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Pentafluoroethyllithium. Generation and Use in Synthesis

Paul G. Gassman* and Neil J. O'Reilly

Department of Chemistry, University of

Minnesota, Minneapolis, Minnesota 55455

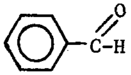
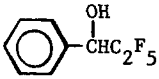
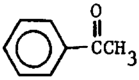
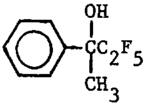
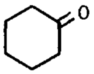
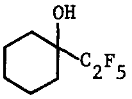
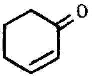
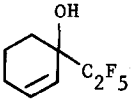
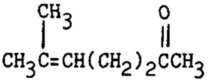
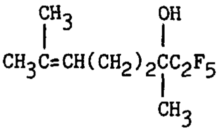
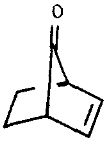
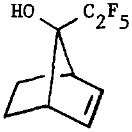
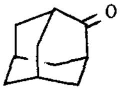
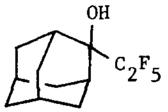
Summary: Pentafluoroethyl iodide undergoes a rapid exchange reaction with methyllithium at -78 °C in the presence of ketones to produce pentafluoroethyl-substituted tertiary carbinols in high yield.

The addition of small perfluorinated alkyl groups to more complex organic substrates is of considerable interest. From a biological point-of-view, the presence of a small perfluoroalkyl moiety often confers unique properties to a molecule in terms of increased lipophilicity, which in turn alters *in vivo* absorption and transport rates. In addition, while small perfluoroalkyl groups are chemically very stable and sterically similar to their hydrocarbon analogues, they are electronically very electron withdrawing. These electronic properties have been utilized by physical organic chemists in the study of carbocation properties.[1-3] It was this latter[3] characteristic which prompted us to develop the method which we report here for the *in situ* generation of pentafluoroethyllithium and the addition of this reagent to ketones to yield pentafluoroethyl-substituted carbinols.[4]

In a typical procedure, 1.2-1.8 equivalents of a 1.6 M solution of methyllithium-lithium bromide in diethyl ether was added to an ethereal solution containing 1.0 equivalent of a ketone or aldehyde and 1.2-1.8 equivalents of pentafluoroethyl iodide, at -78 °C. As shown in Table 1, the yields of purified (distilled) products were excellent, ranging from 81-100%.[11]

It should be noted that no products arising from attack of methyllithium on the starting carbonyl compound could be detected. This indicated that the exchange reaction between pentafluoroethyl iodide and methyllithium occurred at a rate which was much faster than the rate of addition of methyllithium to aldehydes and ketones. In order to gain some insight into the lifetime of pentafluoroethyllithium at -78 °C, we preformed the reagent through the addition of

Table 1. Pentafluoroethylation of Aldehydes and Ketones with Pentafluoroethyllithium

Ketone or Aldehyde	Equiv. of Pentafluoroethyl Iodide	Equiv. of Methyllithium	Time (min.)	Product	% Yield	B.P. °C (mm)
	1.84	1.46	30		91	61-62(2)[a]
	1.51	1.40	30		88	58-59(3)
	1.77	1.77	8		100[b]	58-59(11)
	1.56	1.24	30		81	59(5)
 $CH_3\overset{CH_3}{C}=CH(CH_2)_2\overset{O}{\overset{\|}{C}}CH_3$	1.50	1.30	30	 $CH_3\overset{CH_3}{C}=CH(CH_2)_2\underset{CH_3}{\overset{OH}{C}}C_2F_5$	86	51(1.5)
	1.19	1.17	45		84[b]	71-76(12)
	1.61	1.44	30		93	83-84(2)

(a) Lit.[9b] b.p. 84-85 °C (10 mm). (b) Isolated by column chromatography.

methyllithium to an ethereal solution of pentafluoroethyl iodide. Addition of the carbonyl compound, after 5 min, led to greatly reduced yields. For example, addition of cyclohexanone, after 5 min, to the preformed reagent gave only a 71% yield, whereas the general procedure gave a quantitative yield. This indicates to us that the half-life of pentafluoroethyllithium is 5-10 min at -78 °C.

In summary, we have developed a very convenient and efficient general method for the pentafluoroethylation of aldehydes and ketones.[12]

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References and Footnotes

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(4) Because of the extensive interest in the introduction of small perfluoroalkyl groups onto organic substrates, the literature contains numerous reports of such studies.[5] Special attention has been devoted to the use of organometallics for this purpose with calcium,[6] zinc,[7] manganese,[8] silver,[8] magnesium,[9] and lithium[10] reagents having been reported as transient intermediates. Unfortunately, we have been unsuccessful in repeating some earlier reports[9,10] and in applying certain more recent procedures [7] for the addition of small perfluoroalkyl groups to ketones. Thus, it was necessary for us to develop the procedures reported herein, in order to accomplish our goals. It should be noted that we are unaware of any previous reports of pentafluoroethyllithium.

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(11) Satisfactory elemental analyses and exact mass molecular weights were obtained for all new compounds. In all cases IR, ^{13}C NMR and ^{1}H NMR spectral data were consistent with the assigned structures.

(12) While we feel that this general procedure can be extrapolated to the use of higher molecular weight perfluoroalkyllithiums, we should note that the application to the lower homolog, trifluoromethyllithium, did not yield 1-trifluoromethylcyclohexanol in the presence of cyclohexanone.

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