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A New Synthesis of Hindered Unsymmetrical t-Alkyl Ethers

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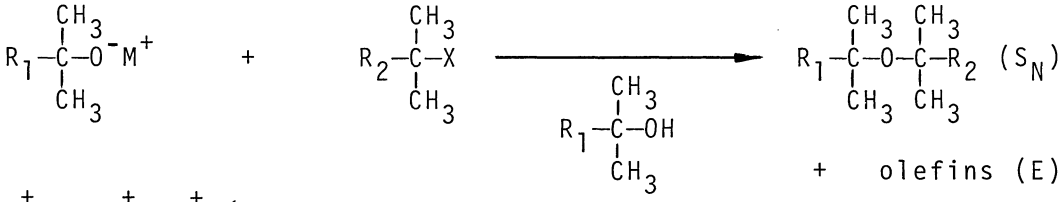
The unusual Williamson reactions of t-butyl and t-pentyl halides with lithium t-alkoxides or with t-alkyl alcohols and amines were carried out at 20–50 °C. Some of the nucleophilic substitution products were new unsymmetrical ethers: t-butyl t-pentyl ether, t-butyl 1,1-dimethyl-2-propenyl ether, t-butyl 1,1-dimethyl-2-propynyl ether, 1,1-dimethyl-2-propynyl t-pentyl ether, and t-butyl 1-ethyl-1-methyl-2-propynyl ether.

t-Butyl t-alkyl ethers are hardly prepared by the Williamson reactions of sodium and potassium t-alkoxides with t-butyl halides because of the steric hindrance and the resultant exhaustive elimination.[1)]

Although several methods for the preparation of symmetrical di-t-alkyl ethers are well-known,[2–7)] no available preparations of the unsymmetrical t-alkyl ethers have been reported.

This paper deals with the reactions of t-alkyl halides with lithium t-alkoxides or with t-alkyl alcohols and amines in order to obtain the desired symmetrical and unsymmetrical t-alkyl ethers.



$M^+ = Li^+, H^+N\lesssim$; X = Br, I;
$R_1 = CH_3$, Et, CH_2=CH-, CH≡C-; $R_2 = CH_3$, Et

Scheme 1.

The results are summarized in Scheme 1 and Table 1. No reactions of t-butyl iodide with t-butyl alcohol took place at 50 °C in 30 h without bases, and the iodide was substantially recovered (Run 1). Potassium

Table 1. Nucleophilic Substitution Reactions of t-Alkyl Halides with t-Alkyl Alcohols and Bases[a)]

Run	t-ROH	t-R'X	Base	Temp °C	Time h	Yield of t-ROR'-t[b)]/%
1	t-BuOH	t-BuI	None	50	30	0
2	t-BuOH	t-BuI	t-BuOK	50	3	0
3	t-BuOH	t-BuI	t-BuONa	50	6	3
4	t-BuOH	t-BuI	t-BuOLi	50	26	13
5	t-BuOH	t-BuI	imidazole	40	19	45 (25)
6	t-BuOH	t-BuBr	imidazole	50	32	30
7	t-BuOH	t-BuI	Et_2NH	40	16	43 (26)
8	t-$C_5H_{11}OH$	t-BuI	imidazole	40	24	29 (20)
9	t-$C_5H_{11}OH$	t-BuI	n-$BuNH_2$	40	22	29 (18)
10	CH_2=CH$(Me)_2COH$	t-BuI	n-$BuNH_2$	40	16	35 (25)
11	CH_2=CH$(Me)_2COH$	t-BuI	imidazole	40	16	34 (18)
12	CH≡C$(Me)_2COH$	t-BuBr	CH≡C$(Me)_2CONa$	50	8	6
13	CH≡C$(Me)_2COH$	t-BuBr	CH≡C$(Me)_2COLi$	50	8	33 (19)
14	CH≡C$(Me)_2COH$	t-BuI	CH≡C$(Me)_2COLi$	40	9	47 (31)
15	CH≡C$(Me)_2COH$	t-BuI	imidazole	20	20	60 (42)
16	CH≡C$(Me)_2COH$	t-BuI	imidazole	30	10	54 (30)
17	CH≡C$(Me)_2COH$	t-BuI	n-$BuNH_2$	30	10	52
18	CH≡C$(Me)_2COH$	t-BuI	Et_3N	30	18	50
19	CH≡C$(Me)_2COH$	t-BuI	pyridine	30	30	41
20	CH≡C$(Me)_2COH$	t-$C_5H_{11}I$	imidazole	30	15	16 (11)
21	CH≡C(Me)(Et)COH	t-BuI	imidazole	30	16	46 (38)

a) t-Alkyl alcohol (t-ROH) 40 or 300 mmol, t-alkyl halide (t-R'X) 4 or 30 mmol, and base 8 or 60 mmol used. The molar ratio of t-ROH/t-R'X/Base =10/1/2. b) GLPC yields of t-alkyl ethers based on t-R'X. Figures in parentheses show the isolated yields.

and sodium t-butoxides were allowed to react with t-butyl iodide in t-butyl alcohol at 50 °C to give 2-methylpropene (E) almost quantitatively (Runs 2 and 3). However, the comparable reaction of lithium t-butoxide with t-butyl iodide gave di-t-butyl ether[8)] (S_N) in 13% yield (Run 4). When imidazole and diethylamine were used instead of lithium t-butoxide, the yield of the ether increased remarkably (Runs 5–7).

Similar substitution reactions of t-pentyl alcohol and 3-methyl-1-butene-3-ol with t-butyl iodide and amines afforded unsymmetrical t-butyl t-pentyl ether[9)] and t-butyl 1,1-dimethyl-2-propenyl ether,[10)] respectively in 29–35% yields (Runs 8–11).

3-Methyl-1-butyn-3-ol, which has a larger polarity than the homologous t-alkyl alcohols described above, reacted more readily with t-butyl halides and various bases at lower temperatures, and afforded t-butyl 1,1-dimethyl-2-propynyl ether[11] in moderate yields (Runs 12–19). Lithium 1,1-dimethyl-2-propynyloxide was much more favorable than sodium 1,1-dimethyl-2-propynyloxide for the S_N reactions (Runs 12–14). Imidazole and butylamine were also suitable bases for the preparation of the ether, while pyridine and hindered triethylamine required longer reaction times (Runs 15–19).

A typical preparative scale experiment was as follows: t-butyl iodide (5.521 g, 30 mmol) was added dropwise to a chilled mixture of 3-methyl-1-butyn-3-ol (25.236 g, 300 mmol) and imidazole (4.085 g, 60 mmol) in a 50 cm^3 flask under nitrogen. The mixture was stirred magnetically at 20 °C for 20 h, extracted with pentane (100 cm^3), washed with water (50 $cm^3 \times 2$), and with ethylene glycol (50 $cm^3 \times 5$), dried over sodium sulfate, and distilled from potassium carbonate. The fractionation gave 1.761 g (41.9%) of pure t-butyl 1,1-dimethyl-2-propynyl ether (Run 15).

The reaction of more hindered substrate, t-pentyl iodide, decreased markedly the yield of the corresponding ether, 1,1-dimethyl-2-propynyl t-pentyl ether,[12] compared with that of t-butyl iodide (Runs 16 and 20).

On the contrary, the reaction of more crowded nucleophile derived from 3-methyl-1-pentyn-3-ol and imidazole gave t-butyl 1-ethyl-1-methyl-2-propynyl ether[13] in a relatively fair yield (Run 21).

The unsymmetrical ethers were characterized by IR, ^1H NMR, ^{13}C NMR, and mass spectra. All of them are volatile liquids, and very sensitive to strong acids but stable to alkalis.

In conclusion, these unusual S_N reactions were significantly governed by the basicity and the steric hindrance of bases, the solvent, and the leaving groups and the bulkiness of t-alkyl halides. The primary and secondary aliphatic amines as well as lithium t-alkoxides were found to improve the yield of the S_N product. Although the S_N1 reactions of t-alkyl halides tend to occur very readily in primary and secondary alcohols, our S_N reactions are apparently different from the typical S_N1 reactions because t-butyl halides cannot react with t-butyl alcohol in the absence of bases under comparable conditions. The studies of the complicated mechanism are now in progress.

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8) bp 106 °C (lit[2] 106 °C); IR (neat) 1162 cm^{-1} (C–O–C); ^1H NMR ($CDCl_3$) δ= 1.26 (18H, s, t-Bu); ^{13}C NMR ($CDCl_3$) δ=31.7 (q, 6C) and 73.6 (s, 2C).
9) bp 126 °C; IR (neat) 1381, 1365 (gem-CH_3, t-Bu), and 1169 cm^{-1} (C–O–C); ^1H NMR ($CDCl_3$) δ=0.89 (3H, t, J=7.0 Hz, CH_3), 1.22 (6H, s, t-CH_3), 1.26 (9H, s, t-Bu), and 1.46 (2H, q, J=7.0 Hz, CH_2); ^{13}C NMR ($CDCl_3$) δ=8.6 (q), 28.5 (q, 2C), 31.6 (q, 3C), 37.4 (t), 73.4 (s), and 75.6 (s); MS (20 eV) m/z (rel intensity) 129 (M^+–Me; 5), 115 (45), 73 (38), 71 (55), 59 (100), and 57 (99).
10) bp 120 °C; IR (neat) 3080 (C=CH_2), 1386, 1361 (gem-CH_3, t-Bu), and 1142 cm^{-1} (C–O–C); ^1H NMR ($CDCl_3$) δ=1.24 (9H, s, t-Bu), 1.33 (6H, s, t-CH_3), 4.93 (1H, dd, J=17.8, 1.2 Hz, C$\underline{H}_2$=CH), 5.04 (1H, dd, J=10.7, 1.5 Hz, C$\underline{H}_2$=CH), and 6.09 (1H, dd, J=17.8, 10.7 Hz, CH_2=C$\underline{H}$); ^{13}C NMR ($CDCl_3$) δ=29.7 (q, 2C), 31.5 (q, 3C), 74.6 (s), 75.1 (s), 110.6 (t), and 148.2 (d); MS (20 eV) m/z (rel intensity) 127 (M^+–Me; 16), 114 (15), 86 (11), 71 (58), 69 (100), 59 (20), and 57 (42).
11) bp 119 °C; IR (neat) 3310 (CH≡C), 1388, 1375, 1363 (gem-CH_3, t-Bu), and 1144 cm^{-1} (C–O–C); ^1H NMR ($CDCl_3$) δ=1.38 (9H, s, t-Bu), 1.51 (6H, s, t-CH_3), and 2.43 (1H, s, CH≡C); ^{13}C NMR ($CDCl_3$) δ=30.5 (q, 3C), 33.2 (q, 2C), 66.9 (s), 72.5 (d), 75.6 (s), and 89.3 (s); MS (20 eV) m/z (rel intensity) 140 (M^+; 6), 135 (100), 125 (M^+–Me; 35), 108 (65), 79 (40), 69 (63), 59 (65), and 57 (41).
12) bp 132 °C; IR (neat) 3310 (CH≡C), 1376, 1363 (gem-CH_3), and 1143 cm^{-1} (C–O–C); ^1H NMR ($CDCl_3$) δ=0.88 (3H, t, J=7.6 Hz, CH_3), 1.36 (6H, s, t-CH_3), 1.50 (6H, s, t-CH_3), 1.60 (2H, q, J=7.6 Hz, CH_2), and 2.42 (1H, s, CH≡C); ^{13}C NMR ($CDCl_3$) δ=8.6 (q), 27.2 (q, 2C), 33.2 (q, 2C), 36.3 (t), 66.7 (s), 72.3 (d), 77.7 (s), and 89.4 (s); MS (20 eV) m/z (rel intensity) 136 (100), 125 (M^+–Et; 8), 109 (21), 83 (35), 71 (44), 69 (56), and 59 (26).
13) bp 138 °C; IR (neat) 3310 (CH≡C), 1388, 1364 (t-Bu), and 1150 cm^{-1} (C–O–C); ^1H NMR ($CDCl_3$) δ=0.99 (3H, t, J=7.0 Hz, CH_3), 1.38 (9H, s, t-Bu), 1.46 (3H, s, CH_3), 1.65 (2H, q, J=7.0 Hz, CH_2), and 2.44 (1H, s, CH≡C); ^{13}C NMR ($CDCl_3$) δ=8.9 (q), 30.4 (q, 3C), 30.6 (q), 38.4 (t), 70.2 (s), 73.6 (d), 75.3 (s), and 88.1 (s); MS (20 eV) m/z (rel intensity) 155 (M^++1; 6), 137 (17), 136 (100), 109 (24), 97 (36), 83 (37), 81 (35), and 57 (88).

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