Published in final edited form as:

J Org Chem. 2007 January 19; 72(2): 683–685. doi:10.1021/jo062296i.

An Expedient Synthesis of Sulfinamides from Sulfonyl Chlorides

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Abstract

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

Sulfinamides, especially chiral sulfinamides, play vital roles in the modern asymmetric chemistry.¹ Furthermore, sulfinamides can also act as *N*-sulfinyl protecting group in ease of removal under mild conditions.² Even though there are various procedures reported for the preparation of sulfinamides from sulfinic acids³, sulfinates⁴, sulfinyl chlorides⁵, disulfides⁶, and homolytic substitution at the sulfur atom⁷, 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 *t*-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 both exploring sulfinamide chemistry and derivatives such as sulfonimidoyl chlorides.

A number of years ago Sharpless¹¹ reported the synthesis of sulfinate esters from sulfonyl chlorides by a one-pot reductive esterification reaction using either phosphites as the reducing agent. Attempts to prepare sulfinamides by the Sharpless group were not successful. We thought however, that the modification of the synthesis of sulfinate esters introduced by Toru¹², which used triarylphosphines as the reductant, would be suitable for the synthesis of such compounds. This letter reports the realization of that idea.

We began our studies by simply using Toru's procedure for sulfinate ester formation.¹¹ The results are summarized in Table 1. When a CH₂Cl₂ solution of triphenylphosphine was added to the mixture of TsCl, TEA (10 equivalents) and BzNH₂ in CH₂Cl₂ at 0 °C, only sulfonamide **6** and PPh₃ were detected by the NMR analysis of the crude mixture (entry 1). However, a small change in the addition sequence offered an encouraging result. When PPh₃ and benzylamine in CH₂Cl₂ 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 the addition of PPh₃ to TsCl in CH₂Cl₂ over 1 hour followed by addition of a mixture of BzNH₂ 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 CH₂Cl₂ solution of PPh₃, TEA (2 equivalents) and BzNH₂ to the TsCl in CH₂Cl₂. 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 CH₂Cl₂ 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 PPh₃ slightly decreased 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 eq of BzNH₂, 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 equivalent was used in the subsequent studies.

We applied the 1st generation reaction conditions (Method B) together with the 2nd generation reaction conditions (Method D) to 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 and 6-membered (entries 2–4). For larger ring systems, the yield was only about 50% (entries 5–6). Perhaps not suprisingly, the sterically hindered amines (*t*-BuNH₂ and *i*-Pr₂NH) 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 a chiral sulfoximine (entry 17) afforded reasonable yields of sulfinyl derivatives, but no diastereoselection was found.¹³ It is not immediately clear why pyrrolidine (entry 8) and propargylamine (entry 16) reacted so poorly, but for the former, a considerable amounts of sulfonamide 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 1–2) 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 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 have 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 applications of this reaction in sulfonimidoyl chloride and benzothiazine chemistry is currently underway.

Experimental Section

General Method B for the Preparation of Sulfinamide

To a solution of *p*-toluensulfonyl chloride (190 mg, 1 mmol) and triethylamine (1.4 ml, 10 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (3.0 ml) solution using 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 rotavap. 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*-toluensulfonyl chloride (190 mg, 1 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (3.0 ml) solution using 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 rotavap 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**). ¹H-NMR and ¹³C-NMR matched with Literature report.¹⁵ ¹H-NMR (250 MHz, CDCl₃): 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); ¹³C-NMR (62.5 MHz, CDCl₃): 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**). ¹H-NMR matched with Literature report.¹⁶ ¹H-NMR (250 MHz, CDCl₃): 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).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We gratefully acknowledge financial support from the NIH (1R01-AI59000-01A1). We thank Dr. Charles L. Barnes for X-ray data.

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Figure 1.
Benzothiazine formation from a sulfinamide.

Table 1

Optimization of solvent and temperature.

entry	TEA (x eq)	Solvent ^f T °C	Sulfonamide 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), BzNH₂ (1.0 eq) and TEA (10.0 eq) in CH₂Cl₂ solution, was added PPh₃ in CH₂Cl₂ solution over 1 h period at 0 °C.

^b Only sulfonamide and PPh₃ were detected by the NMR analysis of crude product.

^c **Method B:** To the mixture of TsCl (1.0) and TEA (10.0) in CH₂Cl₂ solution, was added PPh₃ (1.0) and BzNH₂ (1.0) in CH₂Cl₂ solution over 1 h period at 0 °C.

^d **Method C:** To the mixture of TsCl (1.0) in CH₂Cl₂ solution, was added PPh₃ (1.0) in CH₂Cl₂ solution over 1 h period at 0 °C, followed by addition of the mixture of BzNH₂ and TEA in CH₂Cl₂ solution over 1 h period at 0 °C.

^e **Method D:** To TsCl (1.0) in CH₂Cl₂ solution at 0 °C, was added a mixture of BzNH₂ (1.0), TEA (2.0) and PPh₃ (1.0) in CH₂Cl₂ solution over 1 h period.

^f DCM: dichloromethane; ACN: acetonitrile.

Table 2

Optimization of phosphine.

entry ^a	BzNH ₂ (y eq)	PR ₃ (z eq)	Sulfonamide 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	<i>p</i> -CF ₃ -Ph (1.0)	0	^b
6	1.0	<i>o</i> -tolyl (1.0)	60	10
7	1.0	<i>n</i> -Bu (1.0)	0	^b

^aThese experiments were carried out using Method D.^bOnly sulfonamide and PPh₃ were detected by the NMR analysis of crude product.

Table 3

Preparation of a series of sulfinamides.

$\text{Ar}-\overset{\text{O}}{\underset{\text{O}}{\parallel}}\text{S}-\text{Cl} \quad + \quad \text{R}^1\text{N}(\text{H})\text{R}^2 \xrightarrow[\text{CH}_2\text{Cl}_2, 0^\circ\text{C}]{\text{PPh}_3 (1.0 \text{ eq}), \text{TEA} (2.0 \text{ or } 10.0 \text{ eq})} \text{Ar}-\overset{\text{O}}{\underset{\text{O}}{\parallel}}\text{S}-\text{N}(\text{R}^1)(\text{R}^2) + \text{Ar}-\overset{\text{O}}{\underset{\text{O}}{\parallel}}\text{S}-\text{N}(\text{R}^1)(\text{R}^2)$				
entry ^a	ArSO ₂ Cl 7	R ¹ R ² NH 8	9 (%)	10 (%)
1	Ph	<i>n</i> -PrNH ₂	9a: 62	-
2	Ph	<i>c</i> -pentyl-NH ₂	9b: 59	10b: 13
3	Tol	<i>c</i> -hexyl-NH ₂	9c: 65	10c: 12
4	Ph	<i>c</i> -hexyl-NH ₂	9d: 70	-
5	Tol	<i>c</i> -heptyl-NH ₂	9e: 48	10e: 19
6	Ph	<i>c</i> -C ₁₂ H ₂₃ -NH ₂	9f: 47	10f: 10
7 ^b	Ph	<i>t</i> -BuNH ₂	9g: 92	-
8	Tol	Pyrolidine	9h: 15	10h: 28
9	Tol	Et ₂ NH	9i: 59	10i: 37
10	Ph	<i>i</i> -Pr ₂ NH	9j: 88	-
11	Ph	(Allyl) ₂ NH	9k: 73	-
12	Ph	3,4-OMe-BzNH ₂	9l: 77	-
13	Tol	(<i>R</i>)-1-Phenyl ethyl amine	9m: 39 1.0:1.0 ^c	-
14	Tol	PhCH ₂ CH ₂ NH ₂	9n: 44	10n: 6
15	Ph	PhCH ₂ CH ₂ NH 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	<i>o</i> -Br-aniline	9s: 35 (53 ^d)	-
20	Tol	<i>p</i> -Nitro aniline	^e	-
21	Tol	<i>p</i> -Cl- <i>o</i> -Me aniline	9t: 35 (59 ^d)	-
22	Tol	<i>p</i> - <i>t</i> -Bu aniline	9u: 22	10u: 35
23	Ph	<i>p</i> -anisidine	9v: 8	-
24	Ph	TMS-aniline	9w: 41 ^f	-
25 ^b	Tol	2,6-Di- <i>i</i> -Pr aniline	-	-

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

Table 4

Reactions with different sulfonyl chlorides

$$\text{Ar-SO}_2\text{Cl} \quad \mathbf{11} + \text{Ph-CH}_2\text{NH}_2 \quad \mathbf{4} \xrightarrow[\text{CH}_2\text{Cl}_2, 0^\circ\text{C}]{\text{PPh}_3 (1.0 \text{ eq}), \text{TEA} (2.0 \text{ eq})} \text{Ar-SO}_2\text{NH-Ph} \quad \mathbf{12} \quad \text{or} \quad \text{Ar-SO}_2\text{NH-Ph} \quad \mathbf{13}$$

entry ^a	Ar SO ₂ Cl 11	Sulfinamide 12	Sulfonamide 13
1	<i>p</i> -CF ₃ -Ph	12a : 25	13a : 26
2	<i>o</i> -NO ₂ -Ph	12b : 55	13b : 21
3	2-Naph	12c : 70	13c : 11
4	<i>o</i> -F-Ph	12d : 63	13d : 9
5	<i>o</i> -Cl-Ph	12e : 80	13e : 12
6	<i>o</i> -Br-Ph	12f : 46	13f : 20
7	<i>i</i> -Pr	12g : 3.1	13g : 4.7
8 ^b	CF ₃	12h : 47	0

^a In all cases, the reactions were carried out using method D.^b **Method E**: A solution of CF₃SO₂Cl in CH₂Cl₂ solution and a mixture of TEA, BzNH₂ and PPh₃ were added at the same rate to a 25 ml round bottom flask at 0 °C.