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Arylsulfonate Esters in Solid Phase Organic Synthesis. II. Compatibility with Commonly-Used Reaction Conditions

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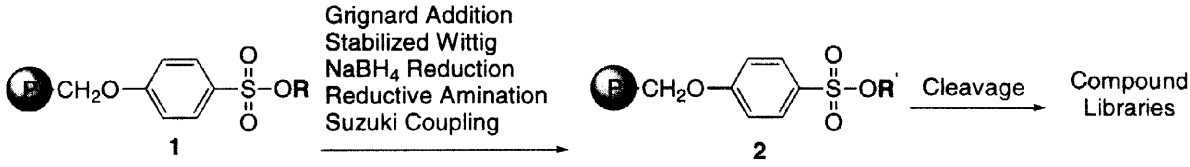
Abstract: The arylsulfonate ester functionality connecting an alkyl chain to a polystyrene resin is compatible with Grignard additions, stabilized Wittig, sodium borohydride reduction, reductive aminations, acylations and addition of various electrophiles, and Suzuki coupling. Cleavage of the resin-bound substrate with amines and other nucleophiles can provide diverse compound libraries.

As described in the preceding paper, arylsulfonate ester resins **1** are useful because alcohols can be immobilized in such a way that cleavage with a variety of nucleophiles such as primary and secondary amines becomes a point at which molecular diversity can be added in solid phase organic synthesis (SPOS).[1] In this paper we show that this arylsulfonate ester functionality is compatible with a variety of commonly-used reaction conditions. When this reaction compatibility is combined with the diversity offered during cleavage, then it is apparent that this approach provides a ready entry to the preparation of novel compound libraries (Scheme 1).



Scheme 1. Reaction compatibility of resin-bound arylsulfonate esters for SPOS.

In order to investigate the compatibility of some typical reactions used in organic synthesis with our particular sulfonate ester, we prepared model resins **3**, **4**, and **6**. Toward this end, resins **3** - **5** were synthesized as described previously[1] from the requisite 4-substituted phenethyl alcohols[2] and a new sulfonyl chloride resin.[3] Nitrophenyl resin **5** was reduced to corresponding amine resin **6**.[4,5] The aldehyde, halide, and amino substituents of these model resins were then transformed by a variety of organic reactions (Scheme 1) followed by cleavage of the substrate from the resin in neat Et_2NH (60 °C, 18 hr),[1] and many of these experiments are shown in Table 1. Generally, there is a wide reaction tolerance exhibited by this sulfonate ester functionality, and the products obtained after Et_2NH cleavage are relatively pure (>90%) after removal of the excess Et_2NH.

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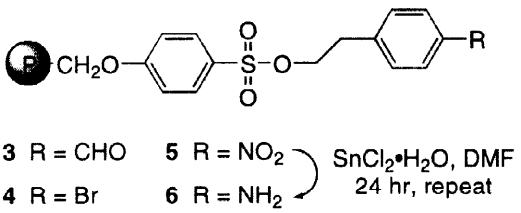


Model resins **3**, **4**, and **6** offered several advantages for us. The 1,4-disubstituted rings that are included as part of the chain are easy to identify, and phenethyl sulfonate substitution tests the base lability for β-elimination to give styrene-derived by-products which were not seen.

Reactions of Aldehyde Resin 3. Reaction with PhMgBr and MeMgBr (10 mol-equiv.) at 0°C worked well to give the expected (diethylamino)ethyl aryl products after Et_2NH cleavage (entries 1 and 2). Although the chemical yields were moderate (40-50%), the products were obtained >90% pure. Conducting this reaction at 23°C resulted in noticeable cleavage of the phenethyl group from the resin. Reduction of the aldehyde group of **3** with sodium borohydride yielded the primary alcohol (entry 3). Stabilized Wittig reaction using recently-described conditions[8] gave the *E*-olefin (>80% purity, entry 4), and products of either amidolysis of the methyl ester or Michael-type addition to the α,β-unsaturated double bond were not detected after Et_2NH cleavage. Alternative reaction conditions employing $Ph_3P{=}CHCO_2Me$ (10 mol-equiv.) in $ClCH_2CH_2Cl$ at reflux did result in some cleavage from the resin. Reductive amination of **3** with a benzyl amine and several anilines (entries 5 - 8) was successful using $NaBH(OAc)_3$ as the reducing agent,[9] and these conditions were superior to the use of $NaCNBH_3$ in trimethyl orthoformate[10] or 1% HOAc-DMF.[11]

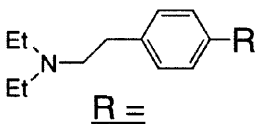
Suzuki Coupling of Resin 4. Coupling of bromide resin **4** with 4-$MePhB(OH)_2$ under conditions reported[12] for a solid-phase Suzuki reaction gave the expected product after Et_2NH cleavage (entry 9). While the yield of this transformation was low (23%), the expected biphenyl product formed cleanly (>90% purity) after the Et_2NH treatment.

Reactions of Amine Resin 6. The amino group of resin **6** was reacted with acid chlorides (entries 10 and 11), a sulfonyl choride (entry 12), and two isocyanates (entries 13 and 14). After cleavage of the modified resins that formed with Et_2NH, the expected products were observed in good yield and high purity. Reductive amination reactions on **6** resulted in mixtures of mono- and bis-alkylation which were difficult to control. Since the sulfonate ester functionality is itself electrophilic in nature, it is not surprising that it is stable to a variety of electrophilic reagents and reaction conditions.

The distinguishing feature of the reactions shown in this paper is the relatively high level of purity that is obtained after the cleavage step with Et_2NH. We have shown that the sulfonate ester moiety which attaches the substrate to a polystyrene resin is sufficiently stable so that many common reactions can be conducted without difficulty. When combined with the range of nucleophiles which cleave and add diversity at the last step,[1] this method has the potential to produce compound libraries via SPOS that will be useful for high-throughput screening or directed synthesis efforts.

Among the interesting future ramifications of this work are intramolecular cyclizations during cleavage providing a variety of saturated and unsaturated heterocycles.

Table 1. Reactions of resin-bound sulfonate ester substrates followed by cleavage with Et_2NH.[6]

Entry	Resin	Reaction Conditions	Product after Et_2NH Cleavage  R =	Yield[7]	NMR Purity[7]
1	**3**	PhMgBr (5 eq), THF, 0°C, 4.5 hr	-CH(OH)Ph	50%	90%
2	**3**	MeMgBr (5 eq), THF, 0°C, 4.5 hr	-CH(OH)Me	42	90
3	**3**	$NaBH_4$ (10 eq), THF:MeOH (1:1), 30 min, repeat 2X	$-CH_2OH$	66	90
4	**3**	$Ph_3P{=}CHCO_2Me$ (5 eq), THF, 70°C, 3 hr	-*E*-$CH{=}CHCO_2Me$	60	80
5	**3**	(4-MeO)$PhCH_2NH_2$ (7 eq), $NaBH(OAc)_3$ (7 eq), HOAc, CH_2Cl_2, 24 hr	$-CH_2NHCH_2$[(4-MeO)Ph]	>95	85
6	**3**	" with (4-MeO)$PhNH_2$ (7 eq)	$-CH_2NH$[(4-MeO)Ph]	53	95
7	**3**	" with $PhNH_2$ (7 eq)	$-CH_2NHPh$	53	95
8	**3**	" with (4-F)$PhNH_2$ (7 eq)	$-CH_2NH$[(4-F)Ph]	54	95
9	**4**	4-MePh$B(OH)_2$ (2.5 eq), $Pd(PPh_3)_4$, 2N aq. Na_2CO_3, tol, EtOH, 90°C, 20 hr	-(4-Me)Ph	23	90
10	**6**	4-(MeO)PhCOCl (5 eq), iPr_2EtN (5 eq), CH_2Cl_2, 24 hr	-NHC(O)[(4-MeO)Ph]	70	90
11	**6**	" with 4-(NO_2)PhCOCl (5 eq)	-NHC(O)[(4-NO_2)Ph]	69	70
12	**6**	4-(MeO)PhSO_2Cl, (2 eq), iPr_2EtN (2 eq), CH_2Cl_2, 24 hr	$-NHSO_2$[(4-MeO)Ph]	53	85
13	**6**	$PhCH_2NCO$ (5 eq), CH_2Cl_2, 24 hr	$-NHC(O)NHCH_2Ph$	61	95
14	**6**	4-(MeO)PhNCO (5 eq), CH_2Cl_2, 24 hr	-NHC(O)NH[(4-MeO)Ph]	45	90

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References and Notes

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2. 4-Bromophenethyl alcohol and 4-nitrophenethyl alcohol were commercially available and used as purchased. Alternatively, 4-(CHO)PhCH$_2$CH$_2$OH was prepared by the method described in: Ackerley, N.; Brewster, A. G.; Brown, G. R.; Clarke, D. S.; Foubister, A. J.; Griffin, S. J.; Hudson, J. A.; Smithers, M. J.; Whittamore, P. R. O. *J. Med. Chem.* **1995**, *38*, 1608-1628.
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5. Resins **3** - **6** and many of the resins prepared as described in Table 1, prior to Et$_2$NH cleavage, were examined by magic angle spinning ^{13}C (90.6 MHz) NMR. Analysis of the two carbons on the phenylsulfonyl ring ortho to the oxygen-bearing carbon was used as diagnostic when determining the extent of loading.[1]
6. Products were characterized by 300-MHz ^1H NMR, MS, and TLC.
7. Yields were determined based on comparison of the loading[1] of the sulfonate ester functionality on the resins and the weight of the obtained products. Product purities were determined by 300-MHz ^1H NMR evaluation (all cases), TLC (all cases), and reversed-phase C-18 HPLC in MeCN/H$_2$O at 220 nM with a photodiode array detector (for entries 10-14: 10, 86%; 11, 86%; 12, 74%; 13, 79%; 14, 68%). The major impurity observed by NMR was the carbonate salt of diethylamine, which could be suppressed by performing the reaction under inert atmosphere and working it up afterword in a timely manner.
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