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NEW APPLICATIONS OF ORGANOFLUORINE REAGENTS IN ORGANIC SYNTHESIS. III. A CONVENIENT SYNTHETIC METHOD FOR ACETYLENIC ETHERS AND THIOETHERS

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Acetylenic ethers and thioethers have been well secured as versatile intermediates in organic synthesis for which there exists only a limited number of synthetic methodology.[1] In our continuing investigation of application of organofluorine reagents in organic synthesis,[2] we now wish to report an exceedingly convenient method for the preparation of acetylenic ethers (**3**) and thioethers (**4**) from the reactions of 2,2,2-trifluoroethyl ethers (**1**) and thioethers (**2**) with various alkyllithium reagents (eq. 1). The formation of the acetylenic products from both ethers **1** and thioethers **2** is of interest in view of the differing reactivities of **1** and **2** toward lithium dialkylamides[3]; the reaction of **1** with the lithium amide produced the difluorovinyllithium (CF_2=CLi-OR^1) whereas that of **2** afforded the thioynamine (R_2N-C≡C-SR^1).

$$CF_3CH_2\text{-}XR^1 \quad + \quad R^2Li \longrightarrow R^2\text{-}C\equiv C\text{-}XR^1 \qquad (1)$$

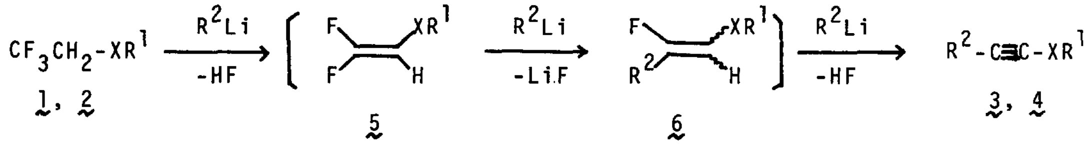
1, X=O → **3**, X=O

2, X=S → **4**, X=S

The notable advantages of the present method compared with previous methods[1,4] are (1) the easy availability of the starting materials (**1** and **2**) which are readily derived from 2,2,2-trifluoroethanol,[5] (2) the simplicity of the procedure (one-pot operation), and (3) the applicability to a wide variety of organolithium reagents including secondary alkyllithiums.

The typical procedure for the preparation of acetylenic ethers **3** is as follows. To a solution of **1** in diethyl ether was added 3 equiv of a solution (diethyl ether or n-hexane) of an organolithium reagent at -78∼-60°C and the resulting mixture was allowed to warm to room temperature over a period of 3 hr. Usual extractive work-up followed by distillation gave the corresponding acetylenic ether (**3**) (Table 1). Similarly, the reactions of thioethers **2** with alkyllithium reagents were carried out in a 1:1 mixture of diethyl ether and n-hexane[6] in place of diethyl ether, giving the corresponding acetylenic thioethers (**4**).

The acetylenic products thus obtained were identified by their IR and NMR spectral data. Although the IR spectra of 3 show strong absorption bands at 2270-2280 cm^{-1} due to the triple bonds, those of 4 exhibit very weak bands at 2120-2200 cm^{-1}. Thus the presence of the triple bonds of 4 was confirmed by the chemical transformation.[7)] The formations of these acetylenic products are rationalized by addition of R^2Li to the first formed difluoroolefins (5) and successive eliminations of LiF and HF (eq. 2).[8)]



(2)

Of particular interest in Table 1 are the formations of symmetrical acetylenes from ethers 1 and some organolithiums (see runs 4,6,7, and 8) which are in stark contrast to the fact that no symmetrical acetylenes were formed with thioethers 2. Such formations of symmetrical acetylenes can be explained by further addition-elimination reactions between the once formed ethers 3 and R^2Li, as previously reported by Arens and co-workers.[9)] Thus it appears from Table 1 that the reactivities of the acetylenic (thio)ethers toward R^2Li decrease in the order of R^2-C≡C-OEt > R^2-C≡C-OAr ≫ R^2-C≡C-SR^1.[10)] Furthermore, both the nature of organolithium reagents and the reaction conditions also play important roles in determining the final products. For example, the reaction of 1 with phenyllithium produced exclusively diphenylacetylene (runs 4 and 8)[11)] and the reaction of 1a with 4 equiv of n-BuLi at -60~room temperature resulted in the sole formation of the symmetrical acetylenes while the normal acetylenic ether was formed with 3 equiv of n-BuLi at -60°~0°C (run 5 vs. 6).

Finally, it is worth noting that the carbon-carbon bond forming reactions of the trifluoroethyl ethers (1) described above is in direct contrast to the reactions of 2,2,2-trichloroalkyl ethers with alkyllithium reagents which involve an initial lithium-chlorine exchange reaction followed by elimination of lithium alkoxide, ultimately producung the lithium acetylide.[12)]

In summary, the one-pot reactions of the trifluoroethyl ethers (1) and thioethers (2) with organolithium reagents permit ready access to a wide variety of acetylenic ethers (3) and thioethers (4), respectively. This work serves to illustrate an example of the potential applicability of organofluorine reagents in organic synthesis.

Table 1. Preparation of Acetylenic Ethers and Thioethers[a]

Run	CF_3CH_2-XR^1	R^2Li[b]	Acetylenic Product[c]	Yield[d]	Bp, °C/mmHg
1	**1a**, R^1=p-Tol[e]	n-C_4H_9Li	n-C_4H_9-C≡C-O-Tol-p[f]	63%	146-147/13
2		sec-C_4H_9Li	sec-C_4H_9-C≡C-O-Tol-p[f]	73%	123-125/8
3		n-$C_5H_{11}Li$	n-C_5H_{11}-C≡C-O-Tol-p[f]	60%	128/2
4		C_6H_5Li	C_6H_5-C≡C-C_6H_5	60%	153/9[g]
5	**1b**, R^1=C_2H_5	n-C_4H_9Li[h]	n-C_4H_9-C≡C-O-C_2H_5	52%	82/55[i]
6		n-C_4H_9Li[j]	n-C_4H_9-C≡C-C_4H_9-n	73%	94-95/48[k]
7		sec-C_4H_9Li	sec-C_4H_9-C≡C-C_4H_9-sec	62%	95/128[l]
8		C_6H_5Li	C_6H_5-C≡C-C_6H_5	65%	153/9[g]
9	**2a**, R^1=p-Tol[e]	n-C_4H_9Li	n-C_4H_9-C≡C-S-Tol-p[f]	63%	146/6
10		sec-C_4H_9Li	sec-C_4H_9-C≡C-S-Tol-p[f]	67%	145/6
11		C_6H_5Li	C_6H_5-C≡C-S-Tol-p	10%[m]	160-165/0.2[n]
12	**2b**, R^1=C_2H_5	n-C_4H_9Li	n-C_4H_9-C≡C-S-C_2H_5	66%	78-79/9[o]

[a] Reactions were done in diethyl ether for ethers **1** and in 1:1 mixtures of diethyl ether and n-hexane for thioethers **2** (see text). [b] Commercial hexane solutions of n- and sec-butyllithiums were used. Other organolithiums were prepared in diethyl ether from the corresponding bromide and lithium metal following the standard procedure. [c] All products exhibited spectral (IR and NMR) data in accord with the assigned structures or with the reported literature values.
[d] Isolated yields based on **1** or **2**. [e] p-Tol≡ p-$CH_3C_6H_4$ [f] This product gave satisfactory elemental analysis. [g] Lit. bp, 170°C/19 mmHg: W. Schlenk and E. Bergmann, Ann., **463**, 76 (1928). [h] The reaction mixture was quenched with water at 0°C. [i] Lit. bp, 55°C/12 mmHg: J. R. Nooi and J. F. Arens, Rec. Trav. Chim., **81**, 517 (1962). [j] The reaction was done with 4 equiv of n-BuLi and quenched with water at room temperature (see text). [k] Lit. bp, 104-106°C/79 mmHg: E. A. Bried and G. F. Hennoin, J. Am. Chem. Soc., **59**, 1310 (1937). [l] Lit. bp, 151°C/753 mmHg: R. Ya. Levine and Yu. S. Schabarov, Dok. Akad. Nauk. S.S.S.R., **84**, 709 (1952). [m] The low yield was due to partial decomposition of the acetylenic thioether during distillation. [n] Lit. mp, 45.5-46.5°C: S. I. Miller, C. E. Orzech, C. A. Welch, G. R. Ziegler, and J. I. Dickstein, J. Am. Chem. Soc., **84**, 2020 (1962).
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References and Notes

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5) Ether **1b** was prepared from ethyl bromide and the sodium trifluoroethoxide: 65%; bp 49-50°C. Other (thio)ethers were obtained from the trifluoroethyl tosylate and the corresponding sodium phenolate or thiolate; **1a**, 76%; bp, 127-128°C/163mmHg; **2b**, 75%; bp, 88-91°C; **2a**, 75%; 88-89°C/13 mmHg.

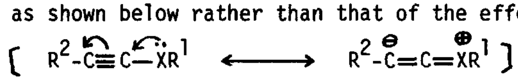
6) The use of diethyl ether as the solvent brought about violent reaction giving rise to dark reaction mixture and resulted in considerable decreases of yields of acetylenic thioethers.

7) For example, **4** (R^1=C_2H_5, R^2=n-C_4H_9) was refluxed in ethanol in the presence of mercuric sulfate and conc. sulfuric acid followed by alkaline hydrolysis to produce pentanoic aicd in 50% overall yield.

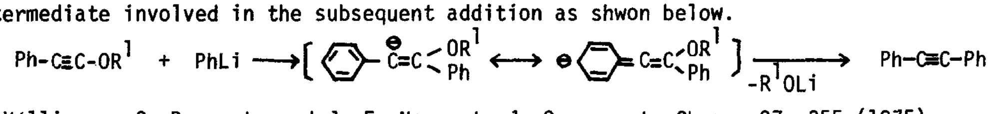
8) An alternative mechanism involving the fluoroacetylene via elimination of HF from **5** followed by addition of R^2Li and elimination of LiF might be ruled out by the fact that, in the reaction of **2** with n-BuLi (2 equiv), the monofluoroenol ether (**6**) was detected by ^{19}F NMR spectroscopy.

9) J. G. A. Kooyman, H. P. G. Hendriks, P. P. Montijin, and J. F. Arens, Rec. Trav. Chim., 87, 69 (1968).

10) The reactivity order is consistent with the order of the decreasing degree of polarization of the triple bonds as shown below rather than that of the effectiveness of $R^1X^{\ominus}$ as the leaving group.



11) The easy formation of diphenylacetylene might be explained in terms of the much higher reactivity of phenylethynyl ethers due to substantial stabilization of the carbanionic intermediate involved in the subsequent addition as shwon below.



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