In Situ Formation and Reactions of Chloromethyl-lithium under Sonochemical Conditions

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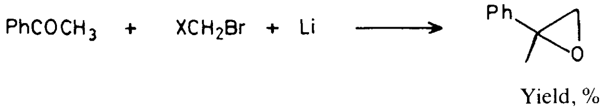
Under sonication, bromochloromethane, a carbonyl compound, and lithium in tetrahydrofuran yield the corresponding α-chlorohydrin, which can cyclise to the epoxide, in excellent yields.

Halogenomethyl-lithium compounds are synthetically valuable reagents, but their use has been severely restricted owing to their extreme thermal instability.[1] They can be generated by halogen–metal exchange at low temperature,[2] or by direct lithiation with the metal,[3] but this technique has received only limited applications.

We have previously demonstrated that organometallic reagents can be efficiently generated and caused to react in a Barbier procedure by using sonochemical methods.[4] As this procedure appears to allow the trapping of unstable species,[5] we investigated the sonochemical preparation of chloromethyl-lithium by the direct reaction of chloromethyl bromide with lithium metal, and its further *in situ* reaction with a carbonyl compound. Successful results are reported in this note. However, the first attempts proved to be disappointing. When sonicated in a laboratory cleaning bath, bromochloromethane (**1**), acetophenone, and lithium in tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), di-butyl ether, or dioxane gave complex mixtures in which the expected epoxide was formed irreproducibly in only 0—35% of the theoretical amount (Table 1). The possibility that the epoxide product (**4**) could react with the organometallic reagent[6] may explain the poor selectivity.

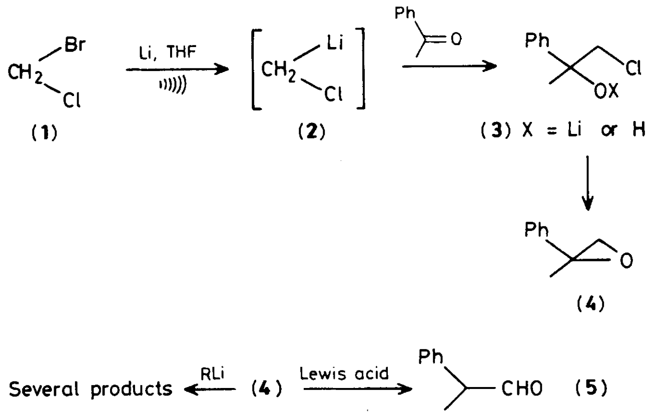
This major drawback was circumvented by accelerating greatly the generation of (**2**) and slowing the cyclisation step.

Table 1. Epoxide formation from acetophenone.



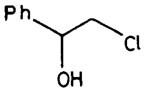
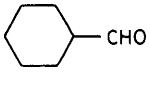
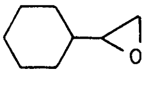
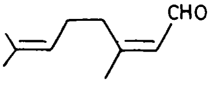
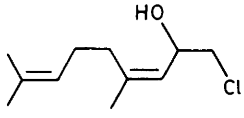
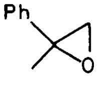
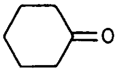
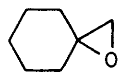
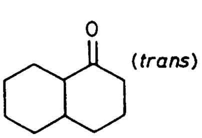
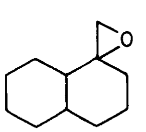
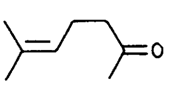
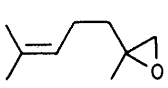
Conditions	X	Solvent	*T*/°C	Yield, % (v.p.c.)[a]
Stirring, 4 h	Cl	THF	+20	55
Sonication:				
Cleaning bath, 45 min	Br	THF	+15	~35
,, 45 min	Br	DME	+15	~20
Sonication:				
Probe, 20 min	Br	THF	−15	75
,, 20 min	Cl	THF	−15	98
,, 20 min	Cl	THF	+20	72

[a] Erba Science Chromatograph, column, SE 30 10% 2 mm × 2 m, 80 °C. Internal standard: benzaldehyde added after hydrolysis of the reaction mixture.



Scheme 1

Table 2. Epoxide formation from various carbonyl compounds.

Carbonyl compound	Equiv. of reagent[a]	Product	%Yield[b]
PhCHO	1.2		90
	1.2		91
	1.2		79
$PhCOCH_3$	2		82
	2		80
	1.2	 [c]	77
	2		72

[a] Typically, the carbonyl compound (3 mmol), CH_2BrCl (3.6 mmol), and lithium wire (*ca.* 150 mg) in dry THF (25 ml) were sonicated (Ultrason Annemasse probe) for 20 min at −15 °C in the case of ketones and −50 °C for aldehydes. After sonication had been stopped, the cooling bath was removed and the mixture stirred for 10 min. After hydrolysis (aq. NH_4Cl) the organic phase was worked up as usual and the residue chromatographed (SiO_2 column). [b] Isolated yields of purified material. Structures are consistent with analytical data. [c] Relative configuration unknown.

We observed recently[7] that in a sonochemical Barbier reaction the rate of consumption of the organic halide is increased by optimising two parameters: the energy and the temperature, and by the use of more efficient probe type ultrasound generators. We applied these results to the present problem. Sonication was thus effected with a probe generator delivering 60 W energy in a cell[8] thermostated at −15 °C for 20 min. Almost quantitative conversion of acetophenone to the corresponding epoxide was achieved (Table 1). This result stresses the importance of the energy parameter in sonochemical processes. For comparison, experiments were carried out with stirring but without sonication, or with dibromomethane, and yields decreased by *ca.* 40 and 20% respectively.

Extension of the process to other carbonyl compounds gave the results in Table 2, showing that the epoxides can be obtained in satisfactory isolated yields. Interestingly, the yields are excellent even if only 1.2 equiv. of bromochloromethane is used. Small amounts (<5%) of the rearranged aldehydes[9] [*e.g.* (**4**) → (**5**)] were detected as contaminants. Reactions using aldehydes frequently stop at the chlorohydrin stage but the small number of examples makes generalisation difficult.

Epoxides can be synthesised from carbonyl compounds with several reagents, *e.g.* di-iodomethane–samarium di-iodide,[10] and sulphur,[11] selenium,[12] or arsenic ylides.[13] The advantages of the present sonochemical method are mainly its great ease and rapidity. It also allows the use of inexpensive reagents and no auxiliary alkyl-lithium is required. It was, however, impossible to obtain successful results with dichloromethane.

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