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A Resin-promoted Williamson's Alkyl Aryl Ether Synthesis. Methylation of 2-*tert*-Butyl-5-methylphenol with Methyl Chloride[1]

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The use of easily recoverable tri-*n*-butylphosphoniummethylated polystyrene resin (phosphonium resin catalyst) under triphasic reaction conditions was proposed in Williamson's alkyl aryl ether synthesis. O-Methylation of 2-*tert*-butyl-5-methylphenol with methyl chloride was easily carried out in the presence of the phosphonium resin catalyst under basic conditions to give 2-*tert*-butyl-5-methylphenyl methyl ether in excellent yield. A few other phenols were also O-alkylated under similar triphasic reaction conditions to give alkyl aryl ethers.

Keywords——phenol; alkyl aryl ether; Williamson's synthesis; triphase catalyst; functionalized polystyrene resin

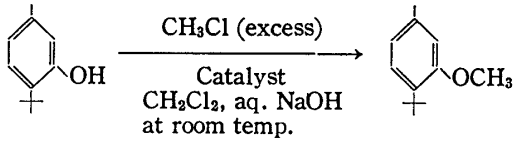
O-Alkylation of phenols is a classical and well-known application of Williamson's ether synthesis, for which a wide variety of procedures have been devised.[2] Among them, the use of phase-transfer catalysts, developed by McKillop and co-workers,[3] seems to be attractive because of its simplicity, rapidity, and efficiency. From the industrial point of view, however, their procedures have at least two disadvantages: (i) the use of phase-transfer catalysts, benzyltri-*n*-butylammonium halides, which are difficult to recover and reuse, and (ii) the use of relatively costly methyl iodide or hazardous dimethyl sulfate for the methylation of phenols.

We describe here the use of an easily recoverable functionalized polystyrene resin as a triphase catalyst for Williamson's alkyl aryl ether synthesis,[4] and the use of cheaper methyl chloride for methylation.

Our initial interest was focused on the methylation of 2-*tert*-butyl-5-methylphenol (I) with methyl chloride, since the product, 2-*tert*-butyl-5-methylphenyl methyl ether (II), is an important intermediate for the industrial preparation of Musk Ambrette, 2-*tert*-butyl-4,6-dinitro-5-methylphenyl methyl ether, widely used as a perfume. First, we surveyed the usual biphase catalysts in a mixture of methylene chloride and aqueous sodium hydroxide. As shown in Table I (runs 1—12), tetra-*n*-butylammonium chloride was the best, and 0.2 equivalent of the catalyst was enough to complete the methylation within 12 hours. Next, resin catalysts containing the *n*-butyl function were prepared from commercially available chloromethylated polystyrene resin (cross-linked with 2% divinylbenzene, 200—400 mesh) by reaction of the resin with either tri-*n*-butylphosphine or tri-*n*-butylamine according to the procedure by Montanari and co-workers.[5] The results of methylation in the presence of the resin catalysts are also summarized in Table I. The phenol (I) was smoothly converted to the methyl ether (II) under mild conditions with 0.2 equivalent of the phosphonium resin catalyst, which was more active than the corresponding ammonium resin catalyst and could be recycled a minimum of three times with only a slight decrease in activity. The anion exchange resin, Amberlite IRA 401, and QAE-Sephadex showed only a weak catalytic action.

Since suitable conditions for the triphasic catalytic reaction using the phosphonium resin had been established for the methylation of 2-*tert*-butyl-5-methylphenol (I) as above, we extended the method to the preparation of several other alkyl aryl ethers. The results are shown in Table II. 2-*tert*-Butylphenol gave the corresponding methyl ether in good yield, but the sterically more hindered 2,4,6-tri-*tert*-butylphenol would not undergo methylation

TABLE I. O-Methylation of 2-*tert*-Butyl-5-methylphenol



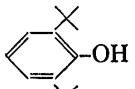
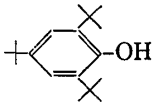
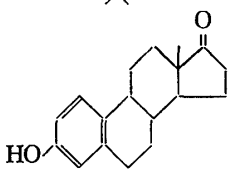
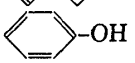
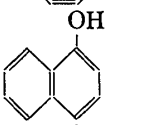
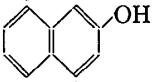
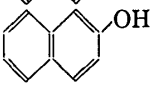
Run	Catalyst	Equivalent of catalyst	Reaction time (h)	GLC yield (%)
1	$(n\text{-}C_4H_9)_3N$	0.1	24	0
2	$(n\text{-}C_4H_9)_4\overset{+}{N}Cl^-$	0.1	24	100
3	$(n\text{-}C_4H_9)_4\overset{+}{N}Cl^-$	0.1	12	25
4	$(n\text{-}C_4H_9)_4\overset{+}{N}Cl^-$	0.2	12	96
5	$(n\text{-}C_4H_9)_4\overset{+}{N}Cl^-$	0.3	12	99
6	$(n\text{-}C_4H_9)_4\overset{+}{N}Cl^-$	0.4	12	100
7	$(n\text{-}C_4H_9)_4\overset{+}{N}Br^-$	0.1	24	80
8	$(n\text{-}C_4H_9)_4\overset{+}{N}I^-$	0.1	24	66
9	$C_6H_5CH_2\overset{+}{N}(CH_3)_3Cl^-$	0.1	24	20
10	$C_6H_5CH_2\overset{+}{N}(C_2H_5)_3Cl^-$	0.1	24	25
11	$n\text{-}C_{16}H_{33}\overset{+}{N}(CH_3)_3Cl^-$	0.1	24	22
12	$C_6H_5CH_2\overset{+}{P}(C_6H_5)_3Cl^-$	0.1	24	51
13	Ⓟ-$CH_2\overset{+}{P}(n\text{-}C_4H_9)_3Cl^-$ [a]	0.2	3	30
14	Ⓟ-$CH_2\overset{+}{P}(n\text{-}C_4H_9)_3Cl^-$ [a]	0.2	6	94
15	Ⓟ-$CH_2\overset{+}{P}(n\text{-}C_4H_9)_3Cl^-$ [a]	0.2	12	96 (94) [b]
16	Ⓟ-$CH_2\overset{+}{P}(n\text{-}C_4H_9)_3Cl^-$ [a]	0.2 [c]	12	93
17	Ⓟ-$CH_2\overset{+}{P}(n\text{-}C_4H_9)_3Cl^-$ [a]	0.2 [d]	12	(76) [b]
18	Ⓟ-$CH_2\overset{+}{N}(n\text{-}C_4H_9)_3Cl^-$ [a]	0.2	12	83
19	Amberlite IRA 401 [e]	0.2	12	14
20	Amberlite IRA 401 [e]	1.0	12	27
21	QAE-Sephadex [f]	0.2	12	0

a) Ⓟ refers to polystyrene resin.
b) Yield after isolation and purification.
c) The resin catalyst used once.
d) The resin catalyst used twice.
e) Ⓟ-$\overset{+}{N}(CH_3)_3Cl^-$
f) Resin-$CH_2CH_2\overset{+}{N}(C_2H_5)_2CH(OH)CH_3Cl^-$.

under analogous reaction conditions. Methylation of estrone under similar reaction conditions proceeded very slowly, probably because estrone was not easily soluble in the reaction solvent. However, the use of potassium carbonate in a mixture of methylene chloride and N,N′-dimethylformamide facilitated the methylation to give O-methylestrone in 73% yield. Alkyl halides other than methyl chloride were used in the alkylation of phenol and 1- and 2-naphthols. Butylation of phenol with *n*-butyl bromide required heating at reflux. The reaction of 1-naphthol with epichlorohydrin proceeded slowly to give 1,2-epoxy-3-(1-naphthoxy)propane, which was further converted to propranolol hydrochloride,[6] a β-blocker, by reaction with isopropylamine followed by hydrochloric acid. Alkylation of 2-naphthol with reactive alkyl halides has often resulted in the formation of the C-alkylated compound as the major product instead of the O-alkylated one,[2a,7] but no C-alkylation occurred in the phosphonium resin-promoted ether synthesis and both allyl chloride and benzyl bromide afforded the O-alkylated products in good yields.

Table II. O-Alkylation of Various Phenols

$$\text{ArOH} \xrightarrow[\text{at room temp.}]{\text{RX, } \textcircled{P}\text{-}CH_2\overset{+}{P}(n\text{-}C_4H_9)_3Cl^- \quad CH_2Cl_2, \text{ aq. NaOH}} \text{ArOR}$$

Run	ArOH	RX	Reaction time (d)	Isolated yield (%)
1		CH_3Cl	1	83
2		CH_3Cl	1	0
3		CH_3Cl	5[a]	73
4		n-C_4H_9Br	5[b]	71[c]
5		CH_2CHCH_2Cl (O)	6	55[d]
6		$CH_2=CHCH_2Cl$	4	89[e]
7		$C_6H_5CH_2Br$	2	96

a) Potassium carbonate and N,N′-dimethylformamide were used. See "Experimental."
b) The reaction mixture was stirred at room temp. for 2 days and then refluxed for 3 days.
c) Accompanied by diphenoxymethane (10%).
d) Accompanied by di-1-naphthoxymethane (13%).
e) Accompanied by di-2-naphthoxymethane (10%).

Although reaction conditions for the preparation of 2-*tert*-butyl-5-methylphenyl methyl ether (II) by methylation of 2-*tert*-butyl-5-methylphenol (I) with methyl chloride have been well established, those for the preparation of the other alkyl aryl ethers should be capable of much improvement. However, the results described above demonstrate the potential of the phosphonium resin catalyst for use in Williamson's alkyl aryl ether synthesis.

Experimental

Melting and boiling points are uncorrected. IR spectra were measured either in nujol mulls for crystalline solids or in liquid films for liquids. NMR spectra were measured in $CDCl_3$ or CCl_4 using tetramethylsilane as an internal standard.

Commercially available phase-transfer catalysts were used in runs 2—12 of Table I. Amberlite IRA-401 and QAE-Sephadex were obtained commercially. Chloromethylated polystyrene beads (2% divinylbenzene, 200—400 mesh) were purchased from the Protein Research Foundation. Silica gel refers to Merck Kieselgel 60 (Art. 7734).

Phosphonium Resin Catalyst——The phosphonium resin catalyst was prepared according to the procedure of Montanari and co-workers[5] as follows. A mixture of the chloromethylated polystyrene (5 g, 4.65 mM) and tri-*n*-butylphosphine (4.6 ml, 18.6 mM) in N,N′-dimethylformamide (20 ml) was heated at 110°C for 4 days. The phosphonium resin was filtered off and successively washed with ethanol (20 ml×8), methylene chloride (20 ml×2), and diethyl ether (20 ml×3). The dried resin weighed 5.95 g (quantitative, 0.78 mM/g).

Ammonium Resin Catalyst——The ammonium resin catalyst was prepared according to the procedure of Montanari and co-workers[5] as follows. A mixture of the chloromethylated polystyrene (5 g, 4.65 mM)

and tri-*n*-butylamine (4.4 ml, 18.6 mM) in N,N'-dimethylformamide (20 ml) was heated at 60°C for 5 days and worked up as described for the phosphonium resin to give the ammonium resin (5.85 g, quantitative, 0.79 mM/g).

General Procedure for the O-Methylation of 2-*tert*-Butyl-5-methylphenol (I); 2-*tert*-Butyl-5-methylphenyl Methyl Ether (II)——To a mixture of 2-*tert*-butyl-5-methylphenol (1.64 g, 10 mM) and the catalyst (1—4 mM, see Table I) in methylene chloride (50 ml) in a 200 ml round-bottomed flask was added sodium hydroxide (0.6 g, 15 mM) in water (10 ml). The stirred mixture was cooled with ice-water, and methyl chloride (*ca.* 10 g) was introduced either as a gas or as a liquid. The flask was closed with a rubber stopper and the mixture was stirred at room temperature for 3—24 h. After filtration, the organic layer was separated, dried with sodium sulfate, and evaporated to give a brown oily residue.

(i) For Isolation (Run 15 in Table I): The residue was diluted with hexane (100 ml), and the mixture was washed with Claisen's alkali (40 ml × 3) and water (40 ml × 1), then dried over sodium sulfate. The solvent was evaporated off and the residue was purified by Kugelrohr distillation at 142—144°C (bath temperature) (48 mmHg) (lit.[8] 222—224°C) to give 2-*tert*-butyl-5-methylphenyl methyl ether (II) (94% yield) as a pale yellow oil. IR ν_{max} cm^{-1}: 1610, 1500. NMR δ ppm: 1.32 (9H, singlet, $(CH_3)_3C$), 2.28 (3H, singlet, 5-CH_3), 3.76 (3H, singlet, CH_3O), 6.60 (1H, singlet, 6-H), 6.64 (1H, broad doublet, $J=8$ Hz, 4-H), 7.08 (1H, doublet, $J=8$ Hz, 3-H).

(ii) For Gas Liquid Chromatographic Analysis: The above residue was diluted with ethyl acetate to 100 ml. This solution (10 ml) was combined with 2-*tert*-butylphenyl methyl ether (1 mM in 10 ml of ethyl acetate) as an internal standard, and analyzed by gas liquid chromatography using a 1 m × 3 mm 10% Thermol-3 column with a nitrogen flow rate of 50 ml/min. The results are summarized in Table I.

2-*tert*-Butylphenyl Methyl Ether——A mixture of 2-*tert*-butylphenol (1.50 g, 10 mM), the phosphonium resin catalyst (2.56 g, 2 mM), methylene chloride (50 ml), sodium hydroxide (0.6 g, 15 mM), water (10 ml), and methyl chloride (15 ml) was stirred at room temperature for 1 day as described for the methylation of I. After filtration, the organic layer was separated and dried over sodium sulfate. The solvent was evaporated off, and the residue was purified by Kugelrohr distillation at 97°C (20 mmHg) (lit.[9] 102.5—104°C (22 mmHg)) to give 2-*tert*-butylphenyl methyl ether (1.223 g, 83%) as a colorless oil. IR ν_{max} cm^{-1}: 1580, 1490, 1235, 1030, 930. NMR δ ppm: 1.37 (9H, singlet, $(CH_3)_3C$), 3.73 (3H, singlet, CH_3O), 7.0 (4H, multiplet, benzene).

Attempted O-methylation of 2,4,6-tri-*tert*-butylphenol as above resulted in the recovery of the starting phenol quantitatively.

Estrone Methyl Ether——A mixture of estrone (270 mg, 1 mM), N,N'-dimethylformamide (2 ml), the phosphonium resin catalyst (250 mg, 0.2 mM), methylene chloride (3 ml), 6 M saturated aqueous potassium carbonate (0.5 ml, 3 mM), and methyl chloride (2 ml) was stirred at room temperature for 5 days. After filtration, the organic layer was separated, dried over sodium sulfate, and evaporated. The residue was purified by silica gel (60 g) column chromatography with benzene–hexane (6: 1) to give a colorless solid (209 mg, 73%) which was recrystallized from ethanol to give colorless crystals, mp 174—176°C (lit.[10] 164—165°C). IR ν_{max} cm^{-1}: 1732, 1033. NMR δ ppm: 0.91 (3H, singlet, CH_3), 3.79 (3H, singlet, CH_3O), 6.65 (1H, singlet, 4-H), 6.76 (1H, doublet, $J=8$ Hz, 2-H), 7.22 (1H, doublet, $J=8$ Hz, 1-H).

***n*-Butyl Phenyl Ether**——A mixture of phenol (940 mg, 10 mM), the phosphonium resin catalyst (2.50 g, 2 mM), methylene chloride (50 ml), sodium hydroxide (0.6 g, 15 mM), water (10 ml), and *n*-butyl bromide (4.3 ml, 40 mM) was stirred at room temperature for 2 days and refluxed for 3 days. After filtration, the organic layer was separated, dried over sodium sulfate, and evaporated to dryness. The residue was chromatographed over silica gel (100 g) with benzene–hexane (1: 6) to give *n*-butyl phenyl ether (1.073 g, 71%) as a colorless oil. IR ν_{max} cm^{-1}: 1596, 1245, 1028, 762. NMR δ ppm: 0.96 (3H, triplet, $J=7$ Hz, CH_3), 1.55 (4H, multiplet, CH_2CH_2), 3.83 (2H, triplet, $J=7$ Hz, CH_2O), 6.78 (3H, multiplet, benzene), 7.13 (2H, multiplet, benzene), 7.13 (2H, multiplet, benzene). MS *m/e*: 150 (M^+), 107, 94, 77, 57.

Further elution of the column with the same solvent afforded diphenoxymethane (114 mg, 10%) as a colorless oil. IR ν_{max} cm^{-1}: 1593, 1205, 1030, 752. NMR δ ppm: 5.62 (2H, singlet, CH_2), 6.82 and 7.28 (10H, multiplet, benzene). MS *m/e*: 200 (M^+), 184, 169, 143, 116, 107, 94, 79, 77.

1,2-Epoxy-3-(1-naphthoxy)propane——A mixture of 1-naphthol (1.44 g, 10 mM), the phosphonium resin catalyst (2.50 g, 2 mM), methylene chloride (50 ml), sodium hydroxide (0.6 g, 15 mM), water (10 ml), and epichlorohydrin (3.1 ml, 40 mM) was stirred at room temperature for 5 days. Epichlorohydrin (3.1 ml, 40 mM) was further added, and the mixture was stirred for 1 day then filtered. The organic layer was dried over sodium sulfate and evaporated. The residue was chromatographed over silica gel (100 g) with hexane–ethyl acetate (6: 1) to give di-1-naphthoxymethane (191 mg, 13%) as colorless crystals. Recrystallization from hexane gave colorless needles, mp 90—91°C (lit.[11] 88°C). IR ν_{max} cm^{-1}: 1020, 765. NMR δ ppm: 6.02 (2H, singlet, CH_2), 7.38 (10H, multiplet), 7.68 (2H, multiplet), 8.19 (2H, multiplet).

Further elution of the column with the same solvent afforded 1,2-epoxy-3-(1-naphthoxy)propane (1.096 g, 55%) as a brown oil. IR ν_{max} cm^{-1}: 3040, 1055, 915. NMR δ ppm: 2.50 (2H, multiplet, CH_2 of epoxide), 3.10 (1H, multiplet, CH), 3.82 (2H, multiplet, CH_2O), 6.43 (1H, doublet, $J=8$ Hz, 2-H), 7.28 (4H, multiplet), 7.61 (1H, multiplet), 8.19 (1H, multiplet, 8-H).

In order to confirm the structure of 1,2-epoxy-3-(1-naphthoxy)propane, the above oil was treated as follows.[12] A mixture of the above oil (370 mg, 1.85 mM) and isopropylamine (0.5 ml, 5.79 mM) was refluxed

for 16 h to give a colorless solid, which was dissolved in 2 N hydrochloric acid (5 ml) and washed with ether (20 ml). The aqueous layer was cooled with ice and basified with 2 N sodium hydroxide (10 ml) to give a white precipitate, which was filtered off, washed with water, and dried. Recrystallization from cyclohexane gave propranolol (369 mg, 77%) as colorless needles, mp 94.5—95°C (lit.[6] 96°C). A solution of the crystals (260 mg) in acetone (2 ml) was treated with 10 N hydrochloric acid (0.1 ml) in a refrigerator for 2 days. The white solid produced was filtered off and washed with acetone. It weighed 254 mg (86%). Recrystallization from *n*-propanol afforded propranolol hydrochloride as colorless needles, mp 163—164°C (lit.[6] 163—164°C).

Allyl 2-Naphthyl Ether——A mixture of 2-naphthol (1.44 g, 10 mM), the phosphonium resin catalyst (2.50 g, 2 mM), methylene chloride (50 ml), sodium hydroxide (0.6 g, 15 mM), water (10 ml), and allyl chloride (3.3 ml, 40 mM) was stirred for 4 days and filtered. The organic layer was dried over sodium sulfate and evaporated. The residue was chromatographed over silica gel (100 g) with hexane to give allyl 2-naphthyl ether (1.647 g, 89%) as a colorless oil. IR ν_{max} cm^{-1}: 3060, 1415, 1265, 1025. NMR δ ppm: 4.42 (2H, doublet, $J=5$ Hz, CH_2=), 5.16 (2H, multiplet, CH_2O), 5.94 (1H, multiplet, CH), 7.17 (4H, multiplet), 7.56 (3H, multiplet). MS *m/e*: 184 (M^+), 169, 155, 143, 115, 41.

Further elution of the column with the same solvent afforded di-2-naphthoxymethane (157 mg, 10%) as a colorless solid. Recrystallization from hexane afforded colorless crystals, mp 133—134°C (lit.[13] 133—134°C). IR ν_{max} cm^{-1}: 1030. NMR δ ppm: 5.91 (2H, singlet, CH_2), 7.32 (8H, multiplet), 7.69 (6H, multiplet).

Benzyl 2-Naphthyl Ether——A mixture of 2-naphthol (0.72 g, 5 mM), the phosphonium resin catalyst (1.25 g, 1 mM), methylene chloride (25 ml), sodium hydroxide (0.3 g, 7.5 mM), water (5 ml), and benzyl bromide (2.4 ml, 20 mM) was stirred at room temperature for 2 days, then filtered. The organic layer was dried over sodium sulfate and evaporated. The residue was chromatographed over silica gel (80 g) with hexane–ethyl acetate (50: 1) to give benzyl bromide (2.269 g) followed by the other products. The latter products were further chromatographed over silica gel (100 g) with benzene–hexane (2: 1) to give benzyl 2-naphthyl ether (1.124 g, 96%) as a colorless solid. Recrystallization from hexane afforded colorless crystals, mp 99—100°C (lit.[14] 99°C). IR ν_{max} cm^{-1}: 1598, 1258, 1022. NMR δ ppm: 5.08 (2H, singlet, CH_2), 7.10—7.52 (9H, multiplet), 7.68 (3H, multiplet).

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