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Arylmethanesulfonates are Convenient Latent Phenols in the Nucleophilic Aromatic Substitution Reaction

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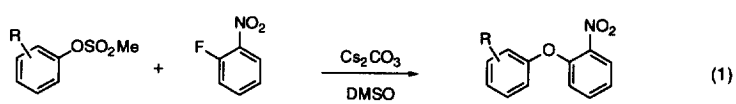
Abstract: The methanesulfonyl protecting group for a phenol is conveniently unmasked under the conditions of the S_NAr reaction with an activated aryl halide, producing diarylether products directly. The method is advantageous when the preparation of a phenol substrate requires *O*-protection, since the selection of the robust methanesulfonate as a latent phenol obviates a deprotection step prior to the S_NAr reaction.

The strategic use of protecting groups is a necessary and time consuming tactic in chemical synthesis. The development of tandem reactions that simultaneously merge protecting group chemistry with other transformations can shorten a reaction sequence and improve synthetic efficiency and convenience. The methanesulfonyl group is a useful protecting group for a phenol because of its robust behavior under a wide variety of reaction conditions.[1] The group is easily installed, withstands a wide variety of oxidative, reductive, mild nucleophilic, Brønsted and Lewis acidic conditions,[1] and is typically removed with strong base (e.g.; warm NaOH,[2a] KO*t*-Bu,[2b] LDA,[2c] Grignard[2d]). Despite its versatile properties, it is a relatively underutilized protecting group. During the course of a recent medicinal chemistry project, the syntheses of phenolic substrates for eventual nucleophilic aromatic substitution (S_NAr) reactions[3] with various activated aryl halides required the use of phenol protection. We have found that an arylmethanesulfonate is conveniently unmasked under conditions for the S_NAr reaction to liberate the required phenoxide, and that a distinct deprotection step is obviated by this protecting group choice. In this report, we describe examples of the reaction of arylmethanesulfonates **1** with a typical S_NAr electrophile **2** to produce diarylether products **3** in a single step (eq 1).



1 **2** **3** (1)

The arylmethanesulfonate **1a** (Table 1), prepared in a synthetic sequence requiring phenol protection, illustrates the utility of the transformation.[4] Warming **1a** and 1-fluoro-2-nitrobenzene **2** with cesium carbonate in DMSO at 80 °C produced the corresponding diarylether over six hours in 97% yield.[5,6] Accumulation of the phenol was not detected in this reaction, suggesting that deprotonation or fragmentation of the methanesulfonyl group is rate limiting.[7] Electron rich arylmethanesulfonates behaved similarly (**1b**, **1c**), but nitro-substituted **1d** underwent rapid deprotection to the phenol followed by rate-limiting S_NAr reaction.[8] Steric hindrance from a bulky *ortho*-substituent was well tolerated in the reaction (**1g**, **1h**). The heterocyclic derivative **1i** was rapidly consumed, resulting in both *O*-arylation and *N*-arylation. The conversion of protected L-tyrosine **1j** to the corresponding diarylether ensued without significant racemization, indicating the potential for use in the synthesis of amino acid-containing compounds.

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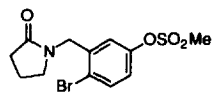
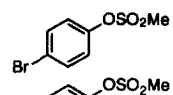
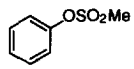
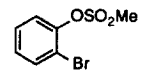
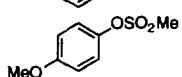
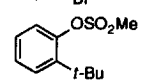
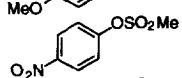
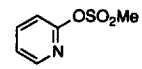
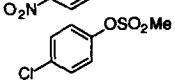
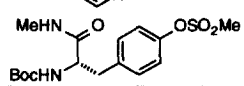
Table 1. S_NAr reaction of arylmethanesulfonates **1** with 1-fluoro-2-nitrobenzene **2** (eq 1)[a]

	substrate	reaction time (h)	yield (%)[b]		substrate	reaction time (h)	yield (%)[b]
1a		6	97	**1f**		24	94
1b		40	94	**1g**		7	95
1c		30	91	**1h**		48	94
1d		8	84	**1i**		2	93[c]
1e		20	96	**1j**		44	57[d]

[a] Reactions were carried out on 1-2 mmol scale according to the conditions in ref 5. [b] Unoptimized yield of purified products **3a-j**. [c] Obtained 7:3 ratio of *N*-aryl (67%) and *O*-aryl (26%) adducts. [d] Product **3j** is ≤5% racemized (ref 9).

In summary, the simultaneous deprotection and S_NAr reaction of methanesulfonyl-protected phenols is accomplished in a single step under mildly basic conditions. The tandem transformation affords a more efficient and convenient preparation of diarylethers in synthetic pathways that benefit from prior phenol protection. Application of this method to the preparation of biologically active molecules will be reported in due course.

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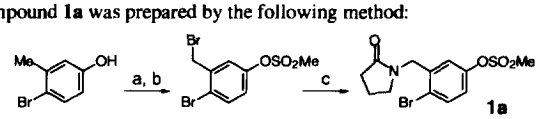
References and Notes:

1. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; Wiley: New York, 1991, p. 169.
2. (a) Looker, J. H.; Thatcher, D. N. *J. Org. Chem.* **1954**, *19*, 784. (b) MaloneyHuss, K. E.; Portoghese, P. S. *J. Org. Chem.* **1990**, *55*, 2957. (c) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem. Int. Ed.* **1998**, *37*, 2700. (d) Baldwin, J. E.; Barton, D. H. R.; Dainis, I.; Pereira, J. L. C. *J. Chem. Soc. C* **1968**, 2283.
3. (a) Paradisi, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p. 423. (b) Sawyer, J. S.; Schmittling, E. A.; Palkowitz, J. A.; Smith, III, W. J. *J. Org. Chem.* **1998**, *63*, 6338, and references cited therein.
4. Compound **1a** was prepared by the following method:



(a) Ms_2O, Et_3N, CH_2Cl_2, 0 °C. (b) NBS, AIBN, CCl_4, reflux. (c) 2-pyrrolidinone, NaH, DMF, 0 °C.

5. Representative procedure: To a solution of **1a** (1.02 mmol) and **2** (1.53 mmol, 1.5 equiv) in 2.0 mL of anhydrous DMSO under an atmosphere of argon was added Cs_2CO_3, (2.04 mmol, 2.0 equiv, Acros 99.5%). The solution was stirred at 80 °C for 6 hours, cooled, then partitioned between EtOAc and water. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by flash chromatography (2 x 8 cm silica; 50% CH_2Cl_2/hexane-5% MeOH/CH_2Cl_2) yielded 385 mg of diarylether **3a** as a yellow solid (97% yield).
6. (a) Although the use of 1.1 equiv. of **2** is sufficient for complete conversion, we have found lower yields in some cases (e.g. **1c**→**3c**, 77%; **1d**→**3d**, 72%). (b) All products gave ^{1}H NMR and HRMS spectral data consistent with the assigned structures.
7. In the absence of Cs_2CO_3, no conversion of **1a** was detected. Despite the use of dry solvent and reagents, the possible role of CsOH (generated by liberation of CO_2 from $CsHCO_3$) should not be excluded.
8. In a competition experiment (1 equiv each **1c** & **1d**, 3 equiv **2**, 4 equiv Cs_2CO_3, DMSO, 80 °C) HPLC analysis indicated complete conversion of **1d** to 4-nitrophenol within 10 minutes, then gradual conversion to diarylether **3d** over 7 hours. Compound **1c** gave diarylether **3c** at a slower rate without detectable accumulation of 4-methoxyphenol.
9. The diarylether **3j** was subjected to Boc-deprotection (HCl, EtOAc, 0 °C), conversion to the (+) and (-)-10-camphorsulfonamides (10-comphorsulfonyl chloride, *i*-Pr_2EtN, DMF, 0 °C), and ^{1}H NMR analysis to confirm ≥95% diastereomer purity.