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A New Synthesis of Neopentyl 2,4,6-Tri-t-butylphenyl Ether and Related Hindered Ethers

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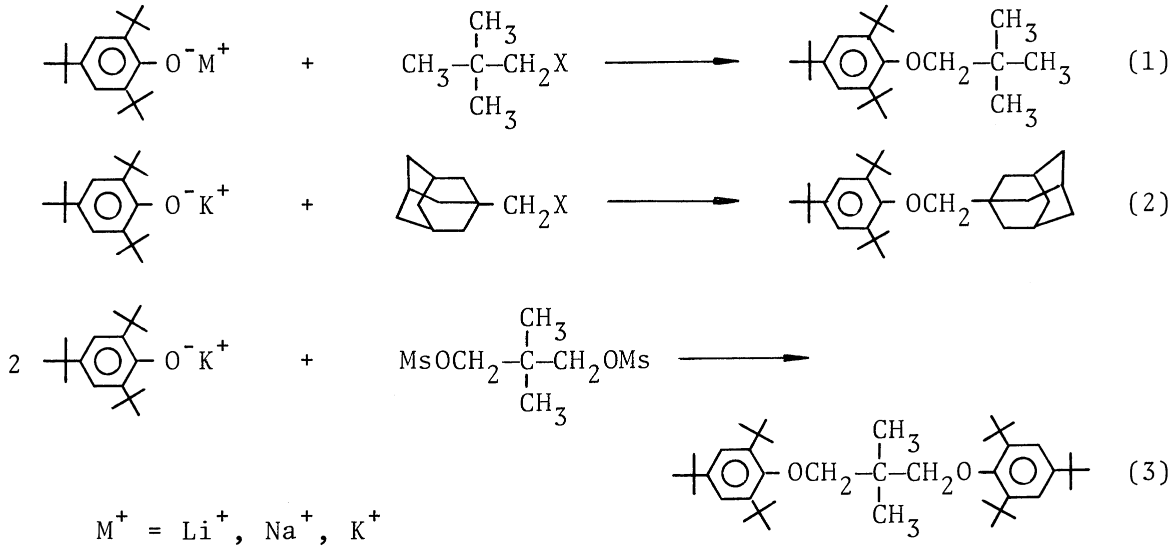
The S_N reactions of neopentyl, (1-adamantyl)methyl, and related substrates with potassium 2,4,6-tri-t-butylphenoxide gave the corresponding highly hindered ethers in moderate yields. They were neopentyl and (1-adamantyl)methyl 2,4,6-tri-t-butylphenyl ethers, and 1,3-bis(2,4,6-tri-t-butylphenoxy)-2,2-dimethylpropane. The kinetics for these reactions suggest the S_N2 mechanism.

In general, the S_N2 reactions of neopentyl substrates are extremely slow because of the steric effect,1) and the derived ethers have proved quite difficult to prepare in appreciable yields.

This report is concerned with the highly hindered substitution reactions of neopentyl and (1-adamantyl)methyl substrates with alkaline metal 2,4,6-tri-t-butylphenoxides, as shown in Scheme 1.



$M^+ = Li^+, Na^+, K^+$
X = OMs, OTs, OBs, OTf

Scheme 1.

Table 1. Reactions of Neopentyl, (1-Adamantyl)methyl, and Related Substrates with Metal 2,4,6-Tri-t-butylphenoxides[a)]

Run	$(t\text{-}Bu)_3C_6H_2O^-M^+$	Substrate[b)]	Solvent	Temp/°C	Time/h	Yield/% of ether[c)]
1	$M^+ = K^+$	$Me_3C\text{-}CH_2\text{-}OMs$	DMI	140	12	52 (67)
2	Na^+	$Me_3C\text{-}CH_2\text{-}OMs$	DMI	140	20	(66)
3	Li^+	$Me_3C\text{-}CH_2\text{-}OMs$	DMI	160	11	(22)
4	K^+	$Me_3C\text{-}CH_2\text{-}OMs$	DMA	140	12	48 (65)
5	K^+	$Me_3C\text{-}CH_2\text{-}OTs$	DMI	140	12	52
6	K^+	$Me_3C\text{-}CH_2\text{-}OBs$	DMI	130	6	51
7	K^+	$Me_3C\text{-}CH_2\text{-}OTf$	DMI	30	4	39
8	K^+	$1\text{-}AdCH_2\text{-}OMs$	DMSO	140	7	32
9	K^+	$1\text{-}AdCH_2\text{-}OTs$	DMSO	140	6	36
10	K^+	$1\text{-}AdCH_2\text{-}OTf$	DMA	30	3	50
11	$K^{+d)}$	$(MsOCH_2)_2CMe_2$	DMSO	140	25	60

a) Substrate (10 mmol), metal 2,4,6-tri-t-butylphenoxide, $(t\text{-}Bu)_3C_6H_2O^-M^+$ (15 mmol), and solvent (40 cm^3) were used unless otherwise stated. b) Neopentyl methanesulfonate ($Me_3C\text{-}CH_2\text{-}OMs$), p-toluenesulfonate (-OTs), p-bromobenzenesulfonate (-OBs), and trifluoromethanesulfonate (-OTf). (1-Adamantyl)methyl substrates ($1\text{-}AdCH_2\text{-}OMs$, -OTs, and -OTf). 2,2-Dimethylpropane-1,3-diyl bis(methanesulfonate), $(MsOCH_2)_2CMe_2$. c) Isolated yields of the corresponding ethers based on substrates. Figures in parentheses show the GLPC yields. d) 30 mmol used.

The results are summarized in Table 1. Potassium 2,4,6-tri-t-butylphenoxide was allowed to react with neopentyl methanesulfonate at 140 °C for 12 h in 1,3-dimethyl-2-imidazolidinone (DMI) under a nitrogen atmosphere. The reaction mixture was extracted with hexane, washed with water, and with nitromethane–methanol(1/1), dried, and distilled to give 1.787 g (52%) of neopentyl 2,4,6-tri-t-butylphenyl ether[2)] (Eq. 1, Run 1). The by-product was neopentyl alcohol which was most probably formed via the fission of the sulfur–oxygen bond by the attack of the phenoxide ion on the sulfur of neopentyl methanesulfonate. Similar reactions of sodium and lithium 2,4,6-tri-t-butylphenoxides were much slower than that of the corresponding potassium complex, and also gave the hindered ether (Runs 2, 3). The counter cation of the phenoxide played an important role in the dilute solution. Neopentyl p-toluenesulfonate, p-bromobenzenesulfonate, and trifluoromethanesulfonate reacted with the potassium complex, as well as methanesulfonate, to yield the ether in DMI and DMA (Runs 4–7). The leaving groups of the substrates provided a great effect on the reaction rate.

On the other hand, (1-adamantyl)methyl methanesulfonate, p-toluenesulfonate, and trifluoromethanesulfonate were allowed to react with the po-

Table 2. Kinetic Data and Distribution of Products for the Reactions of Neopentyl and (1-Adamantyl)methyl Methanesulfonates with Potassium 2,4,6-Tri-t-butylphenoxide[a)]

Substrate	Temp[b)] / °C	Solvent[c)]	k_2[d)] / $dm^3\ mol^{-1}\ s^{-1}$	Distribution/% Ether[e)]	Alcohol[f)]
$Me_3C\text{-}CH_2OMs$	140	DMSO	$(2.83\pm0.02)\times10^{-4}$	51	49
$Me_3C\text{-}CH_2OMs$	140	DMA	$(2.10\pm0.02)\times10^{-4}$	65	35
$Me_3C\text{-}CH_2OMs$	140	DMI	$(1.77\pm0.01)\times10^{-4}$	67	33
$Me_3C\text{-}CH_2OMs$	140	DMF	$(1.30\pm0.01)\times10^{-4}$	65	35
$1\text{-}AdCH_2OMs$	130	DMSO	$(1.54\pm0.01)\times10^{-4}$	65	35

a) Neopentyl and (1-adamantyl)methyl methanesulfonates (5 mmol), potassium 2,4,6-tri-t-butylphenoxide (7.5 mmol), and solvent (30 cm^3) used under a nitrogen atmosphere. b) At 130 and 140±0.1 °C. c) Dimethyl sulfoxide (DMSO), N,N-dimethylacetamide (DMA), 1,3-dimethyl-2-imidazolidinone (DMI), and N,N-dimethylformamide (DMF). d) Duplicate runs agreed to less than ±1% from the mean. Determined by GLPC (2% Silicone GE-SE 30 column, He) using internal standards, and checked by acidimetry (0.01 M-HCl). e) GLPC yields of neopentyl and (1-adamantyl)methyl 2,4,6-tri-t-butylphenyl ethers. f) GLPC yields of neopentyl alcohol and (1-adamantyl)methanol.

tassium complex under comparable conditions, and gave (1-adamantyl)methyl 2,4,6-tri-t-butylphenyl ether[3)] in 32–50% yields (Eq. 2, Runs 8–10). The other product was (1-adamantyl)methanol. Moreover, 2,2-dimethylpropane-1,3-diyl bis(methanesulfonate) having the same two leaving groups also reacted with a large excess of the potassium complex to give an extremely hindered ether, 1,3-bis(2,4,6-tri-t-butylphenoxy)-2,2-dimethylpropane[4)] in 60% yield (Eq. 3, Run 11). The new hindered ethers described above were characterized with IR, ^1H NMR, ^{13}C NMR, and high-resolution mass spectra (HRMS) as shown in references.

The kinetic runs and the product analysis were performed to clarify the mechanism. The reactions of neopentyl and (1-adamantyl)methyl methanesulfonates with potassium 2,4,6-tri-t-butylphenoxide were followed by GLPC and acidimetry until the conversion went up to over 70%. Table 2 shows the results. All runs were proved to be the typical second-order reactions which were first order in both nucleophiles and substrates. No products formed by rearrangement and electron transfer were detected under all conditions employed. The results suggested the absence of primary neopentyl and (1-adamantyl)methyl cations in the system, although secondary 2,2-dimethyl-1-phenylpropyl and 1-(1-adamantyl)ethyl cations gave the corresponding rearranged products with difficulty.[1,5)]

As a rule, the pathways for the second-order S_N reactions include the S_N2 through ion-pair intermediates of tertiary allylic halides,6) the second-order substitution reactions with rearrangement or retention of allylic chlorides,7) and even the S_N1 pathways through Arrhenius intermediates or radicals of diphenylmethyl halides.8) However, these unusual pathways as well as S_N2' and S_Ni modes were inapplicable to our reactions in view of the substrates, the products, and the conditions used.

Therefore, the results of our kinetic runs and product analysis suggest that the formation of the hindered primary ethers proceeds by the S_N2 mode. These S_N2 reactions which are very slow in protic solvents can be extremely promoted by aprotic solvents such as DMSO and DMF.9)

References

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2) White crystal, mp 84 °C; IR (nujol) 1265, 1214, and 1190 cm^{-1} (C–O–C); ^1H NMR ($CDCl_3$) δ=1.12 (9H, s, t-Bu), 1.30 (9H, s, t-Bu), 1.44 (18H, s, t-Bu), 3.60 (2H, s, OCH_2), and 7.25 (2H, s, aromatic); HRMS Found: m/z 332.3077. Calcd for $C_{23}H_{40}O$: M, 332. 3077.

3) White crystal, mp 206 °C; IR (nujol) 1213, 1191, and 1112 cm^{-1}(C–O–C); ^1H NMR ($CDCl_3$) δ=1.29 (9H, s, t-Bu), 1.44 (18H, s, t-Bu), 1.77 (12H, m, CH_2), 2.03 (3H, br.s, CH), 3.49 (2H, s, CH_2), and 7.24 (2H, s, aromatic); ^{13}C NMR ($CDCl_3$) δ=28.5 (d, 3C), 31.6 (q, 3C), 32.3 (q, 6C), 34.5 (s), 35.0 (s), 36.1 (s, 2C), 37.1 (t, 3C), 41.1 (t, 3C), 86.1 (t), 123.5 (d, 2C), 142.7 (s, 2C), 143.8 (s), and 156.5 (s); HRMS Found: m/z 410.3547. Calcd for $C_{29}H_{46}O$: M, 410.3547.

4) White crystal, mp 166 °C; IR (nujol) 1244 and 1036 cm^{-1} (C–O–C); ^1H NMR ($CDCl_3$) δ=1.29 (18H, s, t-Bu), 1.42 (36H, s, t-Bu), 1.45 (6H, s, CH_3), 3.82 (4H, s, CH_2O), and 7.24 (4H, s, aromatic); ^{13}C NMR ($CDCl_3$) δ=25.6 (q, 2C), 31.5 (q, 6C), 32.2 (q, 12C), 34.4 (s, 2C), 36.0 (s, 4C), 38.4 (s), 82.3 (t, 2C), 123.6 (d, 4C), 142.4 (s, 4C), 143.9 (s, 2C), and 155.9 (s, 2C); HRMS Found: m/z 592.5208. Calcd for $C_{41}H_{68}O_2$: M, 592.5215.

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