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Exploiting Differences in Solution vs Solid-Supported Reactivity for the Synthesis of Sulfonic Acid Derivatives

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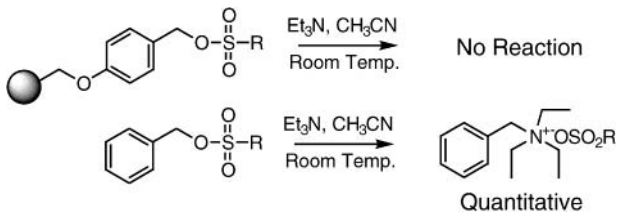
ABSTRACT



We describe a method herein for the protection of aryl and alkyl sulfonates during synthesis which employs commercially available Wang or MBOH resin, both of which terminate as benzyl alcohols, as both a protecting group and "traceless" linker. Given the known instability of benzylic sulfonate esters to nucleophilic displacement in solution, this linkage is surprisingly stable: no loss of either aryl or alkyl sulfonates is observed when the resin is exposed to a wide variety of organic bases and solvents at room temperature. Further elaboration of the resin-bound sulfonates via Suzuki coupling is also described.

The primary use of solid supports in organic synthesis thus far (including combinatorial chemistry) has been as a means of simplifying purification.[1] However, immobilization of a substrate on (or in) a polymer matrix frequently results in an alteration of that substrate's reactivity,[2] due to pseudo-dilution effects,[3] site−site interactions,[4] size selectivity,[5] and differences in polarity between the solvent and polymer matrix.[6] As part of an ongoing program in the development of enabling methodologies for the solid-phase synthesis of complex organic structures,[7] we sought a simple and robust procedure for the immobilization and protection of aryl and alkyl sulfonates. During the course of this work, we observed a striking difference in reactivity between solvated and solid-supported benzylic sulfonates. We will also discuss preliminary experiments designed to determine the utility of such supported compounds in multistep organic synthesis.

Sulfonic acid groups are present in an enormous number of commercial compounds, ranging from detergents to pharmaceuticals. Numerous strategies have been reported for the protection of this functionality during solution-phase synthesis, including neopentyl,[8] isobutyl,[9] and isopropyl[10] groups. When difficulties with a first-generation attempt at preparing a resin-immobilized sulfonate[11] caused us to be concerned that our resin-loading procedure might be at fault, rather than subsequent cleavage of the linker, we decided to examine the reaction of aryl and alkyl sulfonyl chlorides with commercially available Wang and MBOH resins.

(1) For a reivew and lead references, see: Barany, G.; Kempe, M. In *A Practical Guide to Combinatorial Chemistry*; Czarnik, A. W., DeWitt, S. H., Eds.; American Chemical Society: Washington, DC, 1997; pp 51−97.
(2) Reviewed in the following: Hodge, P. *Chem. Soc. Rev.* **1997**, *26*, 417−424.
(3) Mazur, S.; Jayalekshmy, P. *J. Am. Chem. Soc.* **1979**, *101*, 677−683.
(4) Hodge, P.; Waterhouse, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2319−2323.
(5) Grubbs, R. H.; Kroll, L. C. *J. Am. Chem. Soc.* **1971**, *93*, 3062−3063.
(6) Takagi, T. *J. Appl. Polym. Sci.* **1975**, *19*, 1649. Yaroslavsky, C.; Patchornik, A. Katchalski, E. *Tetrahedron Lett.* **1970**, 3629−3632.
(7) (a) Hari, A.; Miller, B. L. *Tetrahedron Lett.* **1999**, *40*, 245−248. (b) Hari, A.; Miller, B. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2777−2779.
(8) (a) Roberts, J. C.; Gao, H.; Gopalsamy, A.; Kongsjahju, A.; Patch, R. J. *Tetrahedron Lett.* **1997**, *38*, 355−358. (b). Roberts, J. C.; Patch, R. J. *Chem. Abstr.* **1996**, *125*, 113929.
(9) Xie, M.; Widlanski, T. S. *Tetrahedron Lett.* **1996**, *37*, 4443−4446.
(10) (a) Musicki, B.; Widlanski, T. S. *J. Org. Chem.* **1990**, *55*, 4231−4233. (b) Musicki, B.; Widlanski, T. S. *Tetrahedron Lett.* **1991**, *32*, 1267−1270.

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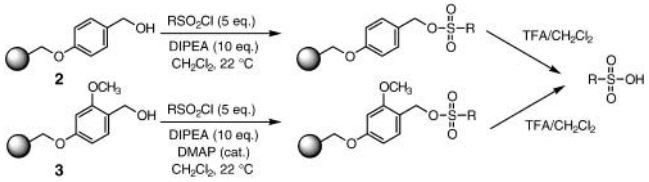
Formation of each sulfonate as the resin−benzyl ester was achieved through reaction of the corresponding sulfonyl chloride[12] with commercial Wang resin[13] (**2**) in the presence of diisopropylethylamine (DIPEA) (Scheme 1), or on

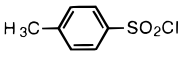
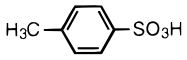
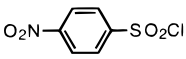
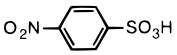
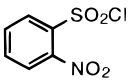
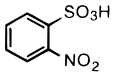
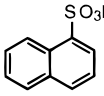
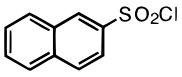
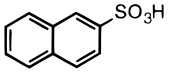
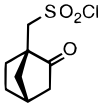
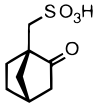
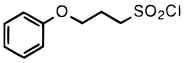
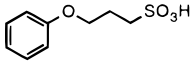
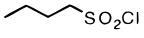
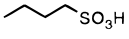
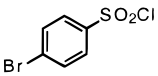
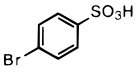
Scheme 1



Argogel−MBOH resin[14] (**3**) in the presence of DIPEA and (dimethylamino)pyridine. After a thorough washing of the resin with a range of solvents (methylene chloride, acetonitrile, and methanol) to remove unreacted sulfonyl chloride, the sulfonic acid was cleaved from the resin using trifluoroacetic acid in dichloromethane.[15] We were gratified to observe that a wide variety of aryl and alkyl sulfonates could be obtained in this manner (Table 1).[16]

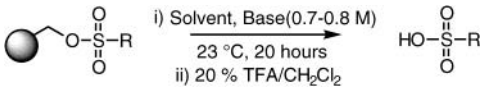
Treatment of either the butanesulfonate-functionalized or *p*-toluenesulfonate-functionalized resin with a solution of triethylamine (0.72 M), DBU (0.67 M), pyridine (1.24 M), or tetramethylguanidine (TMG) (0.8 M) in acetonitrile, methanol, methylene chloride, or DMF at room temperature caused little or no loss of compound from the resin, as judged by examining HPLC traces of the eluent and verified by subsequent cleavage and isolation of the product (Table 2).

Table 1. Recovery of Sulfonic Acids Following Immobilization on Resin

Entry	Sulfonyl Halide	Product Sulfonic Acid	Yield (%)
1			92[a], 95[b]
2			74[a]
3			78[a]
4			85[a]
5			88[a], 94[b]
6			68[a]
7			74[a]
8			70[a], 82[b]
9			90[b]

[a] Wang resin (Advanced Chemtech). [b] Argogel−MBOH resin (Argonaut Technologies, Inc.).

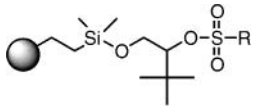
Table 2. Treatment of Resin-Supported Sulfonates with Bases



R	solvent	base	yield (%)
-PhCH$_3$	CH_3CN	Et_3N	90
-PhCH$_3$	CH_3OH	Et_3N	89
-PhCH$_3$	C_2H_5OH	TMG	85
-PhCH$_3$	CH_3OH	pyridine	91
-PhCH$_3$	C_2H_5OH	DBU	84
-PhCH$_3$	CH_2Cl_2	Et_3N	91
-PhCH$_3$	CH_2Cl_2	pyridine	94
-PhCH$_3$	CH_2Cl_2	DBU	85
-PhCH$_3$	DMF	Et_3N	88
-PhCH$_3$	DMF	pyridine	91
-PhCH$_3$	DMF	DBU	85
-$(CH_2)_2CH_3$	CH_3CN	Et_3N	65
-$(CH_2)_2CH_3$	CH_3CN	TMG	60
-$(CH_2)_2CH_3$	CH_3CN	pyridine	62
-$(CH_2)_2CH_3$	CH_3CN	DBU	56

This was an unexpected result and is contrary to the known high reactivity of benzyl tosylates in solution-phase nucleophilic displacements.[17] For example, in our hands treatment

(11) By analogy to work carried out by Darling and co-workers on the solid-supported synthesis of solid-supported organosilicon protecting groups (Stranix, B. R.; Liu, H. Q.; Darling, G. D. *J. Org. Chem.* **1997**, *62*, 6183−6186), we chose silyl linker **1** as our initial target for study. In addition to being structurally similar to previously reported solution-phase protecting groups, attachment of a sulfonyl halide to **1** would presumably allow for fluoride ion-mediated cleavage of the sulfonate. However, despite repeated attempts, we were unable to observe any sulfonate-containing product on loading of the resin with a sulfonyl halide followed by treatment with tetrabutylammonium fluoride (TBAF).



1

(12) Optimal results were obtained with an excess of sulfonyl halide; use of a single equivalent of sulfonyl halide resulted in a reduced yield. For example, treatment of Wang resin with 1 equiv of *p*-toluenesulfonyl chloride followed by hydrolysis provided the sulfonic acid in 49% yield.

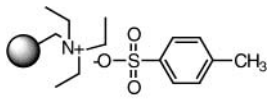
(13) Advanced Chemtech, Inc.

(14) Argonaut Technologies, Inc.

(15) The immobilization of *p*-toluenesulfonate on Wang resin and its recovery is illustrative: to the Wang hydroxy functionalized resin (50 mg, 0.8 mmol/g) in dichloromethane were added 10 equiv of diisopropylethylamine (52 mg) and 5 equiv of the arenesulfonyl chloride (38 mg). The mixture was shaken overnight. Solvent was then drained off, and the resin was washed successively with methylene chloride, acetonitrile, methanol, and again with methylene chloride. Cleavage of the product from the resin was accomplished by treatment with trifluoroacetic acid in methylene chloride (5:95) for 1 h. Collection of the solvent followed by evaporation provided the sulfonic acid (8.7 mg, 92%).

of benzyl tosylate with a 0.7 M solution of triethylamine in acetonitrile resulted in quantitative loss of starting material after 15 min at room temperature. Heating *p*-toluenesulfonate-functionalized Argogel−MBOH resin in acetonitrile in the presence of 10 equiv of triethylamine (0.195 M) at 60 °C for 18 h did show loss of some sulfonic acid, giving the product sulfonic acid in a slightly reduced yield (83%, vs 95% for the non-base-treated resin) following hydrolysis. Curiously, increasing the heating time to 36 h did not further reduce the yield, suggesting that at least a portion of the sulfonates are particularly well protected from nucleophilic displacement.

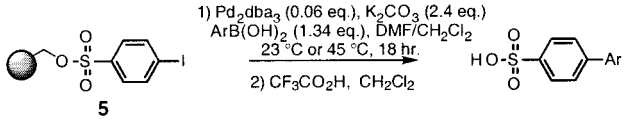
Vágner and co-workers have shown that at most 15% of sites functionalized with a polypeptide are accessible to enzyme-mediated hydrolysis;[18] this is consistent with reports by others that in reactions employing a solid-supported catalyst reaction rates are dependent on the size of the substrate. However, what are we to make of this reaction, in which partial protection is observed even in the presence of a small, readily diffusible nucleophile? Gel-phase NMR (Varian Nanoprobe) of a sample of the *p*-toluenesulfonate resin following 18 h of reflux with 10 equiv of triethylamine in acetonitrile indicated the presence of two separate sets of signals corresponding to the sulfonate. Furthermore, we can also observe triethylammonium resonances, even after extensive washing of the resin. This suggests that a portion (roughly 20%) of the sulfonate may be retained on the resin via an ionic bond (i.e., **4**), resulting from nucleophilic displacement of the sulfonate by triethylamine and its subsequent recapture by the triethylammonium salt, rather than via a covalent bond. The observation that only a portion of the sulfonate is displaced in this manner may be due to differences in surface vs bead interior microenvironmental effects.[2] Alternatively, the more kinetically accessible surface positions of the bead may undergo displacement first, creating a "charge coat" to the bead which prevents further reaction.



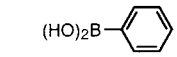
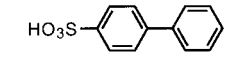
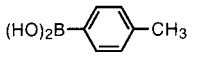
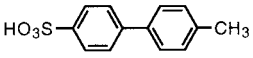
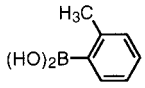
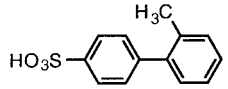
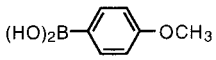
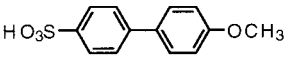
4

Of course, this "protection" scheme is only useful in the context of synthetic chemistry to the extent that it allows additional synthetic transformations to be carried out. As an initial test case, we examined the ability of resin-bound sulfonate **5** to participate in Suzuki coupling reactions.[19] As shown in Table 3, yields for the two-step coupling and cleavage procedure are modest; however, these should be regarded as unoptimized procedures.[20]

Table 3. Suzuki Coupling Reactions of Supported Sulfonate **5**



5

Boronic Acid	Product	Yield
		52%
		55%
		58%
		51%

In summary, differences in the physical environment of a solid-supported compound vis a vis its solvated counterpart can provide significant differences in reactivity; these in turn may be useful in the context of synthetic chemistry. We have observed a significant "resin protection" effect on the nucleophilic displacement of benzyl tosylates. Further experiments examining the structural and mechanistic causes of this observation, as well as synthetic studies on resin-supported sulfonates, are in progress.

Acknowledgment. The authors thank Drs. Frederick Sauter and Steve Godleski for helpful discussions during the course of this work. The authors also thank Dr. William Lenhart for his help with nanoprobe NMR experiments. This research was supported by a generous grant from the Eastman Kodak Corporation.

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(16) All sulfonic acids were analyzed by HPLC, NMR, and MS and exhibit spectroscopic and chromatographic data identical to authentic samples.

(17) (a) Yoh, S.-D.; Cheong, D. Y. *J. Phys. Org. Chem.* **1996**, *9*, 701−705. (b) Yamataka, H.; Ando, T. *Tetrahedron Lett.* **1982**, *23*, 4805−4808. (c) Ando, T.; Tanabe, H.; Yamataka, H. *J. Am. Chem. Soc.* **1984**, *106*, 2084−2088.

(18) Vágner, J.; Barany, G.; Lam, K. S.; Krchnák, V.; Sepetov, N. F.; Ostrem, J. A.; Strop, P.; Lebl, M. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 8194−8199.

(19) **Representative Experimental Procedure:** To the 4-iodobenzenesulfonate bound to Argogel−MBOH resin (100 mg, 0. 037 mmol) taken in a biospin chromatography column (BIO-RAD) in 20% DMF/CH_2Cl_2 were added Pd_2dba_3 (2.2 mg, 0.0024 mmol, 0.06 equiv) and K_2CO_3 (13.8 mg, 0.1 mmol, 2.4 equiv), and the solution was shaken for 15 min. Then *p*-tolylboric acid (7.3 mg, 0.054 mmol, 1.34 equiv) was added, and the solution was further shaken for 18 h. The reaction mixture was then transferred to a round-bottom flask and further heated to reflux temperature for 2 h. Then the resin was tranferred back to the biospin column and washed sequentially with CH_2Cl_2, CH_3CN, H_2O, CH_3OH, and CH_2Cl_2. Cleavage of the product from resin was achieved by treatment with 20% TFA/CH_2Cl_2 for 1 h. The solvent was collected, and the resin washed with CH_3OH. The combined organic elutions were evaporated to give essentially pure 4-methylbiphenylsulfonic acid (5.1 mg, 55%).

(20) All products gave satisfactory NMR and mass spectral data and are identical to published data, where available. Biphenyl-4-sulfonic acid and 4′-methylbiphenyl-4-sulfonic acid have been prepared previously: Kortekaas, T. A.; Cerfontain, H. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1560−1562. Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324−4330.