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

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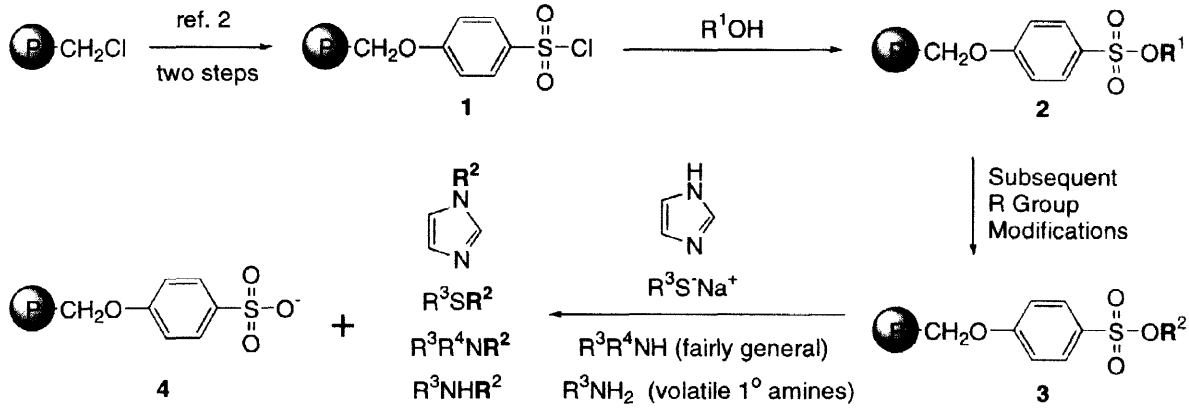
Abstract: The arylsulfonate ester functionality connecting an alkyl chain to a polystyrene resin is cleaved with neat volatile primary or secondary amines to give secondary or tertiary amines, respectively, in high yields and purity. Non-volatile secondary amines, thiols, and imidazole also cleave the alkyl chain efficiently to afford the expected products which can be readily purified by an ion-exchange resin work-up method.

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.[1] We have made use of novel arylsulfonyl resin **1**, recently developed by our colleagues,[2] in reactions with alcohols to prepare arylsulfonate ester resins **2** (Scheme 1).[3] 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.[4] This first paper describes cleavage of **3** with amines, thiolate, and imidazole to yield products of N-substitution and alkylation.[5]



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

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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.[6] Alkylation of a Merrifield polystyrene resin, quaternization, and solvolytic cleavage is another approach.[7-10]

Arylsulfonate ester resins **2** are readily prepared by treatment of **1** with the appropriate alcohol (3-5 mol-equiv.) and Et_3N (3-5 mol-equiv.) in CH_2Cl_2 (10 mL/mmol, rt, 24-48 hr).[11] 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.[2,12-14]

To provide a model system for study, 4-$MePhCH_2CH_2OH$ 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_2NH (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).[12] Volatile primary amines such as $PrNH_2$ (neat) gave *secondary* amine products upon cleavage (entries 1 and 2, Table 1).

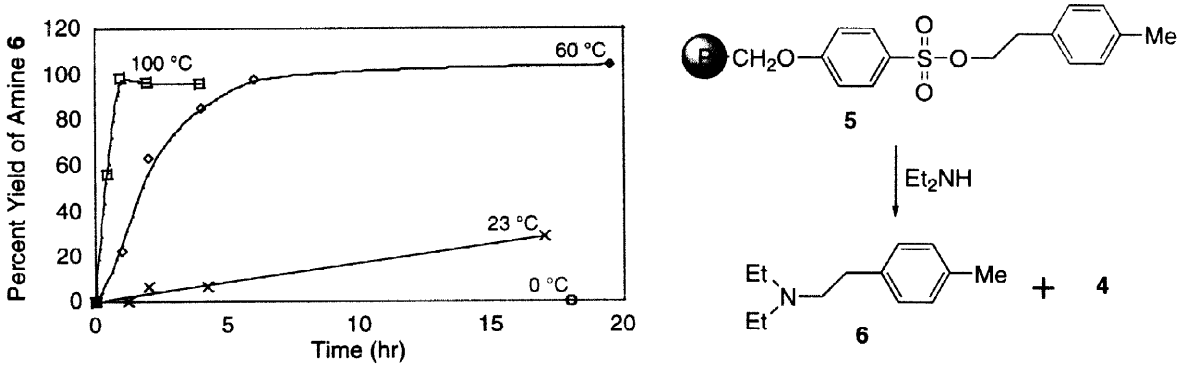

Figure 1. Analysis of the cleavage of sulfonate ester resin **5** with Et_2NH at 0 °C, 23 °C, 60 °C, and 100 °C as a function of time by reversed-phase HPLC analysis.[12] After the requisite time, the solution was filtered and then assayed directly.

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.[15] Excess secondary amine formed the corresponding 2-amidobenzoic acids which adhered to Amberlite IRA-400 basic ion exchange resin (OH^- form) in CH_2Cl_2 (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-volative 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.[9b]

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.

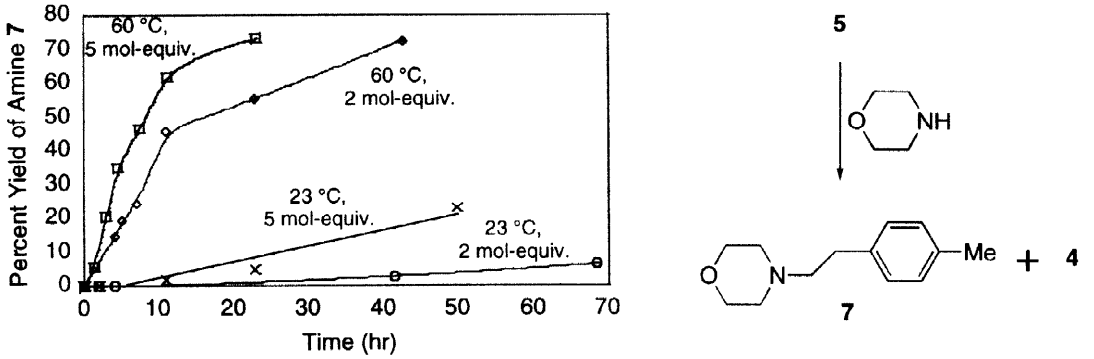

Figure 2. Analysis of the cleavage of resin **5** with 2 or 5 mol-equiv. of morpholine in MeCN at either 23 ° C or 60 ° C as a function of time as determined by reversed-phase HPLC analysis.[12] After the requisite time, the solution was filtered and the beads washed with sat. NH_3/MeOH and CH_2Cl_2.

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.[a]

Entry	Reagent (# mol-equiv.)	Solvent	Product	Yield	Purity
1	$PrNH_2$ (neat, 180 equiv.)	neat	$PrNHCH_2CH_2$(4-Me)Ph	68%	93%
2	*i*$PrNH_2$ (neat, 175 equiv.)	neat	*i*$PrNHCH_2CH_2$(4-Me)Ph	69	94
3[b]	$MeNHCH_2CH_2Ph$ (2)	MeCN	$MeN(CH_2CH_2Ph)CH_2CH_2$(4-Me)Ph	63	80
4	$MeNHCH_2CH_2Ph$ (2)	DMF	$MeN(CH_2CH_2Ph)CH_2CH_2$(4-Me)Ph	59	67
5	$MeNHCH_2CH_2Ph$ (2)	THF	$MeN(CH_2CH_2Ph)CH_2CH_2$(4-Me)Ph	<10	--
6	Piperidine (5)	MeCN	*N*-[(4-Me)$PhCH_2CH_2$]piperidine	68	84
7	2-Methylpiperidine (5)	MeCN	*N*-[(4-Me)$PhCH_2CH_2$]-2-Mepiperidine	46	85
8	cis-2,6-Me_2piperidine (5)	MeCN	*N*-[(4-Me)$PhCH_2CH_2$]-2,6-Me_2piperidine	24	56
9	(4-Ph)piperidine (5)	MeCN	*N*-[(4-Me)$PhCH_2CH_2$]-4-Phpiperidine	73	>95
10	(1-Ph)piperazine (5)	MeCN	*N*-[(4-Me)$PhCH_2CH_2$]-*N'*-Phpiperazine	>75	91
11	1-(4-NO_2Ph)piperazine (5)	MeCN	*N*-[(4-Me)$PhCH_2CH_2$]-*N'*-(4-NO_2Ph)piperazine	95	92
12	Aniline (5)	MeCN	$PhNHCH_2CH_2$(4-Me)Ph	<10	--
13	*N*-Methylanisidine (5)	MeCN	(4-MeO)$PhN(Me)CH_2CH_2$(4-Me)Ph	<10	--
14	NaSEt (5)	MeCN	4-$MePhCH_2CH_2SEt$	73	84
15[c]	Imidazole (10)	MeCN	*N*-[(4-Me)$PhCH_2CH_2$]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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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: CH_2Cl_2 (2X), MeOH (2X), CH_2Cl_2 (2X).
12. Loading of SO_2Cl functionality was determined on a Bruker AM-360 by magic angle spinning ^{13}C (90.6 MHz) NMR comparison of the two carbons on the phenylsulfonyl ring ortho to the oxygen-bearing carbon to CH_3CN as a calibrated standard. Loading can also be estimated by either increase of resin weight, elemental analysis, or the Fmoc-echo procedure.[2] 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 CH_2Cl to $CH_2OPh(4\text{-}SO_2Cl)$ 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 SO_2Cl incorporation in **1** that is determined by the ^{13}C NMR method.
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