A One-step Alternative to the Grignard Reaction

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Summary The reaction between organic halides, lithium, and carbonyl compounds gives products identical with those which would be formed from a Grignard-type process, and the yields, in general, are good.

IN the course of investigations of the reaction between an alkyl halide and vinyl monomer with alkali metals[1] it was found that methyl methacrylate reacted with butyl bromide and lithium to give a high yield of 3-butyl-2-methylhept-1-en-3-ol. Thus a Grignard-type reaction had occurred to give this product in appreciably better yield than in the conventional Grignard process, and in similar yield to that obtained with lithium alkyls in a two-step process.

Carbonyl compound	Halide	% Yield of alcohol
Propionaldehyde	Ethyl bromide	90
Propionaldehyde	Methyl iodide	51
Mesityl oxide	Bromobenzene	67[a]
Paraformaldehyde	n-Hexyl bromide	72
Acetone	Bromobenzene	34
Methyl benzoate	Methyl iodide	74
Benzaldehyde	Bromobenzene	96
Benzaldehyde	Allyl bromide	71
Methyl methacrylate	n-Butyl bromide	89

[a] This was a mixture of 1,3-dimethyl-1-phenylbutadiene (46%) and 1,1-dimethyl-3-phenylbutadiene (54%).

Because of the efficiency of this reaction it was decided to conduct a survey to determine its scope and limitations. Experiments were carried out with a variety of carbonyl compounds and halides (10—15% excess) and some typical yields obtained are listed in the Table.

Experimentally, the process is very simple. A mixture of a carbonyl compound and alkyl halide is added dropwise to a suspension of lithium pieces in tetrahydrofuran. The reaction is highly exothermic and the rate of addition is so adjusted to maintain the reaction temperature at the required value (0° or below).

Yields were determined by g.l.c. using an internal standard. The reactions were essentially complete in 2 hr. and the process appears to be of general applicability. No attempts have so far been made to maximise these yields but in general they compare quite favourably with those obtained in conventional Grignard reactions.[3]

The reaction pathway probably involves initial reaction of the halide with lithium to form an organolithium compound, followed by nucleophilic attack of this reagent on the carbonyl compound.

Alternatively, an electron transfer may occur from the metal to the carbonyl compound to give a transient radical anion which then reacts successively with the halide and with further lithium

$$\mathrm{R^2R^3C{=}O + Li \rightleftarrows R^2R^3C \overset{-}{\underline{\cdots}} OLi^+ \xrightarrow{R^1X}}$$

$$\mathrm{R^1R^2R^3C\text{–}O\cdot \xrightarrow{Li} R^1R^2R^3C\text{–}O^-Li^+}$$

This mechanism is similar to those suggested for dissolving-metal reductions such as the Bouveault–Blanc and Birch reductions.

The mechanism (or mechanisms) involved in this reaction is currently being investigated and experiments using sodium in place of lithium are being conducted.

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[1] D. H. Richards and N. F. Scilly, *J. Chem. Soc.* (*C*), 1969, 55.

[2] I. N. Rozhkov and S. M. Makin, *Zhur. obshchei Khim.*, 1964, **34**, 59.

[3] "Grignard Reactions of Non-metallic Substances," by M. S. Kharasch and Otto Reinmuth, Constable, London, 1954.