

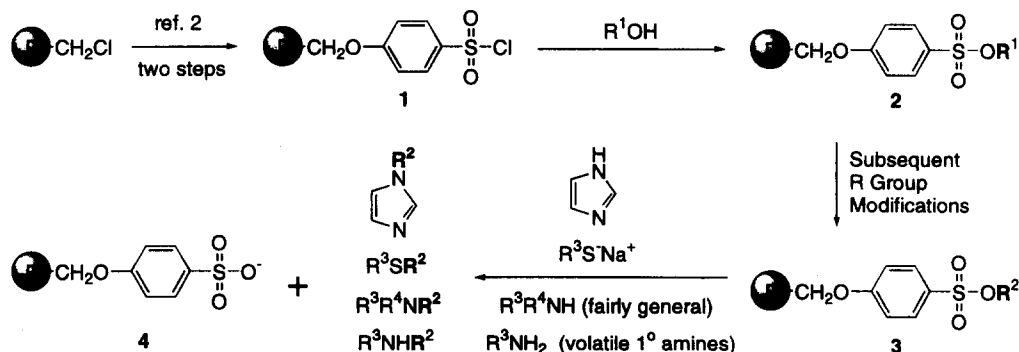
## Arylsulfonate Esters in Solid Phase Organic Synthesis. I. Cleavage with Amines, Thiolate, and Imidazole

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**Abstract:** The arylsulfonate ester functionality connecting an alkyl chain to a polystyrene resin is cleaved with neat volatile primary or secondary amines to give secondary or tertiary amines, respectively, in high yields and purity. Non-volatile secondary amines, thiols, and imidazole also cleave the alkyl chain efficiently to afford the expected products which can be readily purified by an ion-exchange resin work-up method.  
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Solid phase organic synthesis (SPOS) has had a dramatic impact on many areas of chemistry. SPOS is a powerful tool to prepare libraries of compounds and then evaluate the effects of structural diversity upon biological activity, particularly in combination with high-throughput screening.<sup>1</sup> We have made use of novel arylsulfonyl resin **1**, recently developed by our colleagues,<sup>2</sup> in reactions with alcohols to prepare arylsulfonate ester resins **2** (Scheme 1).<sup>3</sup> After linkage of the alcohol to the resin, diversification by functional group interconversion of the resin-bound substrate gave **3**, as demonstrated in a second companion paper. Finally, under defined reaction conditions, library members were released from the polymer upon treatment with various nucleophiles (with formation of sulfonate resin **4**). Unlike other methods in which alcohols are immobilized onto a polymer support, cleavage of **3** transforms the original hydroxyl group into various useful functionalities offering the advantage that an element of diversity is added during the cleavage step.<sup>4</sup> This first paper describes cleavage of **3** with amines, thiolate, and imidazole to yield products of N-substitution and alkylation.<sup>5</sup>

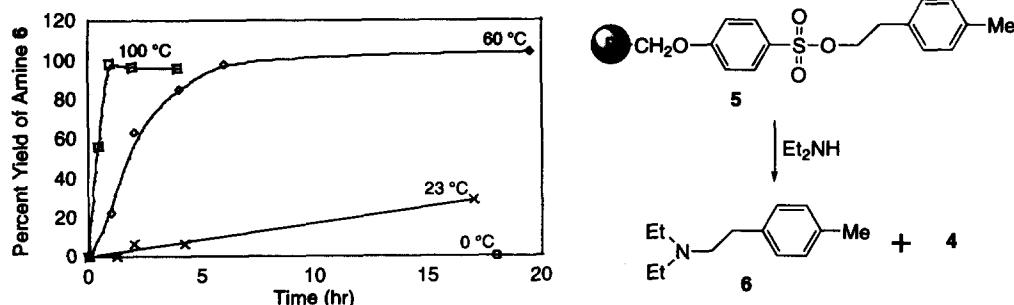


**Scheme 1.** The preparation and use of arylsulfonate ester SPOS resins (R group from resin in bold).

Presently there are only a few methods for the preparation of amine libraries in which the amine functionality is formed during cleavage. Acrylate ester resins undergo Michael-type additions with secondary amines, which can be followed by quaternization and a reverse Michael reaction to liberate tertiary amines.<sup>6</sup> Alkylation of a Merrifield polystyrene resin, quaternization, and solvolytic cleavage is another approach.<sup>7-10</sup>

Arylsulfonate ester resins **2** are readily prepared by treatment of **1** with the appropriate alcohol (3-5 mol-equiv.) and Et<sub>3</sub>N (3-5 mol-equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL/mmol, rt, 24-48 hr).<sup>11</sup> Resin **1** was first used to immobilize guanidyl residues in the synthesis of arginine-containing peptide derivatives, and is conveniently prepared in two chemical steps from the standard Merrifield polystyrene resin.<sup>2,12-14</sup>

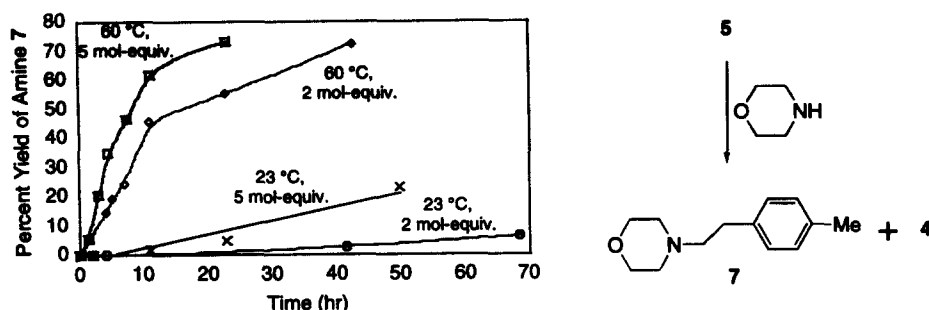
To provide a model system for study, 4-MePhCH<sub>2</sub>CH<sub>2</sub>OH was coupled to **1** producing arylsulfonate ester resin **5**, which was then treated with a variety of nucleophiles (Table 1). Reaction of **5** with Et<sub>2</sub>NH (neat) afforded **6** unaccompanied by other observable products in >95% yield after 2 hrs at 100 °C or 6 hrs at 60 °C (Figure 1).<sup>12</sup> Volatile primary amines such as PrNH<sub>2</sub> (neat) gave *secondary* amine products upon cleavage (entries 1 and 2, Table 1).



**Figure 1.** Analysis of the cleavage of sulfonate ester resin **5** with Et<sub>2</sub>NH at 0 °C, 23 °C, 60 °C, and 100 °C as a function of time by reversed-phase HPLC analysis.<sup>12</sup> After the requisite time, the solution was filtered and then assayed directly.

Cleavage with secondary amines in various solvents (MeCN, DMF, THF) was examined, and several of these work well (e.g. entries 3 and 4). We have used MeCN extensively because of its ease of removal after cleavage. Reaction of **5** with morpholine in MeCN gives amine **7** with a ca. 75-80% chemical yield using either 2 or 5 mol-equiv. of morpholine at 60 °C after 42 and 24 hrs, respectively (Figure 2). In reactions involving non-volatile secondary amines, the mixtures after cleavage were treated with phthalic anhydride (5 mol-equiv.) for 15 min.<sup>15</sup> Excess secondary amine formed the corresponding 2-amidobenzoic acids which adhered to Amberlite IRA-400 basic ion exchange resin (OH form) in CH<sub>2</sub>Cl<sub>2</sub> (1 hr stirring). The corresponding tertiary amine products were then obtained by filtration and removal of solvent (see Table 1). In principle, cleavage with non-volatile primary amines (e.g. 5 mol-equiv.) could give secondary amine targets by use of a recently-described resin-supported method to remove primary from secondary amines.<sup>9b</sup>

A variety of amines, thiols, and imidazole reacted with resin **5** to give the expected products in high yields and purity, except for a sterically hindered amine (entry 8) and anilines (entry 12 and 13). In reaction with imidazole (entry 15), excess reagent was removed readily with ion exchange resin.



**Figure 2.** Analysis of the cleavage of resin **5** with 2 or 5 mol-equiv. of morpholine in MeCN at either 23 °C or 60 °C as a function of time as determined by reversed-phase HPLC analysis.<sup>12</sup> After the requisite time, the solution was filtered and the beads washed with sat.  $\text{NH}_4\text{MeOH}$  and  $\text{CH}_2\text{Cl}_2$ .

Resin-bound arylsulfonate esters can be efficiently cleaved with amines (neat or with solvent), thiols, and imidazole to produce the expected products. In addition, a variety of other nucleophiles may potentially be used in this reaction. When combined with the reaction compatibility described in the subsequent paper, use of arylsulfonate ester resin allows for the preparation of diverse compound libraries via SPOS.

**Table 1.** Reaction of resin **5** with various nucleophiles at 60 °C for 18 hr.<sup>a</sup>

Entry	Reagent (# mol-equiv.)	Solvent	Product	Yield	Purity
1	$\text{PrNH}_2$ (neat, 180 equiv.)	neat	$\text{PrNHCH}_2\text{CH}_2(4\text{-Me})\text{Ph}$	68%	93%
2	$i\text{PrNH}_2$ (neat, 175 equiv.)	neat	$i\text{PrNHCH}_2\text{CH}_2(4\text{-Me})\text{Ph}$	69	94
3 <sup>b</sup>	$\text{MeNHCH}_2\text{CH}_2\text{Ph}$ (2)	MeCN	$\text{MeN}(\text{CH}_2\text{CH}_2\text{Ph})\text{CH}_2\text{CH}_2(4\text{-Me})\text{Ph}$	63	80
4	$\text{MeNHCH}_2\text{CH}_2\text{Ph}$ (2)	DMF	$\text{MeN}(\text{CH}_2\text{CH}_2\text{Ph})\text{CH}_2\text{CH}_2(4\text{-Me})\text{Ph}$	59	67
5	$\text{MeNHCH}_2\text{CH}_2\text{Ph}$ (2)	THF	$\text{MeN}(\text{CH}_2\text{CH}_2\text{Ph})\text{CH}_2\text{CH}_2(4\text{-Me})\text{Ph}$	<10	--
6	Piperidine (5)	MeCN	$N\text{-}[(4\text{-Me})\text{PhCH}_2\text{CH}_2]\text{piperidine}$	68	84
7	2-Methylpiperidine (5)	MeCN	$N\text{-}[(4\text{-Me})\text{PhCH}_2\text{CH}_2]\text{-2-Mepiperidine}$	46	85
8	cis-2,6-Me <sub>2</sub> piperidine (5)	MeCN	$N\text{-}[(4\text{-Me})\text{PhCH}_2\text{CH}_2]\text{-2,6-Me}_2\text{piperidine}$	24	56
9	(4-Ph)piperidine (5)	MeCN	$N\text{-}[(4\text{-Me})\text{PhCH}_2\text{CH}_2]\text{-4-Phpiperidine}$	73	>95
10	(1-Ph)piperazine (5)	MeCN	$N\text{-}[(4\text{-Me})\text{PhCH}_2\text{CH}_2]\text{-N'-Phpiperazine}$	>75	91
11	1-(4-NO <sub>2</sub> Ph)piperazine (5)	MeCN	$N\text{-}[(4\text{-Me})\text{PhCH}_2\text{CH}_2]\text{-N'-(4-NO}_2\text{Ph)piperazine}$	95	92
12	Aniline (5)	MeCN	$\text{PhNHCH}_2\text{CH}_2(4\text{-Me})\text{Ph}$	<10	--
13	<i>N</i> -Methylanisidine (5)	MeCN	$(4\text{-MeO})\text{PhN}(\text{Me})\text{CH}_2\text{CH}_2(4\text{-Me})\text{Ph}$	<10	--
14	NaSEt (5)	MeCN	$4\text{-MePhCH}_2\text{CH}_2\text{SEt}$	73	84
15 <sup>c</sup>	Imidazole (10)	MeCN	$N\text{-}[(4\text{-Me})\text{PhCH}_2\text{CH}_2]\text{imidazole}$	83	95

a. Conditions: 200 mg **5** in 2 mL of solvent, washing with methylene chloride (2X) at end of reaction. Yields were of weighed products after removal of solvent. All products shown were analyzed by 300-MHz H-1 NMR, MS, and TLC. Purity values were obtained by reversed-phase HPLC (C-18) in MeCN/water (220-nm, photodiode array).

b. All secondary amine examples and NaSEt were treated with phthalic anhydride as described in the test.

c. Reaction also works in toluene, DMF, and THF. MeCN example conducted at 100 deg C in a sealed tube for 20 hrs, followed by treatment twice with Amberlite IRA-400 resin which removed all unreacted imidazole.

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## References and Notes

# JKR was a Johnson & Johnson Corporate Office of Science and Technology Graduate Student Intern while also a Ph.D. student with Prof. Murray Goodman at the University of California, San Diego.

1. (a) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1997**, *53*, 5643-5678. (b) Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527-4554. (c) Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288-2337. (d) Früchtel, J. S.; Jung, G. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17-42. (e) Fenniri, H. *Curr. Med. Chem.* **1996**, *3*, 343-378. (f) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555-600. (g) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385-1401.
2. Zhong, H. M.; Greco, M. N.; Maryanoff, B. E. *J. Org. Chem.*, in press.
3. For some other examples involving coupling of alcohols to polymer supports, see: (a) Randolph, J. T.; McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5712-5719. (b) Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333-9336.
4. Roush et al. formed an alkyl iodide upon cleavage of a alkylsulfonate resin with NaI in 2-butanone in good yield: Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc.* **1996**, *118*, 9998-9999. Another example of a "diversification-release" strategy in which displacement of a sulfur-based linker is accompanied by adding an element of diversity can be found in Gayo, L. M.; Suto, M. *J. Tetrahedron Lett.* **1997**, *38*, 211-214.
5. Baxter, E. W.; Rueter, J. K.; Nortey, S. O.; Reitz, A. B. *Tetrahedron Lett.*, subsequent paper in this issue.
6. (a) Brown, A. R.; Rees, D. C.; Randovic, Z.; Morphy, J. R. *J. Am. Chem. Soc.* **1997**, *119*, 3288-3295. (b) Morphy, J. R.; Rankovic, Z.; Rees, D. C. *Tetrahedron Lett.* **1996**, *37*, 3209-2312.
7. Conti, P.; Demont, D.; Cals, J.; Ottenheijm, H. C. J.; Leysen, D. *Tetrahedron Lett.* **1997**, *38*, 2915-2918.
8. Amine libraries can be prepared by manipulations of substrates connected to a polymer support, followed by cleavage under standard conditions. For example, see: Green, J. J. *J. Org. Chem.* **1995**, *60*, 4287-4290.
9. Amine libraries can also be prepared by conventional solution chemistry followed by removal of excess reagents by treatment with scavenger resins: (a) Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997**, *119*, 4874-4881. (b) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193-7196.
10. See also: Ho, C. Y.; Kukla, M. J. *Tetrahedron Lett.* **1997**, *38*, 2799-2802.
11. Procedure for washing the resin:  $\text{CH}_2\text{Cl}_2$  (2X), MeOH (2X),  $\text{CH}_2\text{Cl}_2$  (2X).
12. Loading of  $\text{SO}_2\text{Cl}$  functionality was determined on a Bruker AM-360 by magic angle spinning  $^{13}\text{C}$  (90.6 MHz) NMR comparison of the two carbons on the phenylsulfonyl ring ortho to the oxygen-bearing carbon to  $\text{CH}_3\text{CN}$  as a calibrated standard. Loading can also be estimated by either increase of resin weight, elemental analysis, or the Fmoc-echo procedure.<sup>2</sup> Typical preparations of **1** (50 g scale) have resulted in 1.2 to 1.1 mmol/gm and 1.35 to 1.17 mmol/gm conversion of  $\text{CH}_2\text{Cl}$  to  $\text{CH}_2\text{OPh}(4\text{-SO}_2\text{Cl})$  functionality. Formation of the arylsulfonate ester resin **2** was essentially quantitative: no **1** or **4** were observed in typical experiments. Yields after cleavage were determined by weighing the product or by duplicate calibrated HPLC comparison to independently-prepared products (for **6** and **7**), providing additional support for the level of  $\text{SO}_2\text{Cl}$  incorporation in **1** that is determined by the  $^{13}\text{C}$  NMR method.
13. For a different 4-alkoxyphenyl sulfonyl resin attachment of a guanidine, see: Bonnat, M.; Bradley, M.; Kilburn, J. D. *Tetrahedron Lett.* **1996**, *37*, 5409-5412.
14. Sulfonyl chloride resins have been prepared previously (Roush, W. R.; Feitler, D.; Rebek, J. *Tetrahedron Lett.* **1974**, *15*, 1391-1392). The advantage of resin **1** is that the  $\text{SO}_2\text{Cl}$  functionality is controlled in a chemically-defined manner because of the amount of  $\text{CH}_2\text{Cl}$  functionality in the starting Merrifield resin.
15. Parlow, J. J.; Naing, W.; South, M. S.; Flynn, D. L. *Tetrahedron Lett.* **1997**, *38*, 7959-7962. Although Parlow et al. use tetrafluorophthalic anhydride in their work, we found that phthalic anhydride works just as well for removal of dialkyl secondary amines from tertiary amines. Excess phthalic anhydride is hydrolyzed by the basic ion exchange resin, and the *o*-phthalic acid that is formed adheres to the resin.