Displacement of an Aromatic Nitro Group using Phenoxides

P. G. Sammes,* D. Thetford, and M. Voyle

Department of Synthetic and Isotope Chemistry, Smith Kline and French Research Limited, The Frythe, Welwyn, Hertfordshire AL6 9AR, U.K.

1,4-Dinitrobenzene undergoes nucleophilic substitution with sodium phenoxide and several hindered 2,6-substituted phenoxides to afford diphenyl ethers.

SK&F L-94901 (**1**), a selective thyromimetic showing hypocholesterolaemic activity,[1] contains a hindered 2,6-disubstituted diphenyl ether system. The formation of such hindered diphenyl ethers has proved troublesome and there are few reported syntheses.[2] In earlier investigations, it was found that the classic method of nucleophilic aromatic displacement of a leaving group by a 2,6-dihalogenophenoxide anion gave poor results.[3] We report here a new method for the preparation of diphenyl ethers by the displacement of an aromatic nitro group.

Phenoxides have previously been used to displace a nitro group on an activated furan ring.[4] In fact, nitro groups on benzenoid aromatic systems have been substituted with other nucleophiles, *e.g.* thiolates, alkoxides, carbanions, and cyanide,[5] but there are few examples using phenoxide as the anion, *viz.* with 4-nitrobenzophenone.[5a,b]

The substituted nitrobenzenes (**2a**—**d**) were converted into the respective diphenyl ethers (**3a**—**d**)[6] using sodium phenoxide in dry dimethyl sulphoxide at 90 °C for 16 h (Scheme 1); a decreased yield of these products was observed when the reaction was carried out at lower temperatures. However, 2,6-dibromophenoxide (**4a**) did not react with the nitrobenzenes (**2a**—**c**) in the required manner even at 90 °C. In these cases, the nitrobenzenes (**2a**—**c**) were recovered (>90%).

In contrast, the hindered phenoxide (**4a**) did react with the nitrobenzene (**2d**) (Me_2SO, 90 °C, 16 h), to give the diphenyl ether (**5a**),† in 65% yield (Scheme 2). In a comparative experiment, the ether (**5a**) was prepared from the phenoxide

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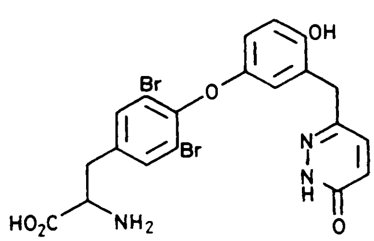
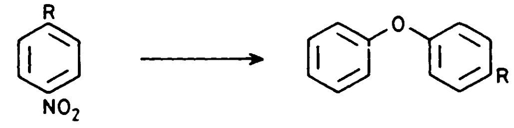
† All new compounds gave satisfactory spectroscopic and analytical data.



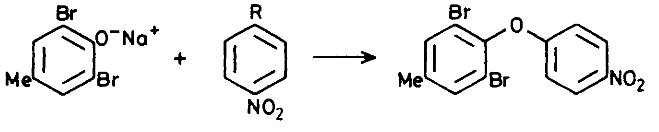
(1)



(2) (3)

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

Scheme 1. *Reagents*: NaOPh, Me_2SO, 90 °C.



(4a) (2d), (6) (5a)

	R	% Yield of (5)
(**2d**)	NO_2	65
(**6**)	F	8

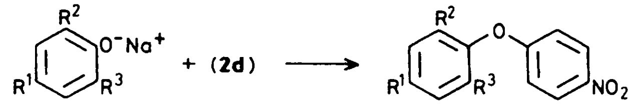
Scheme 2. *Conditions*: Me_2SO, 90 °C, 16 h.

(**4a**) and the fluoronitrobenzene (**6**) (Me_2SO, 90 °C, 16 h), in only 8% yield, thus showing the greater leaving ability of the aromatic nitro group over the fluorine atom under the reaction conditions.

A series of inhibition studies provided information on the mechanism of the reaction of the nitrobenzene (**2d**) with the phenoxide (**4a**). In the presence of 10 mol% of 1,1-diphenyl-2-picrylhydrazyl,[7] a free radical, the diphenyl ether (**5a**) was isolated from the nitrobenzene (**2d**) and phenoxide (**4a**) in reduced yield (56%). When 1 equiv. of the hydrazyl was used, only the nitrobenzene (**2d**) was isolated from the reaction mixture (80% recovery). The same results were observed with elemental sulphur[8] as the free radical scavenger. It therefore seems likely, in this instance, that the displacement of the aromatic nitro group does not involve an anionic nucleophilic displacement mechanism but is radical in nature.

Several hindered diphenyl ethers (**5b**—**g**) were also prepared from the nitrobenzene (**2d**) in good yields using the respective 2,6-disubstituted phenoxides under the usual reaction conditions (Scheme 3). Sodium 1-naphthoxide also reacted with nitrobenzene (**2d**) to give the ether (**7**),[10] in 89% yield.

In summary, the displacement of a nitro group from suitably substituted nitrobenzenes by phenoxides represents a versatile synthesis of substituted diphenyl ethers. The method is particularly useful since it allows the preparation of hindered diphenyl ethers from weakly nucleophilic phenoxides.

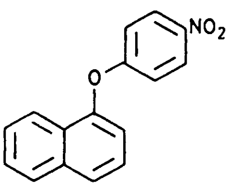


(4) (5)

		% Yield	M.p. (°C)
a;	$R^1 = Me, R^2 = R^3 = Br$	65	111—113
b;	$R^1 = H, R^2 = R^3 = F$	54	122—124
c;	$R^1 = H, R^2 = R^3 = Cl$	71	122—123.5[a]
d;	$R^1 = H, R^2 = R^3 = Me$	38	59—60[b]
e;	$R^1 = H, R^2 = R^3 = Pr^i$	76	93—93[c]
f;	$R^1 = H, R^2 = R^3 = OMe$	90	111—112
g;	$R^1 = H, R^2 = Me, R^3 = CH_2CH{=}CH_2$	54	[d]

[a] Lit.,[9a] 92—93 °C; lit.,[9b] 115—117 °C. [b] lit.,[2b] 61—63 °C. [c] lit.,[2b] 92—93 °C. [d] B.p. 230—235 °C at 0.2 mmHg.

Scheme 3. *Conditions*: Me_2SO, 90 °C, 16 h.



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References

1 A. H. Underwood, J. C. Emmett, D. Ellis, S. B. Flynn, P. D. Leeson, G. M. Benson, R. Novelli, N. J. Pearce, and V. P. Shah, *Nature* (*London*), 1986, **324**, 425.
2 (a) E. C. Jorgensen, 'Hormonal Proteins and Peptides', ed. Choh Hao Li, Academic Press, New York, 1978, vol. 6, p. 57; (b) J. Wright and E. C. Jorgensen, *J. Org. Chem.*, 1968, **33**, 1245.
3 M. B. Mitchell, Department of Synthetic and Isotope Chemistry, Smith Kline and French Research Limited, personal communication.
4 A. Tanaka, T. Usui, and M. Shimadzu, *J. Heterocycl. Chem.*, 1981, **18**, 1241.
5 (a) N. Kornblum, L. Cheng, R. C. Kerber, M. M. Kestner, B. N. Newton, H. W. Pinnick, R. G. Smith, and P. A. Wade, *J. Org. Chem.*, 1976, **41**, 1560; (b) E. Radlmann, W. Schmidt, and G. E. Nischk, *Makromol. Chem.*, 1969, **130**, 45; (c) J. H. Gorvin, *Chem. Commun.*, 1971, 1120; (d) F. Pietra and D. Vitali, *J. Chem. Soc., Perkin Trans. 1*, 1972, 385; (e) G. Bartoli, A. Latrofa, F. Naso, and P. E. Todesco, *J. Chem. Soc., Perkin Trans. 1* 1972, 2671; (f) E. J. Corey and R. H. K. Chen, *J. Org. Chem.*, 1973, **38**, 4086; (g) R. D. Knudsen and H. R. Snyder, *J. Org. Chem.*, 1974, **39**, 3343; (h) J. R. Beck, *Tetrahedron*, 1978, **34**, 2057; (i) J. H. Clark and D. K. Smith, *Tetrahedron Lett.*, 1985, 2233; (j) G. Iwasaki, S. Saeki, and M. Hamana, *Chem. Lett.*, 1986, 31.
6 (a) A. Kreutzberger, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 940; (b) R. West, S. Ornstein, D. McKee, and R. Layzer, *J. Am. Chem. Soc.*, 1952, **74**, 3960; (c) C. M. Suter, *J. Am. Chem. Soc.*, 1929, **51**, 2581; (d) R. Q. Brewster and T. Groening, *Org. Synth.*, 1943, Coll. Vol. II, 19, 445.
7 R. H. Poirier, E. J. Kahler, and F. Benington, *J. Org. Chem.*, 1952, **17**, 1437.
8 P. D. Bartlett and H. Kwart, *J. Am. Chem. Soc.*, 1950, **72**, 1051.
9 (a) R. J. Cremlyn, T. Cronje, and K. Goulding, *Aust. J. Chem.*, 1979, **32**, 445; (b) Neth. Pat. 6 405 727/1964.
10 Eur. Pat. 13 414/1980.