JOC*Note*

Expedient Synthesis of Sulfinamides from Sulfonyl Chlorides

Michael Harmata,* Pinguan Zheng, Chaofeng Huang, Maria G. Gomes, Weijiang Ying, Kanok-On Ranyanil, Gayatri Balan, and Nathan L. Calkins

Department of Chemistry, University of Missouri—Columbia, Columbia, Missouri 65211

HarmataM@Missouri.edu

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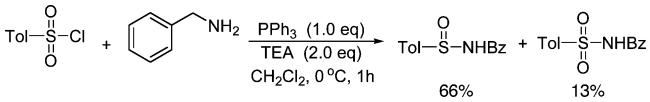
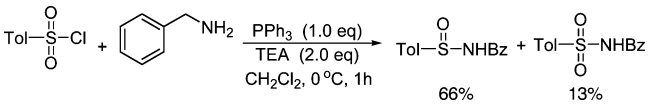


Sulfinamides were synthesized from sulfonyl chlorides using a procedure involving in situ reduction of sulfonyl chlorides. The reaction is broad in scope and easy to perform.

Sulfinamides, especially chiral sulfinamides, play vital roles in modern asymmetric chemistry.[1] Furthermore, sulfinamides can also act as *N*-sulfinyl protecting group for ease of removal under mild conditions.[2] Even though there are various procedures reported for the preparation of sulfinamides from sulfinic acids,[3] sulfinates,[4] sulfinyl chlorides,[5] disulfides,[6] and homolytic substitution at the sulfur atom,[7] these reactions often require two or more synthetic steps. A one-step process would be useful and increase the exploration of sulfinamide chemistry.

Sulfinamides are useful compounds and can be transformed to a number of other important functional groups.[8] For example, they can be converted to sulfonimidoyl chlorides, whose chemistry is both interesting and useful.[9] We reported that benzothiazines can be prepared from *N*-aryl sulfinamides by oxidation with *tert*-butyl hypochlorite and subsequent treatment with an alkene or alkyne in the presence of a Lewis acid. (Scheme 1).[10] The requisite sulfinamide was prepared from a sulfinyl chloride in high yield. While sulfinyl chlorides are not exceptionally difficult to make, they are sensitive to hydrolysis and require preparation using noxious reagents such as thionyl chloride. We thought that a procedure to quickly access sulfinamides would be useful in exploring both sulfinamide chemistry and derivatives such as sulfonimidoyl chlorides. A number of years ago Sharpless[11] reported the synthesis of sulfinate esters from sulfonyl chlorides by a one-pot reductive esterification reaction using phosphites as the reducing agent. Attempts to prepare sulfinamides by the Sharpless group were not successful. We thought, however, that modification of the synthesis of sulfinate esters introduced by Toru,[12] which used triarylphosphines as the reductant, would be suitable for the synthesis of such compounds. This note reports the realization of that idea.

SCHEME 1



We began our studies by simply using Toru's procedure for sulfinate ester formation.[11] The results are summarized in Table 1. When a CH_2Cl_2 solution of triphenylphosphine was added to the mixture of TsCl, TEA (10 equiv), and $BzNH_2$ in CH_2Cl_2 at 0 °C, only sulfonamide **6** and PPh_3 were detected by NMR analysis of the crude mixture (entry 1). However, a small change in the addition sequence offered an encouraging result. When PPh_3 and benzylamine in CH_2Cl_2 were added to a mixture of triethylamine and tosyl chloride, the desired sulfinamide was isolated in 62% yield (entry 2). Only a 14% yield of sulfinamide, accompanied by 40% sulfonamide, was isolated when the reaction was performed by addition of PPh_3 to TsCl in CH_2Cl_2 over 1 h followed by addition of a mixture of $BzNH_2$ and TEA (entry 3). The low yield of sulfinamide was due to over-reduction of the sulfonyl chloride and presumably disproportionation. The yield was improved slightly (entry 4, sulfinamide 66%; sulfonamide 13%) by adding a CH_2Cl_2 solution of PPh_3, TEA (2 equiv), and $BzNH_2$ to the TsCl in CH_2Cl_2. We also examined temperature and solvent effects in this reaction. A slightly lower yield was obtained at 25 °C (entry 5). A significant amount of sulfonamide was isolated at −20 °C (entry 6). A poor yield of sulfinamide was realized when the reactions were carried out in acetonitrile, THF, and EtOAc (entries 7−9). In short, the best reaction conditions were found to be addition of benzylamine and triphenylphosphine (1 equiv) to a CH_2Cl_2 solution of TEA (2.0 equiv) at 0 °C.

Next, we studied the effects of substituent changes on the phosphine (Table 2). A 50% excess of PPh_3 slightly decreased

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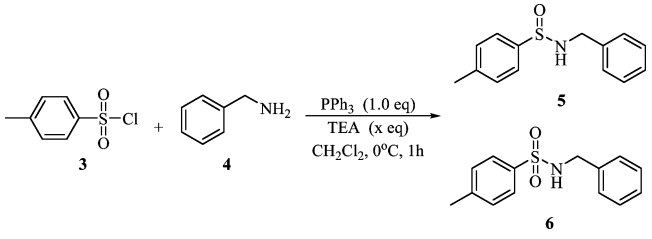
FIGURE 1. Benzothiazine formation from a sulfinamide.

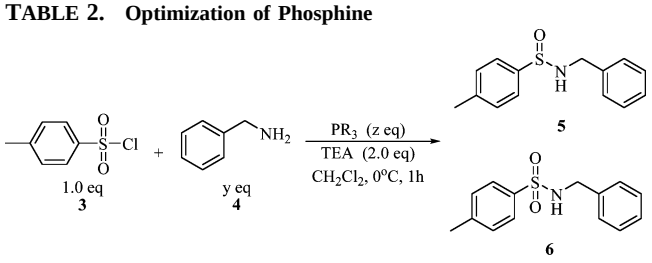
TABLE 1. Optimization of Solvent and Temperature



entry	TEA (x equiv)	solvent,[f] T (°C)	sulfinamide **5** (%)	sulfonamide **6** (%)
1[a]	10	DCM, 0	0	b
2[c]	10	DCM, 0	62	0
3[d]	10	DCM, 0	14	40
4[e]	2.0	DCM, 0	66	13
5[e]	2.0	DCM, 25	60	8
6[e]	2.0	DCM, −20	53	21
7[e]	2.0	ACN, 0	26	40
8[e]	2.0	THF, 0	49	30
9[e]	2.0	EtOAc, 0	49	32

[a] Method A: To the mixture of TsCl (1.0 eq), $BzNH_2$ (1.0 eq), and TEA (10.0 eq) in CH_2Cl_2 solution was added PPh_3 in CH_2Cl_2 solution over a 1 h period at 0 °C. [b] Only sulfonamide and PPh_3 were detected by NMR analysis of the crude product. [c] Method B: To the mixture of TsCl (1.0 equiv) and TEA (10.0 equiv) in CH_2Cl_2 solution was added PPh_3 (1.0 equiv) and $BzNH_2$ (1.0 equiv) in CH_2Cl_2 solution over a 1 h period at 0 °C. [d] Method C: To the mixture of TsCl (1.0 equiv) in CH_2Cl_2 solution was added PPh_3 (1.0 equiv) in CH_2Cl_2 solution over a 1 h period at 0 °C, followed by addition of the mixture of $BzNH_2$ and TEA in CH_2Cl_2 solution over a 1 h period at 0 °C. [e] Method D: To TsCl (1.0 equiv) in CH_2Cl_2 solution at 0 °C was added a mixture of $BzNH_2$ (1.0 equiv), TEA (2.0 equiv), and PPh_3 (1.0 equiv) in CH_2Cl_2 solution over a 1 h period. [f] DCM: dichloromethane. ACN: acetonitrile.

TABLE 2. Optimization of Phosphine

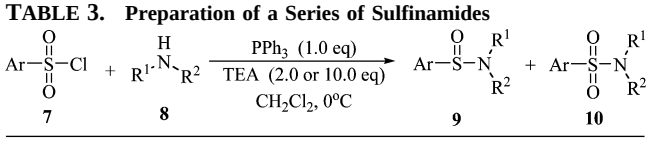


entry[a]	$BzNH_2$ (y equiv)	PR_3(z equiv)	sulfinamide **5** (%)	sulfonamide **6** (%)
1	1.0	Ph (1.0)	66	13
2	1.0	Ph (1.5)	68	4
3	1.5	Ph (1.0)	55	32
4	1.0	2-furyl (1.0)	0	b
5	1.0	p-CF_3-Ph (1.0)	0	b
6	1.0	o-tolyl (1.0)	60	10
7	1.0	n-Bu (1.0)	0	b

[a] These experiments were carried out using Method D. [b] Only sulfonamide and PPh_3 were detected by NMR analysis of the crude product.

the amount of sulfonamide obtained in the reaction but did little to improve the yield of the sulfinamide (entry 2). The yield of sulfonamide increased to 32% with the use of 1.5 equiv of

TABLE 3. Preparation of a Series of Sulfinamides



entry[a]	$ArSO_2Cl$ **7**	R^1R^2NH **8**	**9** (%)	**10** (%)
1	Ph	n-$PrNH_2$	**9a**:62	
2	Ph	c-pentyl-NH_2	**9b**:59	**10b**:13
3	Tol	c-hexyl-NH_2	**9c**:65	**10c**:12
4	Ph	c-hexyl-NH_2	**9d**:70	
5	Tol	c-heptyl-NH_2	**9e**:48	**10e**:19
6	Ph	c-$C_{12}H_{23}$-NH_2	**9f**:47	**10f**:10
7[b]	Ph	t-$BuNH_2$	**9g**:92	
8	Tol	pyrolidine	**9h**:15	**10h**:28
9	Tol	Et_2NH	**9i**:59	**10i**:37
10	Ph	i-Pr_2NH	**9j**:88	
11	Ph	$(allyl)_2NH$	**9k**:73	
12	Ph	3,4-OMe-$BzNH_2$	**9l**:77	
13	Tol	(*R*)1-phenyl ethyl amine	**9m**:39 1.0:1.0[c]	
14	Tol	$PhCH_2CH_2NH_2$	**9n**:44	**10n**:6
15	Ph	$PhCH_2CH_2NH_2$	**9o**:53	
16	Ph	propargyl	**9p**:32	**10p**:15
17	Tol	(−)-sulfoximine	**9q**:44 (53[d]) 1.2:1.0[c]	
18	Ph	aniline	**9r**:38	**10r**:8
19	Tol	o-Br-aniline	**9s**:35 (53[d])	
20	Tol	p-nitroaniline	e	
21	Tol	p-Cl-o-Me aniline	**9t**:35 (59[d])	
22	Tol	p-t-Bu-aniline	**9u**:22	**10u**:35
23	Ph	p-anisidine	**9v**:8	
24	Ph	TMS-aniline	**9w**:41[f]	
25[b]	Tol	2,6-di-i-Pr-aniline		

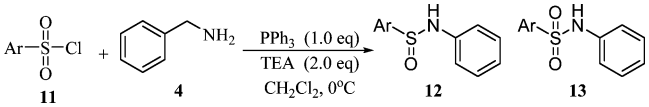
[a] In all cases, the reactions were carried out using method C except where noted. [b] Reactions were carried out using method D. [c] Diastereomeric ratios were determined by ^1H NMR analysis of the crude mixture. [d] Yields were corrected for the recovered starting material. [e] A complicated mixture was isolated from the reaction mixture. [f] Desilylated product was isolated in 41% yield.

$BzNH_2$, suggesting that the substrate amine should remain the limiting reagent in the reaction (entry 3). Electron-rich phosphines (trifuryl phosphine, tri-n-butyl phosphine) or an electron-poor phosphine (tri-p-trifluoromethyl phosphine) did not produce any of the desired sulfinamide. Interestingly, tri-o-tolyl phosphine gave an acceptable yield of the desired product. All things considered, triphenylphosphine is the reductant of choice and only 1 equiv was used in the subsequent studies.

We applied the first-generation reaction conditions (method B) together with the second-generation reaction conditions (method D) to perform further studies of this reductive amination reaction. Results are summarized in Table 3. With cyclic, primary amines, the yield of the sulfinamide increased slightly when the ring size changed from 5 to 6 membered (entries 2−4). For larger ring systems, the yield was only about 50% (entries 5−6). Perhaps not surprisingly, the sterically hindered amines (t-$BuNH_2$ and i-Pr_2NH) gave excellent yields (entries 7 and 10). We conclude that their reaction with sulfonyl chloride is slow but quite rapid with the corresponding sulfinyl chloride or other active sulfinylating agent formed in the reaction mixture. A chiral amine (entry 13) and chiral sulfoximine (entry 17) afforded reasonable yields of sulfinyl derivatives, but no diastereoselection was found.[13] It is not immediately clear why pyrollidine (entry 8) and propargylamine (entry 16) reacted so poorly, but for the former, a considerable amount of sulfonamide

(13) An enantioselective version of the reaction is conceivable, see: Nakamura, S.; Tateyama, M.; Sugimoto, H.; Nakagawa, M.; Watanabe, Y.; Shibata, N.; Toru, T. *Chirality* **2005**, *17*, 85 and references therein.

TABLE 4. Reactions with Different Sulfonyl Chlorides



entry[a]	Ar SO_2Cl **11**	sulfinamide **12**	sulfonamide **13**
1	*p*-CF_3-Ph	**12a**:25	**13a**:26
2	*o*-NO_2-Ph	**12b**:55	**13b**:21
3	2-Naph	**12c**:70	**13c**:11
4	*o*-F-Ph	**12d**:63	**13d**:9
5	*o*-Cl-Ph	**12e**:80	**13e**:12
6	*o*-Br-Ph	**12f**:46	**13f**:20
7	*i*-Pr	**12g**:3.1	**13g**:4.7
8[b]	CF_3	**12h**:47	0

[a] In all cases, reactions were carried out using method D. [b] Method E: A solution of CF_3SO_2Cl in CH_2Cl_2 solution and a mixture of TEA, $BzNH_2$, and PPh_3 were added at the same rate to a 25 mL round-bottom flask at 0 °C.

was isolated. The triple bond in propargylamine may be reactive under the reaction conditions.

With acceptable results using aliphatic amines in hand, we turned our attention to less nucleophilic amines, namely, anilines. With aniline itself, only a 38% yield of sulfinamide along with 8% of the corresponding sulfonamide was isolated (entry 18). Adding an electron-withdrawing nitro group to the aromatic ring gave a complicated mixture, perhaps due to reaction between the nitro group and triphenylphosphine (entry 20).[14] *o*-Bromoaniline and *p*-chloro-*o*-methylaniline gave results similar to that of aniline (entries 19 and 21). Furthermore, neither an increase in the electron density on the phenyl ring (entries 22−23) nor an increase in the steric bulk on or near the aniline nitrogen gave acceptable yields of sulfinamides (entries 24 and 25).

We also carried out reactions with different sulfonyl chlorides. The results are shown in Table 4. Strongly electrophilic arylsulfonyl chlorides (entries 1 and 2) gave significant amounts of sulfonamides. Of the *o*-haloarylsulfonyl chlorides examined, the chloro compound seems to have an appropriate balance between steric and electronic effects to afford high yields of sulfinamide relative to the corresponding fluoro and bromo species (entries 4−6). While 2-propanesulfonyl chloride afforded a poor yield of sulfinamide (entry 7), triflyl chloride gave a respectable yield of sulfinamide (entry 8).

In conclusion, we developed a simple and effective methodology to synthesize sulfinamides from sulfonyl chlorides. The scope of the process is reasonably broad and may expand further with continued investigation. Further application of this reaction in sulfonimidoyl chloride and benzothiazine chemistry is currently underway.

(14) Though one might not expect such a reaction at low temperatures, see: Masaki, M.; Fukui, K.; Kita, J. *Bull. Soc. Chem. Jpn.* **1977**, *50*, 2013.

Experimental Section

General Method B for the Preparation of Sulfinamide. To a solution of *p*-toluenesulfonyl chloride (190 mg, 1 mmol) and triethylamine (1.4 mL, 10 mmol) in CH_2Cl_2 (3.0 mL) solution at 0 °C was added a solution of triphenylphosphine (262 mg, 1 mmol) and benzylic amine (109 μL, 1 mmol) in CH_2Cl_2 (3.0 mL) solution using a syringe pump over a period of 1 h. After addition, TLC showed all of the sulfonyl chloride was consumed. The reaction mixture was concentrated by rotary evaporation. Crude mixture was purified by column chromatography (20% EtOAc) to give the desired sulfinamide **5** (152 mg, 62%).

General Method D for the Preparation of Sulfinamide. To a solution of *p*-toluenesulfonyl chloride (190 mg, 1 mmol) in CH_2Cl_2 (3.0 mL) solution at 0 °C was added a mixture of triphenylphosphine (262 mg, 1 mmol), benzylic amine (109 μL, 1 mmol), and triethylamine (278.7 μL, 2.0 mmol) in CH_2Cl_2 (3.0 mL) solution using a syringe pump over a period of 1 h. After addition, TLC showed all of the sulfonyl chloride was consumed. The reaction mixture was concentrated by rotary evaporation and purified by flash chromatography on silica.

***N*-Benzyl-*p*-toluenesulfinamide (5).** According to the general procedure, **5** was obtained by column chromatography (hexane/EtOAc = 5:1) as a white solid (62%, method B; 66%, method D). ^{1}H NMR and ^{13}C NMR matched literature values.[15] ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.64−7.68 (m, 2H), 7.27−7.34 (m, 7H), 4.22−4.28 (m, 2H), 3.91 (dd, J = 14.6, 8.5 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 141.2, 140.8, 137.8, 129.5, 128.5, 128.2, 127.5, 125.9, 44.2, 21.2.

***N*-Benzyl-*p*-toluenesulfonamide (6). 6** was obtained as a white solid (13%, method D). ^{1}H NMR matched literature values.[16] ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.76 (d, J = 7.5 Hz, 2H), 7.18−7.33 (m, 7H), 4.78 (t, J = 6.0 Hz, 1H), 4.12 (d, J = 6.2 Hz, 2H), 2.44 (s, 3H).

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Supporting Information Available: Experimental procedures as well as characterization and copies of proton and carbon spectra for all previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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