Ring Opening Alkylation of Tetrahydrofuran with Some Heterosubstituted Organolithium Reagents by the Aid of Boron Trifluoride Etherate

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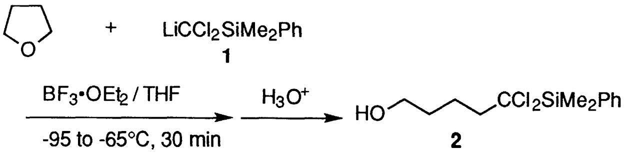
Organolithium reagents stabilized by halogeno, thio, silyl, vinyl and/or phenyl substituent(s) can cleave THF effectively under the influence of boron trifluoride etherate at lower temperatures. The softness of these carbanionic reagents seems to be important for the successful reaction.

Recently, we reported that α-halogenoalkyllithium reagents, *e.g.* $LiCCl_3$, can be utilized for oxirane and oxetane ring opening reactions in the presence of BF_3•OEt_2 in THF.[1, 2] Additionally, it was found that the solvent THF itself can be cleaved by these combined reagents, though less effectively.[1] In our ongoing study in this area, we faced to somewhat peculiar behavior of a silylated carbenoid, dichloro(dimethylphenylsilyl)methyllithium (**1**), an attempted reaction of which with 1-hexene oxide under the previously reported conditions in THF provided the solvent cleavage product exclusively. In the previous study, we have observed competitive cleavage of the solvent in some reactions with less reactive oxiranes such as epichlorohydrin but always as a minor pathway even in those cases.[1,3]

In the literature, there are some scattered examples for such direct alkylative opening of non-activated THF ring by organometallic reagents. They fall into two classes, *i.e.* trityl metal reagents[4, 5] and allylic lithium reagents.[3, 6] The reactions have been performed at elevated temperatures for the former reagents and at lower temperatures in the presence of BF_3•OEt_2 for the latter. The conditions of our reaction are similar to those of the latter.

Here, we briefly studied on the generality of this basic transformation by examining some organolithium species substituted by halogen, thio, silyl, vinyl and/or phenyl group(s) and found that they are all effective for acquiring this reactivity (Table 1).[7]

The reaction of **1** is representative. Thus, to a stirred solution of **1** (5.0 mmol) in THF (20 ml) was added n-butyllithium (1.6 M hexane solution, 5.0 mmol) slowly at -80°C, and the stirring was continued at the temperature for 10 min. The mixture was cooled down to -95°C, and BF_3•OEt_2 (6.0 mmol) was added rapidly with vigorous stirring. The mixture was allowed to come to -65°C in *ca.* 30 min. After ordinary work-up, 5,5-dichloro-5-(dimethylphenylsilyl)-1-pentanol (**2**) was isolated by flash chromatography (silica gel/ether-hexane), 1.12 g (77 %).



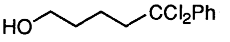
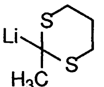
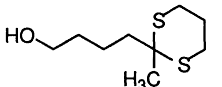
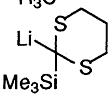
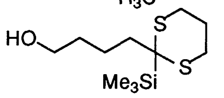
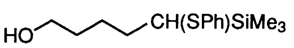
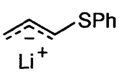
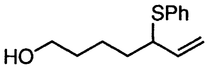
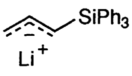
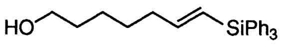
In contrast, *n*-butyllithium (a representative of ordinary organolithiums) on similar treatment but with oxidative work-up (30 % H_2O_2/3 N NaOH) gave 1-octanol and 1-butanol in 17 and 60 % GC yields, respectively. The latter product is expected from the formation of butylboron species and subsequent oxidation. This indicates that the unsubstituted alkyllithium prefers attack on the boron atom rather than that on the α position of the THF molecule complexed by the Lewis acid.

It should also be noted that highly stabilized carbanionic reagents, *e.g.* alkynyllithium and α-lithio methyl phenyl sulfone, did not give the corresponding THF cleavage product under these conditions.

From these results, the following comments can be made on the effect of substituents for acquiring this reactivity: (i) both halogens[1] and trimethylenedithio group[6] are effective but not essential, and a silyl group is equally effective; (ii) vinyl and phenyl groups also bring about the positive effect though they are not essential again; (iii) combination of these substituents seems to be even more effective; (iv) excessive stabilization, however, may cause a deteriorating effect probably due to the loss of enough nucleophilicity required.

As already pointed out by Fang *et al.* in the related study,[6] the effect of the substituents studied here can be rationalized in terms of the softness of the resulting carbanionic reagents. Thus, relatively soft organolithium reagents bearing these charge dispersing group(s) should preferably attack the softer

Table 1. THF Ring Opening with Various Organolithium Reagents in the Presence of Boron Trifluoride Etherate[a]

Entry	Reagent	Product	Yield/%[b]
1	$LiCCl_2Ph$		65
2	**1**	**2**	77
3			51
4			69
5	$LiCH(SPh)_2$		34
6	$LiCH(SPh)SiMe_3$		58
7			72[c]
8			69[d]

[a] To a THF (20 mL) solution of organolithium reagent generated from the corresponding precursor (5.0 mmol) was added BF_3•OEt_2 (6.0 mmol) at -95°C with rapid stirring, and the mixture was allowed to come to a temperature between -65 and -40°C in *ca.* 0.5 - 1 h. [b] Yield is given for the isolated product based on the amount of the organolithium precursor used. [c] Only the α-attack product was obtained. [d] Only the γ-attack product was obtained.

electrophilic center, *i.e.* α-carbon atom of the BF_3-complexed THF.

The present study demonstrated that a variety of organolithium reagents can be applied to this simple four-carbon homologation reaction.

References and Notes

1 T. Imai, S. Nishida and T. Tsuji, *J. Chem. Soc., Chem. Commun.*, **1994**, 2353.

2 Later, we learned by a private communication from Professor R. W. Hoffmann that there is a precedent for this approach in their preparation of 1,1-dibromo-4,4-dimethyl-3-pentanol by the ring opening of *tert*-butyloxirane with dibromomethyllithium [R. W. Hoffmann, M. Bewersdorf, M. Krüger, W. Milolaiski, and R. Stürmer *Chem. Ber.*, **124**, 1243 (1991)].

3 A similar problem has been noted for some reactions of allylic lithium reagents with oxiranes [L. E. Overman and P. A. Renhowe, *J. Org. Chem.*, **59**, 4138 (1994)].

4 G. Wittig and A. Ruckert, *Liebigs Ann. Chem.*, **566**, 101 (1950); G. Wittig and O. Bub, *Liebigs Ann. Chem.*, **566**, 113 (1950).

5 F. D. Jensen and R. L. Bedard, *J. Org. Chem.*, **24**, 874 (1959).

6 J.-M. Fang, M.-Y. Chen and W.-J. Yang, *Tetrahedron Lett.*, **29**, 5937 (1988).

7 All the products gave ^1H and ^{13}C NMR, IR as well as HR MS spectra which agree well with the reported structures. ^1H (90 MHz) and ^{13}C (22.6 MHz) NMR spectral data obtained as $CDCl_3$ solutions for some selected products are given below. 5,5-Dichloro-5-(dimethylphenylsilyl)-1-pentanol (**2**): ^1H NMR δ 0.58 (s, 6H), 1.25 (br s, 1H, exchangeable with D_2O), 1.3-2.2 (m, 6H), 3.4-3.8 [m, 2H, changing to t (J = 6.0 Hz) on the addition of D_2O], 7.3-7.8 ppm (m, 5H); ^{13}C NMR δ -5.3, 20.1, 32.0, 42.9, 62.2, 86.6, 127.7, 130.0, 133.3, 134.8 ppm. 5-Phenylthio-5-trimethylsilyl-1-pentanol: ^1H NMR δ 0.13 (s, 9H), 1.15 (br s, 1H, exchangeable with D_2O), 1.35-1.95 (m, 6H), 2.45 (t, J = 5.3 Hz, 1H), 3.55 (t, J = 5.4 Hz, 2H), 7.1-7.45 ppm (m, 5H); ^{13}C NMR δ -2.2, 24.3, 31.4, 32.5, 34.4, 62.2, 125.5, 128.5, 129.4, 138.1 ppm. 7-Triphenylsilyl-6-hepten-1-ol (mp 79-81.5°C): ^1H NMR δ 1.15 (t, J = 5.5 Hz, 1 H, exchangeable with D_2O), 1.2-1.8 (m, 6H), 2.1-2.4 (m, 2H), 3.6 [q, J = 5.8 Hz, changing to t (J = 6.0 Hz) on the D_2O addition, 2H], 6.1-6.25 (narrow m, 2H), 7.2-7.7 ppm (m, 15H); ^{13}C NMR δ 25.3, 28.2, 32.5, 36.8, 62.7, 123.5, 127.7, 129.3, 134.9, 135.8, 153.1 ppm.