M.ps are uncorrected. IR spectra were determined with a Perkin-Elmer Model 257 Infracord spectrophotometer. Only predominant peaks are reported (cm^{-1}). NMR spectra were recorded on Varian A 100 instrument, chemical shifts were measured in ppm (δ) (J in Hz) from TMS as internal standard. Mass spectra were measured on a Hitachi–Perkin–Elmer RMU6D (single focus) spectrometer at 70 eV. TLC were performed on silica gel HF_{254} (Merck-Darmstadt). Column chromatography on silica gel 0·05–0·20 mm (Merck–Darmstadt) using hexane–ether as solvent.

General procedure for the synthesis of epoxides

Method A: with lithium dispersion. In a 3-necked flask equipped with mechanical stirrer, reflux condenser and dropping funnel, 0·04 g atoms[*] of 30% Li dispersion in dry THF (30 ml) and 10 mmoles of carbonyl compound were placed under argon. To the well-stirred solution CH_3CHBr_2 (20 mmoles)[*] in dry THF (20–25 ml) was added over 15 min at 0°. The mixture was allowed to rise to room temp and left for 6 hr. poured into ice-water and extracted with ether. After washing with water, drying and evaporating, the products were isolated by chromatography on silica gel. In most cases only epoxides and starting material were isolated.

Method B: with BuLi. (a). (Ethylidene bromide, isopropylidene bromide and benzylidene bromide). In a 3-necked flask equipped with mechanical stirrer and 2 dropping funnels, were placed under argon 20 mmoles[*] of the dibromide in 30 ml of dry THF. To this well stirred solution 10 mmoles of carbonyl compound in 30 ml of dry THF and 20 mmoles[*] of BuLi in hexane were separately but contiguously added over 30 min at −78°. The stirring continued at −78° for 1 hr. and at room temp for 6 hr. The mixture was

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[*] The use of a two-fold amount of dibromide and lithium or butyllithium has been shown to considerably increase the oxirane yield.

poured into ice–water and ether extracted. After washing with water, drying and evaporating, the products were isolated by chromatography on silica gel. In general only epoxides and starting material were isolated.
(b). Ethyl dibromoacetate (VI). In a 3-necked flask equipped with a mechanical stirrer and 2 dropping funnels. were placed under argon 20 mmoles* of VI. in 30 ml of dry THF. To this well stirred solution 20 mmoles of BuLi in hexane were added over 30-min at −78°, followed by the addition over a period of 30 min at −78° of 10 mmoles carbonyl compound in 30 ml of THF. The stirring continued at −78° for 1 hr. and at room temp for 6 hr. The mixture was poured into ice–water and ether extracted. After washing with water, drying and evaporating, the products were isolated by chromatography on silica gel. In general only epoxides and starting materials were isolated.

All products listed were identified by NMR, IR, Mass spectra, elemental analysis and by comparison with literature data or with authentic samples.

2-*Methyl*-3-*heptyl-oxirane*. Obtained in 35%‡ yield (Method A) and 80%‡ yield (Method B). Mass: M^+ 156 *m/e*. (Found C, 75·8; H, 12·6; $C_{10}H_{20}O$ requires C, 76·9; H, 12·9%). NMR spectrum in agreement with this structure.

2-*Methyl*-3-*methyl*-3-*hexyl-oxirane*. Obtained in 50%‡ yield (A) and 95%‡ yield (B). Mass: M^+ 156, (M^+ $-H_2O$) 138 *m/e*. (Found C, 77·2; H, 12·6; $C_{10}H_{20}O$ requires C, 76·9; H, 12·9%). NMR spectrum in agreement with this structure.

2-*Methyl*-3-*methyl*-3-*phenyl-oxirane*. Obtained in 25%‡ yield (A) and 85%‡ yield (B). IR (neat) 1690, 1600, 1450, 1210, 765, 700 cm^{-1}. Mass: M^+ 148 *m/e*. (Found: C, 81·3; H, 8·3; $C_{10}H_{12}O$ requires C, 81·0; H, 8·2%). NMR in CCl_4 mixture of isomers (ratio about 1 : 1) CH_3—$\underline{CH}$—, q 3δ, J=6 Hz and q 3·3 δ, J=6 Hz $\underline{CH}_3$—CH—, d 0·91 δ, J=6 Hz and d 1·36 δ, J=6 Hz.

2-*Methyl*-3,3-*diphenyl-oxirane*. Obtained in 35% yield (A). IR 1490, 1450, 1020, 760, 750 cm^{-1}. Mass: M^+ 210 *m/e*. (Found C, 85·6; H, 6·6; $C_{15}H_{14}O$ requires C, 85·7; H, 6·7%). NMR in CCl_4 $\underline{CH}_3$—CH—, d 1·1 δ, J=6 Hz CH_3—$\underline{CH}$—, q. 3·3 δ, J=6 Hz.

3,3′-*Epoxy*-3′-*methyl*-5α-*cholestane*. Obtained in 65%‡ yield (A) m.p. 103–104°. IR(nujol) CO bands absent. Mass: M^+ 414 *m/e*. (Found: C, 84·0; H, 12·0 $C_{29}H_{50}O$ requires C, 83·9; H, 12·1%). NMR spectrum in agreement with this structure.

2-*Phenyl*-3,3-*pentamethylene oxirane*. Obtained in 55% yield (B). IR (neat) 1490, 1450, 910, 870, 840, 745, 700 cm^{-1}. Mass: M^+ 188, (M^+ $-H_2O$) 170 *m/e*. (Found C, 83·2; H, 8·5; $C_{13}H_{16}O$ requires C, 82·9; H, 8·6%). NMR in CCl_4 —$(C\underline{H}_2)_5$ — m (0·9–2) δ C_6H_5—C$\underline{H}$— s 3·66 δ; $C_6\underline{H}_5$—CH— (7·1–7·4) δ.

3,3′-*Epoxy*-3′-*phenyl*-5α-*cholestane*. Obtained in 65%‡ (B) m.p. 101°–103° IR (nujol) CO band absent. Mass: M^+ 476, (M^+ —H_2O) 458 *m/e*. (Found: C, 85·4; H, 10·8 $C_{34}H_{52}O$ requires C, 85·6; H, 10·9%). NMR spectrum in agreement with this structure.

2-*Methyl*-2-*hexyl*-3-*carbethoxy-oxirane*. Obtained in 50%‡ (B). IR (neat) 1750 cm^{-1} Mass: M^+ 214 (M^+ —H_2O) 196 *m/e*. (Found: C, 67·6; H, 9·9 $C_{12}H_{22}O_3$ requires C, 67·3; H, 10·3%). NMR spectrum in agreement with this structure.

3,3′-*Epoxy*-3′-*carbethoxy*-5α-*cholestane*. Obtained in 60%‡ yield (B) m.p. 129–130° IR (nujol) 1740 cm^{-1}. Mass: M^+ 472 *m/e*. (Found: C, 78·3; H, 11·1 $C_{31}H_{52}O_3$ requires C, 78·7; H, 11·1%). NMR spectrum in agreement with this structure.

Acknowledgements.—We wish to thank Mr. A. Tambone for his valuable contribution to this research. This work was supported by a grant from the Consiglio Nazionale delle Ricerche, Rome.

REFERENCES

[1] G. Cainelli, A. Umani Ronchi, F. Bertini, P. Grasselli and G. Zubiani, *Tetrahedron* **27**, 6109 (1971)

[2] [a]E. J. Corey and M. Chaykowsky *J. Am. Chem. Soc.* **87**, 1353 (1965); [b] A. W. Johnson, *Ylid Chemistry* p. 304 Academic Press, New York (1966)

[3] H. Weil, *Methoden der Organischen Chemie* Vol. 5/4 p. 501, Thieme Verlag (1960)

[4] G. Köbrich and R. H. Fischer, *Tetrahedron* **24**, 4343 (1968)

[5] F. Fischer and H. Ronsch, *Chem. Ber.* **94**, 901 (1961)

[6] E. J. Corey and W. Oppolzer, *J. Am. Chem. Soc.* **86**, 1899 (1964)

[7] G. A. Razvavev, V. S. Etlis and E. P. Morozova, *Zh. Orgam. Khim.* **1** (9), 1567 (1965)

[8] E. J. Corey, M. Jautelat and W. Oppolzer, *Tetrahedron Letters* 2325 (1967)

‡ No attempts were made to preparatively separate the *cis-trans* oxirane isomers.

[9] [a]H. O. House, *J. Am. Chem. Soc.* **77**, 3070 (1955); [b] A. W. Johnson, V. J. Hruby and J. L. Williams, *Ibid.* **86**, 918 (1964)

[10] [a] G. Darzens and G. Levy, *C.R. Acad Sci, Paris* **24**, 272 (1937); [b] V. R. Valente and J. L. Wolfhagen, *J. Org. Chem.* **31**, 2509 (1966); [c] B. Deschamps and J. Seyden-Penne, *Tetrahedron* **27**, 3959 (1971)