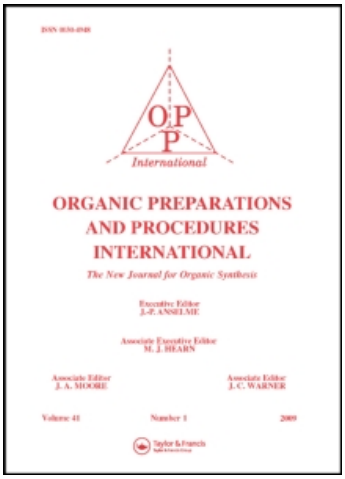

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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Online publication date: 26 May 2010

To cite this Article Bunce, Richard A. and Easton, Kerry M.(2004) 'A VERSATILE AND CONVENIENT SYNTHESIS OF ALKYL NITROAROMATIC ETHERS BY NUCLEOPHILIC AROMATIC SUBSTITUTION', Organic Preparations and Procedures International, 36: 1, 76 — 81
To link to this Article: DOI: 10.1080/00304940409355375
URL: http://dx.doi.org/10.1080/00304940409355375

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A VERSATILE AND CONVENIENT SYNTHESIS OF ALKYL NITROAROMATIC ETHERS BY NUCLEOPHILIC AROMATIC SUBSTITUTION

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One of our current projects required a series of allyl 2-nitroaromatic ethers as substrates for a new synthesis of benzoxazines.[1] During the preparation of several of these substrates, we found that conversion of the required allylic alcohol to the bromide and *O*-alkylation of 2-nitrophenol under basic conditions gave low yields of the desired products. We, therefore, sought a more direct approach involving nucleophilic substitution of an allylic alkoxide on 2-fluoro-1-nitrobenzene. Nucleophilic aromatic substitution of alkoxides and phenoxides on fluoronitroaromatics has recently found wide use in the synthesis of both natural[2] and unnatural[3] products. A number of the protocols that can be used for this transformation, however, have limitations with respect to the alcohols that will react[2,3a-d] or the cost of reagents.[3e] Typical conditions include CsF in DMSO (for phenols[2a-d]), KOH in PhOH (for phenol itself[3a-b]), K_2CO_3 in DMF (for 1° allylic, propargylic and benzylic alcohols[3c-d] as well as phenols[2]), potassium hexamethyldisilazide (KHMDS) in THF (for 3°, and presumably 1° and 2° alcohols[3e]), and NaH in DMF (for 1° alcohols[4a-c] and phenols[4d]). Of these five procedures, the last two appear to be the most versatile, though KHMDS is considerably more expensive than NaH. To date, no single set of conditions has been used to promote substitutions of all types of alcohols. Thus, in addition to our own target molecules, we wished to explore the possibility of optimizing one protocol applicable to the synthesis of a variety of alkyl nitroaromatic ethers. We report here a general procedure using NaH in DMF that permits the substitution of primary, secondary and tertiary alcohols as well as phenols to 2- and 4-fluoronitrobenzenes.

Table 1. Yields, Mps and Elemental Analyses for Compounds **1** and **2**.

a) R = $-CH_2C(n\text{-}C_4H_9)=CH_2$ b) R = $-CH_2C(C_6H_5)=CH_2$ c) R = $-CH_2CH_2CH=CH_2$
d) R = $-CH_2(CH_2)_2C_6H_5$ e) R = $-i\text{-}C_3H_7$ f) R = $-t\text{-}C_4H_9$
g) R = $-C_6H_5$

Cmpd	Yield (%)	mp[a] (°C)	Elemental Analysis (Found) C	H	N
1a	96	oil	66.38 (66.52)	7.23 (7.26)	5.96 (5.83)
1b	92	53-54	70.59 (70.38)	5.10 (5.03)	5.49 (5.61)
1c	85	oil	62.18 (62.29)	5.70 (5.74)	7.25 (7.16)
1d	96	oil	70.04 (69.83)	5.84 (5.90)	5.45 (5.51)
1e	92	oil	59.67 (59.94)	6.08 (6.16)	7.73 (7.58)
1f	88	oil		[b]	
1g	96	oil		[c]	
2a	96	oil	66.38 (66.65)	7.23 (7.31)	5.96 (5.71)
2b	96	59-60	70.59 (70.80)	5.10 (5.17)	5.49 (5.37)
2c	83	oil	62.18 (62.41)	5.70 (5.77)	7.25 (7.12)
2d	96	71-72	70.04 (69.89)	5.84 (5.87)	5.45 (5.49)
2e	84	30-31[d]		[e]	
2f	91	oil		[f]	
2g	96	58-59[g]		[h]	

a) Products were light yellow oils or solids. Compounds **1b**, **2b**, **2d** and **2e** were recrystallized from petroleum ether; **2g** was recrystallized from ethanol. b) Known compound (ref. 3e). c) Known compound (ref. 11). d) *Lit.* mp 32-33°C (ref. 7a). e) Known compound (ref. 7a). f) Known compound (ref. 12). g) *Lit.* mp 58-59°C (ref. 7a). h) Known compound (ref. 7a).

The results of our study are summarized in *Tables 1 and 2*. Best yields were achieved using 1.5 equivalents of the alcohol relative to the aromatic substrate. The alkoxides were prepared by treatment of the alcohols with 1.1 equivalents of NaH in DMF.[5] The deprotonation was generally carried out a room temperature except in the case of *tert*-butanol where proton removal was facilitated by heating at 40°C. Following deprotonation of the alcohol, the aromatic substrate was added and the reaction was stirred at room temperature for 1 h and at 50°C for 12 h. Mild acid workup and purification by crystallization or chromatography then gave the alkyl nitroaromatic ether.

Table 2. Spectroscopic Data for Compounds **1** and **2**

Cmpd	IR (cm^{-1})	^1H NMR[a] (δ)	^{13}C NMR (δ)	HRMS (m/z) (Found)
1a	1654 1524 1351	7.83 (dd, 1 H, J = 8.2, 1.8), 7.50 (ddd, 1 H, J = 8.5, 7.4, 1.8), 7.07 (dd, 1 H, J = 8.5, 1.2), 7.02 (ddd, 1 H, J = 8.2, 7.4, 1.2), 5.19 (m, 1 H), 5.03 (m, 1 H), 4.60 (s, 2 H), 2.16 (t, 2 H, J = 7.1), 1.48 (m, 2 H), 1.34 (m, 2 H), 0.92 (t, 3 H, J = 7.3)	152.0, 143.5, 140.1, 133.9, 125.6, 120.3, 114.7, 112.5, 71.9, 32.6, 29.6, 22.4, 13.9	235.1208 (235.1206)
1b	1633 1521 1349	7.84 (dd, 1 H, J = 8.1, 1.6), 7.55-7.42 (complex, 3 H), 7.40-7.31 (complex, 3 H), 7.12 (dd, 1 H, J = 8.5, 1.0), 7.03 (ddd, 1 H, J = 8.2, 7.5, 1.2), 5.61 (m, 1 H), 5.57 (m, 1 H), 5.02 (t, 2 H, J = 1.3 Hz)	151.8, 141.7, 140.0, 137.9, 134.0, 128.5, 128.2, 126.0, 125.7, 120.6, 115.0 (2), 70.7	255.0895 (255.0896)
1c	1641 1525 1351	7.81 (dd, 1 H, J = 8.1, 1.8), 7.51 (ddd, 1 H, J = 8.4, 7.4, 1.8), 7.07 (dd, 1 H, J = 8.4, 1.1), 7.01 (ddd, 1 H, J = 8.1, 7.4, 1.1), 5.91 (ddt, 1 H, J = 17.2, 10.3, 6.8), 5.18 (dm, 1 H, J = 17.2), 5.12 (dm, 1 H, J = 10.3), 4.14 (t, 2 H, J = 6.8), 2.59 (qt, 2 H, J = 6.8, 1.3)	152.2, 140.1, 133.9, 133.6, 125.5, 120.2, 117.6, 114.5, 68.9, 33.3	193.0739 (193.0738)
1d	1523 1351	7.81 (dd, 1 H, J = 8.4, 1.8), 7.47 (ddd, 1 H, J = 8.2, 7.7, 1.8), 7.30-7.11 (complex, 5 H), 6.99 (m, 2 H), 4.06 (t, 2 H, J = 6.2), 2.85 (t, 2 H, J = 7.4), 2.14 (tt, 2 H, J = 7.4, 6.2)	152.3, 141.0, 139.9, 134.0, 128.5, 128.4, 126.0, 125.5, 120.1, 114.3, 68.1, 31.7, 30.4	257.1052 (257.1051)
1e	1522 1356	7.76 (dd, 1 H, J = 8.1, 1.8), 7.48 (ddd, 1 H, J = 8.4, 7.4, 1.8), 7.07 (dd, 1 H, J = 8.4, 1.2), 6.98 (ddd, 1 H, J = 8.1, 7.4, 1.2), 4.67 (septet, 1 H, J = 6.2), 1.39 (d, 6 H, J = 6.2)	151.2, 140.8, 133.6, 125.4, 120.0, 116.1, 72.6, 21.9 (2)	181.0739 (181.0740)
1f,g	For compounds **1f** and **1g**, the spectral data matched those reported in references 3e and 11.			
2a	1653 1511 1341	8.20 (d, 2 H, J = 9.0), 6.98 (d, 2 H, J = 9.0), 5.12 (s, 1 H), 5.05 (s, 1 H), 4.56 (s, 2 H), 2.14 (t, 2 H, J = 7.2), 1.49 (m, 2 H), 1.37 (m, 2 H), 0.93 (t, 3 H, J = 7.4)	163.8, 143.7, 141.5, 125.8, 114.7, 112.7, 71.4, 32.6, 29.6, 22.4, 13.9	235.1208 (235.1205)
2b	1633 1511 1337	8.21 (d, 2 H, J = 9.2), 7.44 (m, 2 H), 7.35 (m, 3 H), 7.02 (d, 2 H, J = 9.2), 5.65 (s, 1 H), 5.46 (s, 1 H), 5.00 (s, 2 H)	163.5, 141.9, 141.6, 137.7, 128.6, 128.3, 125.9 (2), 115.5, 114.8, 70.3	255.0895 (255.0894)
2c	1643 1511 1341	8.20 (d, 2 H, J = 9.4), 6.96 (d, 2 H, J = 9.4), 5.89 (ddt, 1 H, J = 17.2, 10.3, 6.8), 5.22 (dm, 1 H, J = 17.2), 5.15 (dm, 1 H, J = 10.3), 4.11 (t, 2 H, J = 6.6), 2.59 (qt, 2 H, J = 6.6, 1.5)	163.9, 141.4, 133.6, 125.9, 117.7, 114.4, 68.0, 33.3	193.0739 (193.0739)
2d	1514 1337	8.19 (d, 2 H, J = 9.4), 7.34-7.17 (complex, 5 H), 6.93 (d, 2 H, J = 9.4), 4.04 (t, 2 H, J = 6.3), 2.83 (t, 2 H, J = 7.2), 2.16 (tt, 2 H, J = 7.2, 6.3)	164.0, 141.6, 140.9, 128.5, 128.4, 126.1, 125.9, 114.4, 67.7, 31.9, 30.4	257.1052 (257.1049)
2e-g	For compounds **2e**, **2f** and **2g**, the spectral data matched those reported in references 7, 12 and 13 respectively.			

a) Coupling constants (*J*) are reported in Hz.

The reaction proceeded in high yield for primary, secondary and tertiary alcohols as well as for phenol. The reaction was equally successful for 2- and 4-fluoronitrobenzenes and, surprisingly, even 3-fluoronitrobenzene gave *ca* 10% of 3-isopropoxy-1-nitrobenzene (**3**) when reacted with sodium isopropoxide. While it is well-documented that fluoride is a superior leaving group in nucleophilic aromatic substitutions,[6] we attempted the addition of sodium isopropoxide to 2- and 4-chloronitrobenzenes under the present conditions and found the yields to be nearly 30% lower (62-64%) than for the corresponding fluoro compounds. Finally, there were no significant problems involving reduction of the nitro group[7] when the reactions were conducted in DMF.

In conclusion, an optimized procedure for nucleophilic substitution of alkoxides on 2- and 4-fluoronitrobenzenes has been developed. It uses readily available, inexpensive reagents and allows for the addition of a broad range of structurally diverse alcohols and phenol. The final products are obtained in high yield and are readily purified by crystallization or column chromatography.

EXPERIMENTAL SECTION

DMF (EM Science, GR grade), from a freshly opened bottle, was dried over 4Å molecular sieves under nitrogen and transferred by syringe into each reaction. All reactions were performed under dry N_2 in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates. Preparative separations were carried out using flash column chromatography[8] on silica gel (grade 62, 60-200 mesh) mixed with UV-active phosphor (Sorbent Technologies UV-5); band elution was monitored using a hand-held UV lamp. Melting points are uncorrected. IR spectra were run as thin films on NaCl disks and were referenced to polystyrene. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 300 MHz and 75 MHz, respectively, and were referenced to internal TMS; coupling constants (*J*) are given in Hz. High-resolution mass spectra (EI/DP) were obtained at 70 eV.

The 2-butyl-2-propen-1-ol[9] and 2-phenyl-2-propen-1-ol[10] used in this study were prepared by literature procedures. All other alcohols were commercially available.

***CAUTION**: Though we did not experience any problems, isopropyl ethers may tend to form explosive peroxides upon prolonged storage.*

Typical Procedure for Nucleophilic Aromatic Substitution of 2- and 4-Fluoro-1-nitrobenzene by Alkoxides. 2-[(2-Butyl-2-propenyl)oxy]-1-nitrobenzene (1a).- In a 100-mL, three-necked, round-bottomed flask equipped with an addition funnel, a magnetic stir bar and a condenser, 0.32 g of 60% NaH in mineral oil (8.0 mmol) was washed with hexane (3x) and suspended in 10 mL of DMF. Stirring was started and a solution of 0.86 g (7.5 mmol) of 2-butyl-2-propen-1-ol in 10 mL of DMF was added dropwise at room temperature. The mixture was stirred for 1 h at room temperature and 0.71 g (5.0 mmol) of 2-fluoro-1-nitrobenzene in 2 mL of DMF was added dropwise. The reaction became warm and turned dark brown in color. The reaction was stirred for 1 h at room temperature and for 12 h at 50°C, then added to saturated NH_4Cl

and extracted with ether (3x). The combined ether layers were washed with 1 M HCl and saturated NaCl, dried ($MgSO_4$) and concentrated under vacuum. The crude product was flash chromatographed on a 60 cm x 2 cm silica gel column using 5% ether in hexane to afford 1.13 g (96%) of **1a** as a light yellow oil. Physical and spectral data for all new compounds prepared are given in *Tables 1 and 2*.

2-(*tert*-Butoxy)-1-nitrobenzene (1f).- In the procedure to prepare **1f**, the deprotonation of *tert*-butanol was carried out at 40°C. The spectral data matched those reported previously.[3e]

2-Phenoxy-1-nitrobenzene (1g).- Prior to the 1 M HCl wash in the work-up for **1g**, the combined ethereal extracts were washed with 0.2 M NaOH (until the aqueous washes remained colorless) to remove any unreacted phenol. The spectral data matched those reported previously.[11]

4-(*tert*-Butoxy)-1-nitrobenzene (2f).- In the procedure to prepare **2f**, the deprotonation of *tert*-butanol was carried out at 40°C. The spectral data matched those reported previously.[12]

4-Phenoxy-1-nitrobenzene (2g).- Prior to the 1 M HCl wash in the workup for **2g**, the combined ethereal extracts were washed with 0.2 M NaOH (until the aqueous washes remained colorless) to remove any unreacted phenol. The spectral data matched those reported previously.[13]

3-Isopropoxy-1-nitrobenzene (3).- This compound (0.09 g, 10%) was isolated as a light yellow oil. IR 1528, 1348 cm^{-1}; ^1H NMR: δ 7.79 (ddd, 1 H, J = 8.2, 2.2, 0.8), 7.71 (t, 1 H, J = 2.2), 7.40 (t, 1 H, J = 8.2), 7.19 (ddd, 1 H, J = 8.2, 2.3, 0.9), 4.64 (septet, 1 H, J = 6.0), 1.38 (d, 6 H, J = 6.0); ^{13}C NMR: δ 158.5, 140.9, 129.9, 122.7, 115.4, 109.8, 70.8, 21.8 (2); HRMS *m/z*: Calcd for $C_9H_{11}NO_3$: 181.0739. Found: 181.0737.

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.67; H, 6.08; N, 7.73. Found: C, 59.92; H, 6.19; N, 7.61.

Acknowledgment.- We wish to thank the Oklahoma Center for the Advancement of Science and Technology (HR01-015) for support of this research. K. M. E. wishes to thank the Chemistry Department at Oklahoma State University for a Skinner Scholarship. Funds for the 300 and 400 MHz NMR spectrometers of the Oklahoma Statewide Shared NMR Facility were provided by the NSF (BIR-9512269), the Oklahoma State Regents for Higher Education, the W. M. Keck Foundation, and Conoco, Inc. Partial support for our mass spectrometers by the NSF and the Oklahoma Center for the Advancement of Science and Technology is also appreciated.

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‡ Undergraduate Research Participant, Summer 2003.

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