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CHEMISTRY OF α-HALOMETAL COMPOUNDS

BROMOLITHIUMMETHANE, SYNTHESIS OF EPOXIDES FROM ALDEHYDES AND KETONES

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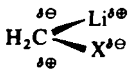
Abstract—The reaction between bromolithiummethane and carbonyl compounds has been studied. The organometallic species has been generated *in situ* by reacting dibromomethane and butyllithium, lithium suspension or amalgam in THF. Aliphatic, alicyclic and aromatic aldehydes and ketones give rise to the corresponding epoxides generally in satisfactory yields. α,β-unsaturated carbonyl compounds do not react under the mentioned conditions and this is useful if selectivity is required. The influence of the solvent on the reaction course is also discussed.

Molecules bearing a carbon atom connected to a ligand of lower electronegativity (*e.g.* an alkali metal) and a group of higher electronegativity (*e.g.* a halogen atom) are an interesting class of reagents. extensively investigated recently.[1]

The halomethyl derivatives of Li of general formula I are also members of this class.

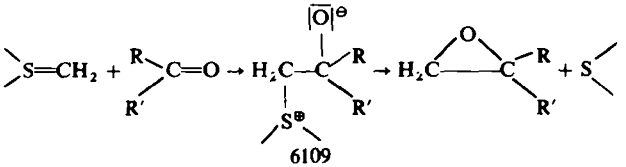


$$H_2\overset{\delta\ominus}{\underset{\delta\oplus}{C}}\begin{smallmatrix}Li^{\delta\oplus}\\ X^{\delta\ominus}\end{smallmatrix}\qquad X = Cl, Br, I$$

I

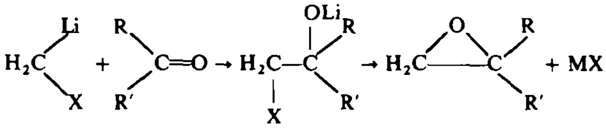
These very reactive and unstable compounds can be compared at low temp. and in ethereal solvents to normal lithium alkyls resembling in many aspects the dimethylsulphonium and dimethyloxosulphonium methylides.

In fact both α-halolithium compounds and the sulphurylides can be considered as carbanions or carbanionoidic species in which the negative charge on the carbon is more or less stabilized by a neighbouring electronegative function. Moreover in both types of compounds the electronegative group directly linked to the carbanion has leaving group properties.



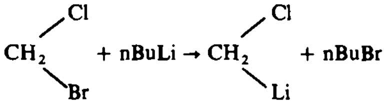
This structure similarity allows us to predict a certain parallelism in chemical behaviour. The reactivity towards carbonyl compounds was of interest to us. It is well known that sulphur ylides react with carbonyl compounds yielding oxiranes.[4]

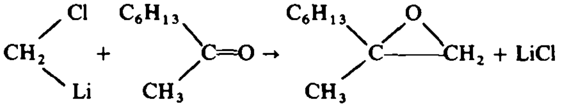
One could therefore expect the halolithiummethanes to give the oxiranes like Corey's reagents. through the formation of an intermediate halohydrin salt.



To check this possibility we first studied the chlorolithiummethane. obtained by Koebrich[2a] by reacting CH_2ClBr and BuLi in THF at $-110°$. This derivative, although very unstable also at $-110°$, reacts as a normal alkyllithium yielding chloroacetic acid on carboxylation.

We have now found that this species reacts immediately after its formation at $-110°$ with methyl hexyl ketone to give the expected oxirane in low yield.

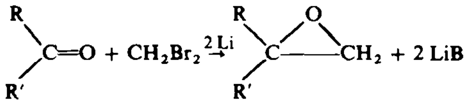




Br is in general a better leaving group than Cl. thus it should be expected bromolithiummethane to react with carbonyl compounds to give oxiranes more easily than the corresponding chloroderivative.

$LiCH_2Br$ however is very unstable and is practically impossible to prepare even at $-110°$. We tried therefore to prepare it *in situ* in the presence of the carbonyl compound. For this purpose an equimolar solution of 5α-cholest-3-one and CH_2Br_2 in THF were treated at $-78°$ with a mole of BuLi in hexane. Work up yielded 20% of the expected oxirane together with the carbinol derived from the direct addition of BuLi to the carbonyl group.

To avoid the lowering of yield caused by carbinol formation we tried to achieve the Br–Li exchange directly with Li metal (or. although less convenient. with lithium amalgam) instead of BuLi. In fact if equimolar amounts of a carbonyl compound and CH_2Br_2 were treated under N_2 in THF with two gram-atoms of Li dispersion the corresponding oxiranes were formed:



Epoxides were produced by this process from a variety of aldehydes and ketones. Some experimental results are summarized in Table 1.

TABLE 1. EPOXIDES OBTAINED FROM THE REACTION OF METHYLENE. BROMIDE AND LITHIUM WITH CARBONYL COMPOUNDS

Carbonyl compound	Epoxide obtained	Yield %[*]
Dodecanal	2-n-undecyl-oxirane	35%[a]
Benzaldehyde	2-phenyl-oxirane[4a]	37%[a]
Acetophenone	2-methyl-2-phenyl-oxirane	45%[a, b]
Cyclohexanone	2.2-pentamethylen-oxirane[5]	48%[a]
Methyl hexyl ketone	2-methyl-2-hexyl-oxirane	52%[a]
5α-Cholest-3-one	3.3'-epoxy-5α-cholestane[6]	95%[a, d] 65%[c, d]
Pregn-5-en-3β-acetoxy-20-one	20.21-epoxy-20-methyl-3β-acetoxy-pregn-5-ene	40%[a, e]
Pregn-4-en-3.20-dione	20.21-epoxy-20-methyl-pregn-4-en-3-one	50%[a, e]
11β-acetoxy-pregn-4-en-3.20-dione	20.21-epoxy-20-methyl-11β-acetoxy-pregn-4-en-3-one	45%[a, e]

[*] The yield indicated refers to pure isolated compounds

[a] With Li dispersion

[b] Isolated as 2-phenylpropanal ref. 9

[c] With Li/Hg

[d] Mixture of isomers as demonstrated by NMR

[e] Pure by TLC. The stereochemistry of C_{20} not determined

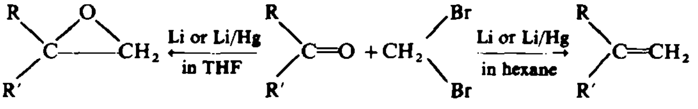
The temp. does not seem to be critical, because no great difference was observed from −78° to room temperature. Yield is in the order of 40–50% but, since a considerable amount of unchanged starting material was always recovered, the actual amount of the carbonyl compound converted was correspondingly higher.

The satisfactory yields and simplicity of the procedure make this reaction useful in synthesis as an alternative to the Corey method.[4] α.β-Unsaturated carbonyl compounds do not react under these conditions and can be quantitatively recovered. This behaviour, which is analogous to that of the dimethyloxosulphonium methylide,[4a] is probably a consequence of enolate ion formation.

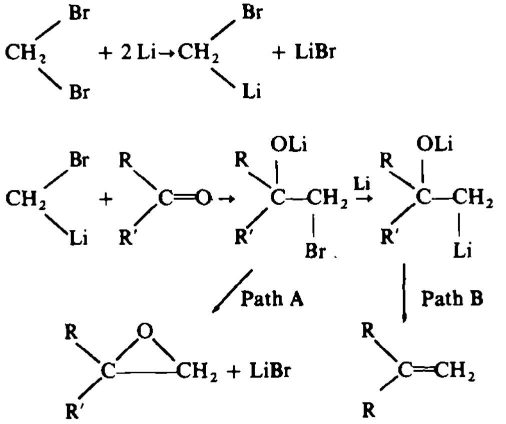
We have obtained, for instance, 20.21-epoxy-20-methyl-pregn-4-en-3-one from pregn-4-en-3.20-dione and 20.21-epoxy-20-methyl-11β-acetoxy-pregn-4-en-3-one from 11β-acetoxy-pregn-4-en-3-one.

Products seem to be pure by TLC. No attempt was made to ascertain the stereochemistry at C_{20}.

The course of the reaction is dependent on the solvent. THF leads to monosubstituted oxiranes, whereas the reaction takes another course in hexane giving rise to the corresponding olefine.



The following scheme clearly illustrates the probable course of this reaction.



The α-bromolithiummethane formed first reacts *in situ* with the carbonyl compound to give the metal salt of a halohydrin. This compound can either undergo a 1.3-elimination (Path A) or can further react with the metal to give a metal promoted 1.2-elimination (Path B). Since both paths are irreversible, it follows that the epoxide–olefin ratio is kinetically controlled and solvent dependent.

In THF, which increases the nucleophilicity of the oxygen atom, the epoxidation is greatly accelerated and consequently the epoxide is the sole isolated product. In hexane the nucleophilicity of the oxygen atom is lowered and the attack of the metal on the halogen-atom of the halohydrin is more difficult and therefore both epoxidation and olefination rates are decreased.

The over all effect however is remarkably in favour of the formation of the methylenic olefin which is the sole product isolated although in low yields. In ether, whose properties are between THF and hexane, the two rates of reaction become comparable and consequently both epoxide and methylenic olefin are formed.

In order to enlarge the scope of this reaction and to extend it to other geminal halogenides further work has been undertaken in our laboratories.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined on a Beckmann DK2 spectrophotometer in 95% EtOH. λ_{max} (nm) and ε are reported. IR spectra were determined with a Perkin–Elmer Mod 137 Infracord spectrophotometer. Only predominant peaks are reported (cm^{-1}). NMR spectra were recorded on Varian A 60 and A 100 instruments. Mass spectra were measured on a Hitachi-Perkin-Elmer RMU6D (single focus) spectrometer at 70 eV. TLC were performed on silica gel HF_{254} (Merk-Darmstadt). Column chromatography on silica gel 0·05–0·20 mm (Merk-Darmstadt).

General procedure for the synthesis of epoxides. In situ with lithium dispersion. In a 3-necked flask equipped with mechanical stirrer, reflux condenser and dropping funnel, were placed 0·04 g atoms of 30% Li dispersion in dry THF (30 ml) and 10 mmoles of carbonyl compound under argon. To the well-stirred solution CH_2Br_2 (20 mmoles) in dry THF (20–25 ml) was added over 15-min at −78°. 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.

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

2-n-*Undecyl-oxirane*. The epoxide was obtained in 35% yield (700 mg) from 1·85 g of dodecanal. IR (neat film) 1460; Mass: M^+ *m/e* 198. (Found C, 78·2; H, 13·4. $C_{13}H_{26}O$ requires: C, 78·7; H, 13·2%). NMR spectrum in agreement with this structure.

2-*Methyl-2-hexyl-oxirane*. The epoxide was obtained in 52% yield (740 mg) from 1·28 g methyl hexyl ketone. IR (neat film) 1450; Mass: M^+ *m/e* 142. (Found: C, 75·7; H, 12·6. $C_9H_{18}O$ requires: C, 76·0; H, 12·7%). NMR spectrum in agreement with this structure.

20,21-*Epoxy-20-methyl-3β-acetoxy-pregn-5-ene*. The epoxide was obtained by the same procedure in 40% yield (750 mg) from 1·8 g of 3β-acetoxy-pregn-5-ene-20-one. M.p. 144–146° from MeOH; $[\alpha]_D = -61$; IR (nujol) 1740, 1250. 1040; Mass: (M^+ —CH_3COOH) *m/e* 312. (Found: C, 77·2; H, 9·7. $C_{24}H_{36}O_3$ requires: C, 77·4; H, 9·7%). NMR spectrum in agreement with this structure.

20.21-*Epoxy-20-methyl-pregn-4-en-3-one*. The epoxide was obtained in 50% (820 mg) yield from 1·57 g of pregn-4-en-3,20-dione. M.p. 140° from MeOH; $[\alpha]_D = +89°$; IR (nujol) 1665, 1620, 880; UV 242 (15.200); Mass: M^+ *m/e* 328. (Found: C, 79·9; H, 9·9. $C_{22}H_{32}O_2$ requires C. 80·4; H. 9·8%). NMR spectrum in agreement with this structure.

20.21-*Epoxy-20-methyl-11β-acetoxy-pregn-4-en-3-one*. The epoxide was obtained in 45% yield (870 mg) from 1·86 g of 11β-acetoxy-pregn-4-en-3,20-dione. IR (nujol) 1725, 1680, 1610, 1250; UV 241 (14.600); Mass: M^+ 386, (M^+ —CH_3COOH) *m/e* 326.

Reaction of 5α-cholestan-3-one with methylene bromide and lithium amalgam. (*a*) *in* THF. 0·5 g (1·3 mmoles) of 5α-cholestan-3-one and 0·376 g (1·95 mmoles) of CH_2Br_2 in THF (30 ml) were added over 15 min at 0° to lithium amalgam prepared by stirring 100 g Hg and 0·027 g Li (0·0038 g atoms) in dry THF (30 ml). The mixture was left at room temp. for an additional hr. poured into ice-water and extracted with ether. After washing with water, drying and evaporating by chromatography on silica gel gave 0·34 g of a mixture of isomeric 3,3′-epoxy-5α-cholestane. IR (nujol) CO-Bands absent; Mass: M^+ *m/e* 400. The NMR spectrum shows two signals at 2·33 δ and 2·41 δ (integral ratio 1:2) corresponding to the —CH_2—O— of the two isomeric epoxides.

By the same procedure a mixture of 40 mg of 3,3′-epoxy-5α-cholestane (mixture of isomers), 50 mg of 3,3′-methylen-5α-cholestane and starting material was obtained.

Also by the same procedure a mixture of 75 mg of 3-methylene-5α-cholestane and starting material was obtained.

Reaction of 5α-cholestan-3-one with methylene bromide and n-butyllithium. To a solution of 0·5 g (1·3 mmoles) of 5α-cholestan-3-one and 0·12 ml (1.5 mmoles) of CH_2Br_2 in dry THF (25 ml), 1·2 ml (1·5 mmoles) of n-BuLi in hexane were added in 15 min at −78% under argon. The mixture was allowed to remain at room temp. for an additional hr, poured into ice-water and extracted with ether. After washing with water, drying and evaporating, 0·1 g of 3.3′-epoxy-5%-cholestane (mixture of isomers) were isolated by chromatography on silica gel.

Reaction of methyl hexyl ketone with chlorolithiummethane. To a solution of 2 g (15 mmoles) of chlorobromomethane in 70 ml "Trapp mixture",[1] 12 ml (15 mmoles) of n-BuLi in hexane were added over 30 min at −110° under argon. Thereafter 2 g (15 mmoles) of methyl hexyl ketone in 20 ml "Trapp mixture" was added. The mixture was heated at 50° for 3 hr, poured into ice-water and extracted with ether. After washing with water, drying and evaporating, 0·1 g of 2-methyl-2-hexyl-oxirane was isolated by chromatography on silica gel.

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