A Novel, Simple Method for the Preparation of Hindered Diphenyl Ethers

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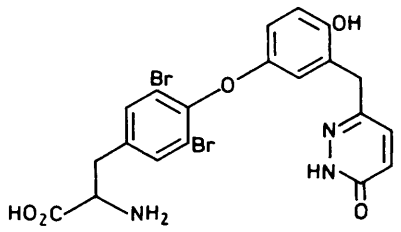
The displacement of the nitro group from substituted nitrobenzenes is used for the synthesis of diphenyl ethers. 1,4-Dinitrobenzene has been converted into a variety of hindered diphenyl ethers using 2,6-disubstituted phenoxides and studies show that the mechanism of formation of the ether (**5a**) is radical in nature.

Substituted diphenyl ethers occur in antibiotics such as the vancomycin family[1] and in alkaloids[2] as well as the thyroxines.[3] SK&F L-94901 (**1**), a selective thyromimetic showing

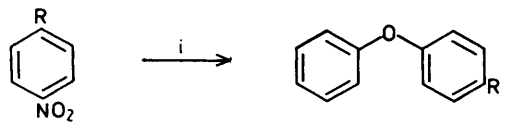


(1)

hypocholesterolaemic activity,[4] contains a 2,6-disubstituted diphenyl ether. We became interested in new routes for the generation of such hindered diphenyl ethers because synthetic methods are sparse,[5] *e.g.*, oxidative coupling generally leads to C–C bond formation rather than generation of the ether link.[6]

It has been shown that, in certain cases, aromatic nitro groups are susceptible to nucleophilic substitution by phenoxides.[7] In our recent communication we described the substitution of an aromatic nitro group by hindered phenoxides giving hindered diphenyl ethers.[8] In this paper, details of this new, general method for the preparation of hindered diphenyl ethers are given.

The activated nitrobenzenes (**2a**—**e**) were converted into the respective diphenyl ethers (**3a**—**e**),[9] using sodium phenoxide in dry dimethyl sulphoxide at 90 °C for 15 h (Scheme 1). When the reactions were conducted at room temperature for 24 h, a decreased yield or no products at all were observed. In contrast, the hindered phenoxide (**4a**) did not react with the nitrobenzenes (**2a**—**d**) to give the expected products; in these cases, the reagents were recovered in greater than 90% yield.

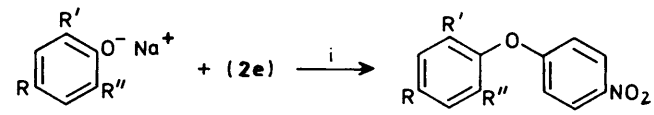


(2) (3)

R	% Yield (3)
a; CHO	24
b; CO_2Me	43
c; CF_3	45
d; CN	62
e; NO_2	77

Scheme 1. *Reagents and conditions:* i, NaOPh, DMSO, 90 °C, 15 h.

With the nitrobenzene (**2e**), the phenoxide (**4a**) reacted under the optimum conditions, to give the diphenyl ether (**5a**) in 65% yield (Scheme 2). This unexpected result



(4) (5)

	R	R′	R″	% Yield (5)
a;	CH_3	Br	Br	65
b;	H	F	F	54
c;	H	Cl	Cl	71
d;	H	CH_3	CH_3	76
e;	H	Pr^i	Pr^i	76
f;	H	OCH_3	OCH_3	90
g;	H	CH_3	$CH_2CH{=}CH_2$	54

Scheme 2. *Reagents and conditions:* i, DMSO, 90 °C, 15 h.

prompted an investigation into the possible mechanism of the reaction especially when it was found that under exactly the same reaction conditions, the diphenyl ether (**5a**) was obtained in only 8% yield from the fluoronitrobenzene (**6a**) and the phenoxide (**4a**). The greater leaving ability of the aromatic nitro group over the fluorine atom under the above reaction conditions suggests that the mechanisms of the two reactions were different. We have also briefly examined a triflate as a leaving group; reaction of the dibromophenoxide (**4a**) with nitrotriflate (**6b**)[10] gave the diphenyl ether in only 10% yield.

Information on the possible mechanism of the reactions was provided by a series of inhibition studies. Reaction of the nitrobenzene (**2e**) with the phenoxide (**4a**) under the usual conditions in the presence of 10 mol% of 1,1-diphenyl-2-picrylhydrazyl,[11] gave the diphenyl ether (**5a**) in a reduced yield of 56%. In the presence of 1 equiv. of the hydrazyl, the nitrobenzene (**2e**) was recovered in 95% yield and no ether (**5a**) was detected. These results were repeated using elemental sulphur[12] as the free radical scavenger. [Note, however, that di-

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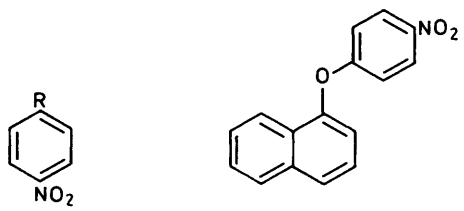
t-butylnitroxyl did not inhibit formation of the diphenyl ether (**5a**) and that copper catalysis (copper powder or cuprous iodide) did not affect the yield of the ether (**5a**) significantly.] On the basis of these results and reports that electron transfer occurs in the reactions of phenoxides with nitro aromatics,[13] it seems likely that the formation of the diphenyl ether (**5a**) from the nitrobenzene (**2e**) is radical in nature.

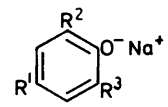
Repeating the inhibition studies for the reaction of the fluoronitrobenzene (**6a**) with the phenoxide (**4a**) did not affect the formation of the diphenyl ether (**5a**) which was isolated in 5—10% yield. It seems likely that the displacement of the fluorine atom does not involve a radical mechanism but is probably a straightforward aromatic nucleophilic substitution. The mechanism of the reaction of the nitrobenzene (**2e**) with sodium phenoxide was also investigated. Using 1 equiv. of the free radical scavengers mentioned above, the diphenyl ether (**5e**) was isolated in reduced 59% yield. In this particular case, two mechanisms may be in operation, an anionic nucleophilic displacement and a radical mechanism.



(**6a**) R = F

(**6b**) R = OSO_2CF_3

(**7**)



(**8**)

	R^1	R^2	R^3
a;	H	NO_2	NO_2
b;	NO_2	I	I
c;	I	I	I
d;	CH_3	Bu^t	Bu^t

The synthesis of the diphenyl ether (**5a**) from the nitrobenzene (**2e**) indicated a potentially useful method for the preparation of other hindered diphenyl ethers. The scope of this reaction has now been investigated using a variety of phenoxides. Good yields of several hindered diphenyl ethers (**5b**—**g**)[14] were obtained from the reaction of the nitrobenzene (**2e**) with the respective 2,6-disubstituted phenoxides and sodium 1-naphthoxide gave the ether (**7**)[14c] in 89% yield. However, no diphenyl ether products were obtained when using the phenoxides (**8a**—**c**), the nitrobenzene (**2e**) being recovered (80—95%); using the di-t-butylphenoxide (**8d**) only led to decomposition of the reagents.

In conclusion, the displacement of a nitro group from suitably activated nitrobenzenes by phenoxides represents a particularly useful method since it allows the preparation of hindered diphenyl ethers from weakly nucleophilic phenoxides.

Experimental

M.p.s were determined on an electrothermal melting point apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 298 spectrophotometer, either on film or, for solids, in chloroform solution. ^{1}H N.m.r. spectra were recorded on a Bruker AM250 (250 MHz) spectrometer and are quoted in p.p.m. relative to tetramethylsilane (internal reference) for solutions in deuteriochloroform. Mass spectra were obtained with a VG analytical 7070F instrument. Microanalytical determinations were performed by the Department of Physical Organic Chemistry, microanalytical section.

Dimethyl sulphoxide and methanol were dried using the methods given by Perrin.[15] Column chromatography was carried out on Kieselgel 60G (Merck) and columns were generally packed and run under pressure. Solvent ratios for chromatography are described in ratios of volumes before mixing. Light petroleum refers to the fraction of the boiling range 60—80 °C and ether refers to diethyl ether throughout. Solutions of organic compounds were dried over anhydrous calcium chloride. All the nitrobenzenes except the nitrotriflate (**6b**) are commercially available.

General Procedure for Phenoxides.—Sodium metal (10 mmol) was dissolved in dry methanol (30 ml) with stirring. The phenol (10 mmol) was added to the stirred solution at room temperature and the solvent was evaporated off under reduced pressure to give the phenoxides as white solids except for (**5e**)-brown green solid, (**5g**)-dark blue liquid, (**8a**) and (**8b**)-orange solids, (**8c**)-pale yellow solid, and (**8d**)-pale purple solid.

General Procedures for Diphenyl Ethers.—The phenoxide (3.5 mmol) and the nitrobenzene (3.0 mmol) were stirred in dry dimethyl sulphoxide (5 ml) at 90 °C for 15 h under a calcium chloride guard tube. The reaction mixture was poured into ice–water (100 ml) and the whole extracted with ether (3 × 100 ml). The combined organic extracts were washed with aqueous 5% potassium hydroxide (50 ml) and water (50 ml), dried, filtered, and the solvent was evaporated off under reduced pressure to give the crude diphenyl ethers.*

4-*Phenoxybenzaldehyde* (**3a**).[9a] The yellow oil was chromatographed on silica using 1:8 ethyl acetate–light petroleum as eluant to give a pale yellow oil which was distilled to give a colourless oil, b.p. 200—205 °C/0.3 mmHg. The oil solidified on standing to give a white solid (0.14 g, 24%), m.p. 22—24 °C.

Methyl 4-*phenoxybenzoate* (**3b**).[9b] The yellow solid was recrystallised in an ether–light petroleum mixture to give a white solid (0.29 g, 43%), m.p. 56—58 °C.

4-*Phenoxybenzylidyne trifluoride* (**3c**).[9c] The yellow oil was distilled to give a colourless oil (0.32 g, 45%), b.p. 150—155 °C/0.6 mmHg.

4-*Phenoxybenzonitrile* (**3d**).[9d] The yellow oil was chromatographed on silica using 1:4 ethyl acetate–light petroleum as eluant to give a colourless oil which solidified on cooling to give a white crystalline solid (0.36 g, 62%), m.p. 22—24 °C.

1-*Nitro*-4-*phenoxybenzene* (**3e**).[9e] The orange oil solidified on standing. The solid was recrystallised from an ether–light petroleum mixture to give pale yellow crystals (0.50 g, 77%), m.p. 55—56 °C.

1-(2,6-*Dibromo*-4-*methylphenoxy*)-4-*nitrobenzene* (**5a**). The orange solid was recrystallised from an ether–light petroleum to give pale yellow *crystals* (0.75 g, 65%), m.p. 111—113 °C (Found: C, 40.75; H, 2.4; N, 3.65. $C_{13}H_9Br_2NO_3$ requires C, 40.35; H, 2.35; N, 3.6%); $\nu_{max.}$ 1 590, 1 440, 1 335, 1 100, 865, and 835 cm^{-1}; δ 2.39 (3 H, s, Me), 6.92 (2 H, d, *J* 8.5 Hz, 2-H and 6-H), 7.46 (2 H, s, 3′-H and 5′-H), and 8.23 (2 H, d, *J* 8.5 Hz, 3-H and 5-H); *m*/*z* 385 (M^+, 24.3%), 369 (1.5), 355 (14.4), 306 (100), and 305 (66.9).

1-(2,6-*Difluorophenoxy*)-4-*nitrobenzene* (**5b**). The brown solid

* Spectral and analytical data for compound (**3a**—**e**) correspond to the structure of the compound.

was recrystallised in ether to give pale yellow, needle-like *crystals* (0.41 g, 54%), m.p. 122—124 °C (Found: C, 57.55; H, 3.05; N, 5.5. $C_{12}H_7F_2NO_3$ requires C, 57.4; H, 2.8; N, 5.6%); $\nu_{max.}$ 1 620, 1 595, 1 490, 1 480, 1 350, 1 300, 1 110, 1 010, 880, and 845 cm^{-1}; δ 7.05 (4 H, m, 2-H, 6-H, 3'-H, and 5'-H), 7.2 (1 H, m, 4'-H), and 8.22 (2 H, d, *J* 9 Hz, 3-H and 5-H); *m/z* 251 (M^+, 100%), 221 (45.0), and 205 (10.0).

1-(2,6-*Dichlorophenoxy*)-4-*nitrobenzene* (**5c**). The pale yellow solid was recrystallised in ether to give pale yellow flake-like *crystals* (0.60 g, 71%), m.p. 122—123.5 °C (Found: 50.55; H, 2.45; N, 4.9. $C_{12}H_7Cl_2NO_3$ requires C, 50.7; H, 2.5; N, 4.95%); $\nu_{max.}$ 1 620, 1 600, 1 575, 1 515, 1 490, 1 450, 1 350, 1 115, 880, and 850 cm^{-1}; δ 6.92 (2 H, d, *J* 9 Hz, 2-H and 6-H), 7.23 (1 H, t, *J* 9 Hz, 4'-H), 7.45 (2 H, d, *J* 8 Hz, 3'-H and 5'-H), and 8.22 (2 H, d, *J* 9 Hz, 3-H and 5-H); *m/z* 283 (M^+, 100%), 253 (29.0), and 202 (54.6).

1-(2,6-*Dimethylphenoxy*)-4-*nitrobenzene* (**5d**). The yellow oil was chromatographed on silica using 1:4 ethyl acetate–light petroleum to give a pale yellow oil which was distilled to give a colourless oil, b.p. 230—235 °C/0.07 mmHg. Ethanol (1 ml) was added, the solution was cooled, and the white needle-like *crystals* which formed were filtered off (0.55 g, 76%), m.p. 59—60 °C (Found: C, 68.9; H, 5.25; N, 5.7. $C_{14}H_{13}NO_3$ requires C, 69.1; H, 5.4; N, 5.75%); $\nu_{max.}$ 1 615, 1 600, 1 590, 1 510, 1 490, 1 475, 1 350, 1 070, 875, and 850 cm^{-1}; δ 2.11 (6 H, s, Me), 6.84 (2 H, d, *J* 9 Hz, 2-H and 6-H), 7.13 (3 H, s, 3'-H, 4'-H, and 5'-H), and 8.17 (2 H, d, *J* 9 Hz, 3-H and 5-H); *m/z* 243 (M^+, 100%), 228 (7.4), and 196 (13.4).

1-(2,6-*Di-isopropylphenoxy*)-4-*nitrobenzene* (**5e**). The brown gum was chromatographed on silica using 1:6 ethyl acetate–light petroleum as eluant to give a white, crystalline *solid*, (0.68 g, 76%), m.p. 91—93 °C (Found: C, 72.3; H, 7.1; N, 4.5. $C_{18}H_{21}NO_3$ requires C, 72.2; H, 7.05; N, 4.7%); $\nu_{max.}$ 1 615, 1 600, 1 585, 1 490, 1 350, 1 330, 1 165, 1 115, 875, and 850 cm^{-1}; δ 1.14 (12 H, d, *J* 7 Hz, Me), 2.92 (2 H, quint, *J* 7 Hz, $CHMe_2$), 6.85 (2 H, d, *J* 9 Hz, 3-H and 5-H), 7.25 (3 H, m, 3'-H, 4'-H, and 5'-H), and 8.17 (2 H, d, *J* 9 Hz, 2-H and 6-H); *m/z* 300 (M^+H, 100%), 285 (25.0), and 224 (70.0).

1-(2,6-*Dimethoxyphenoxy*)-4-*nitrobenzene* (**5f**). The pale yellow solid was recrystallised in an ether–light petroleum mixture to give pale yellow, needle-like crystals (0.74 g, 90%), m.p. 111—112 °C (Found: C, 61.1; H, 4.75; N, 5.0. $C_{14}H_{13}NO_5$ requires C, 61.1; H, 4.75; N, 5.1%); $\nu_{max.}$ 1 600, 1 585, 1 480, 1 345, 1 305, 1 110, 870, and 845 cm^{-1}; δ 3.78 (6 H, s, OMe), 6.68 (2 H, d, *J* 8.5 Hz, 3'-H and 5'-H), 6.92 (2 H, d, *J* 9 Hz, 2-H and 6-H), 7.21 (1 H, t, *J* 8.5 Hz, 4'-H), and 8.16 (2 H, d, *J* 9 Hz, 3-H and 5-H); *m/z* 275 (M^+, 100%), 243 (5.0), and 213 (10.0).

1-(2-*Allyl*-6-*methylphenoxy*)-4-*nitrobenzene* (**5g**). The red oil was chromatographed on silica using 1:4 ethyl acetate–light petroleum to give a pale yellow oil which was distilled to give a colourless oil (0.43 g, 54%), b.p. 215—220 °C/0.1 mmHg (Found: C, 71.45; H, 5.7; N, 5.2. $C_{16}H_{15}NO_3$ requires C, 71.35; H, 5.6; N, 5.2%); $\nu_{max.}$ 1 615, 1 600, 1 490, 1 350, 1 070, 1 015, 995, 915, 870, and 850 cm^{-1}; δ 2.12 (3 H, m, Me), 3.2 (1 H, m), 3.37 (1 H, m), 4.9—5.15 (2 H, m, $C{=}CH_2$), 5.72—6.1 (1 H, m, CH=C), 6.8—7.1 (3 H, m, 2-H, 6-H, and 4'-H), 7.1—7.17 (2 H, m, 3'-H and 5'-H), and 8.17 (2 H, d, *J* 9 Hz, 3-H and 5-H); *m/z* 269 (M^+, 100%), 254 (20.0), 253 (15.0), 229 (30.4), and 222 (24.6).

1-(4-*Nitrophenoxy*)*naphthalene* (**7**). The brown solid was chromatographed on silica using 1:4 ethyl acetate–light petroleum as eluant to give an orange solid which was recrystallised in an ether–light petroleum mixture to give a pale orange solid (0.70 g, 89%), m.p. 144—146 °C (Found: C, 72.35; H, 4.2; N, 5.0. $C_{16}H_{11}NO_3$ requires C, 72.45; H, 4.2; N, 5.3%); $\nu_{max.}$ 1 615, 1 600, 1 575, 1 515, 1 490, 1 390, 1 115, 890, 860, and 850 cm^{-1}; δ 7.01 (2 H, d, *J* 9 Hz, 2'-H and 6'-H), 7.17 (1 H, d, *J* 7.5 Hz, 2-H), 7.4—7.6 (3 H, m, 3-H, 6-H, and 7-H), 7.78 (1 H, d, *J* 9.5 Hz, 8-H), 7.92 (2 H, d, *J* 9 Hz, 4-H and 5-H), and 8.18 (2 H, d, *J* 9 Hz, 3'-H and 5'-H); *m/z* 265 (M^+, 100%), 218 (17.3), and 189 (13.4).

Acknowledgements

We thank the Department of Physical Organic Chemistry for spectral and analytical data of the compounds. D. T. acknowledges receipt of a Smith Kline and French research fellowship during the course of this work.

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Received 14*th March* 1988; *Paper* 8/01044G