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Sulfonylation of arenes with sulfonamides

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ABSTRACT

In the presence of triflic anhydride, sulfonylation of arenes with sulfonamides proceeded smoothly in $Cl_2CHCHCl_2$ at 80–140 °C, which gave rise to the desired products in good to excellent yields.

The aryl sulfones are common structures in valuable molecules in fields such as pharmaceuticals, agrochemicals, and polymer sciences.[1] In particular, their immense utilities in medicinal chemistry and their unique bioactivities have attracted considerable attention on their synthesis. For example, diaryl sulfones have been reported to inhibit HIV-1[2] reverse transcriptase, and diphenyl sulfone[3] is used as an intermediate for the synthesis of 4,4′-diamino-diphenyl sulfone (**DAPSONE**), which is effective for leprosy treatment.[4] The aryl sulfones can be prepared from the transition metal-catalyzed reactions using sulfonic acids or sulfonyl chloride,[5] but the pre-functionalizing such as metallization or halogenations of arenas are required. A well-known process involving the formation of new C–S bond from aromatic C–H bonds is the Friedel–Crafts (**FC**) sulfonylation of various arenes, especially electron-rich arenes.[6,7] Sulfonchlorides or sulfonanhydrides are general substrates employed in the **FC** sulfonylation. However, sulfonamides, which are much cheaper than sulfonchlorides and sulfonanhydrides, can be easily available by reacting sulfinic acid salts with an electrophilic nitrogen sources such as hydroxylamine-O-sulfonic acid, have not been explored as a substrate of **FC** sulfonylation. The stability of sulfonamides to air and moisture requires no special caution to handle and is amenable to long-term storage. In these respects sulfonamides have a clear advantage as the sulfonylation substrates over the sulfonchlorides and sulfonanhydrides. Herein, we report the **FC** sulfonylation of arenes using sulfonamides in the presence of triflic anhydride.[8]

To examine the reactivity of sulfonamides to the **FC** sulfonylation, we carried out the sulfonylation of *p*-xylene with *p*-toluenesulfonamide as a model reaction. A variety of Lewis acids and Brϕnsted acids were tested and the results are presented in Table 1. The sulfone product was not observed in the presence of 2 equiv $AlCl_3$, 2 equiv $FeCl_3$ (Table 1, entries 1–2). $Cu(OTf)_2$ (20 mol %) was fully inactive to the reaction (Table 1, entry 3). Among the various Brϕnsted acids (H_2SO_4, CF_3COOH, and CF_3SO_3H), a 58% yield was obtained using triflic acid (Table 1, entries 4–6). When the sulfonylation reaction was carried out in the presence of 1 equiv triflic anhydride, we obtained quite satisfactory results in $Cl_2CHCHCl_2$ at 120 °C for 12 h (Table 1, entry 7). The solvents exerted remarkable effect on the sulfonylation reaction and low conversions were obtained in nitrobenzene, nitromethane, and benzenenitrile (Table 1, entries 8–10). The reaction became slower at lower temperature and no reaction occurred at room temperature (Table 1, entries 11–12).

Due to its great activity and ready availability, Tf_2O was subsequently used to a range of **FC** sulfonylation reactions and the results are summarized in Table 2. The sulfonylation of various arenes furnished sulfones with good to excellent isolated yields. The reaction of volatile benzene was performed at 80 °C due to its lower boiling point and a 70% yield was obtained for 24 h (Table 2, entry 1). *p*-Xylene and mesitylene delivered excellent yields at 120 °C for 12 h (Table 2, entries 2–3), and the sulfonylation of *meta*-xylene afforded exclusively the less hindered *ortho*-substituted product in high yield (Table 2, entry 4). These impressive results were comparable with bismuth(III) triflate catalytic system using sulfonchloride and sulfonanhydride and showed sulfonamide was a good alternative substrate for sulfones.[4,9] Activated arenes such as anisole and toluene afforded the corresponding sulfones in good yields, and similar with the Lewis acid catalyzed systems, isomers were observed (Table 2, entries 5–6). When the

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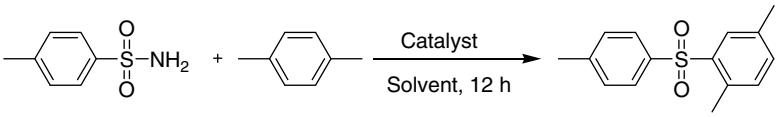
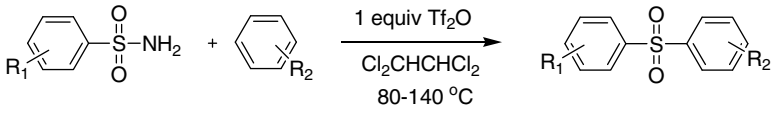
Table 1
Sulfonylation of 4-methylbenzenesulfonamide with *p*-xylene[a]



Entry	Catalyst	Solvent	Temp. (°C)	Yield[b] (%)
1	$AlCl_3$, 2 equiv	$CHCl_2CHCl_2$	120	NR
2	$FeCl_3$, 2 equiv	$CHCl_2CHCl_2$	120	NR
3	$Cu(OTf)_2$, 20 mol %	$CHCl_2CHCl_2$	120	NR
4	H_2SO_4, 1 equiv	$CHCl_2CHCl_2$	120	Trace
5	CF_3CO_2H, 1 equiv	$CHCl_2CHCl_2$	120	NR
6	CF_3SO_3H, 1 equiv	$CHCl_2CHCl_2$	120	58
7	$(CF_3SO_2)_2O$, 1 equiv	$CHCl_2CHCl_2$	120	95
8	$(CF_3SO_2)_2O$, 1 equiv	$PhNO_2$	120	Trace
9	$(CF_3SO_2)_2O$, 1 equiv	CH_3NO_2	120	NR
10	$(CF_3SO_2)_2O$, 1 equiv	PhCN	120	NR
11	$(CF_3SO_2)_2O$, 1 equiv	$CHCl_2CHCl_2$	80	42
12	$(CF_3SO_2)_2O$, 1 equiv	$CHCl_2CHCl_2$	rt	NR

[a] Reaction conditions: 4-methylbenzenesulfonamide 0.5 mmol (85 mg), *p*-xylene 1.0 mmol (106 mg), solvent 3 mL, 12 h.
[b] Isolated yields.

Table 2
Sulfonylation reactions of sulfonamide catalyzed by triflic anhydride[a]



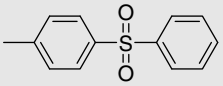
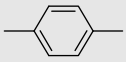
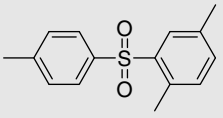
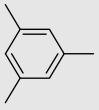
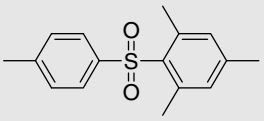
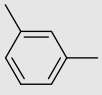
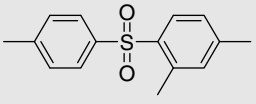
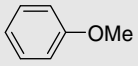
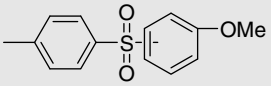
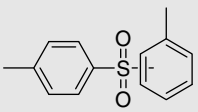
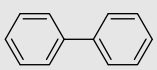
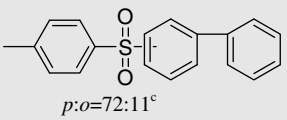
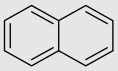
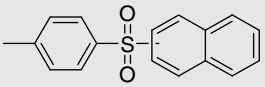
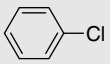
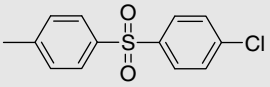
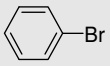
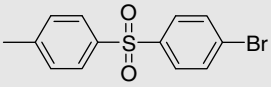
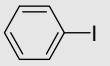
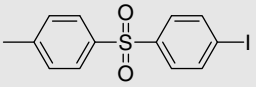
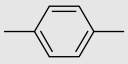
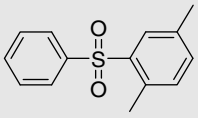
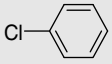
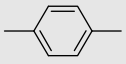
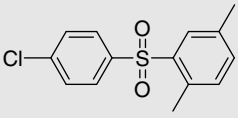
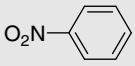
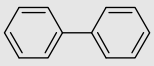
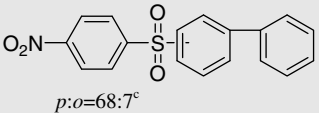
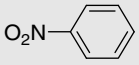
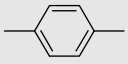
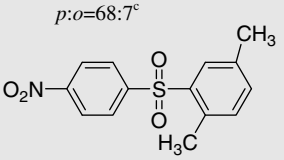
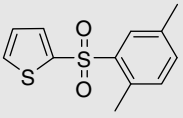
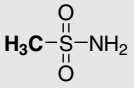
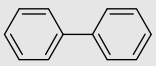
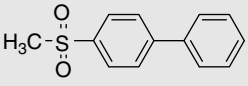
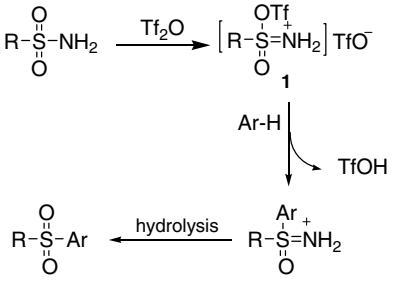
Entry	Aryl	Arene	Product	Yield[b] (%)
1				70
2				95
3				89
4				90
5			 *p*:*o*:*m* =63:20:3[c]	86
6			 *p*:*o*:*m* =68:14:4[c]	86
7			 *p*:*o*=72:11[c]	83

Table 2 (*continued*)

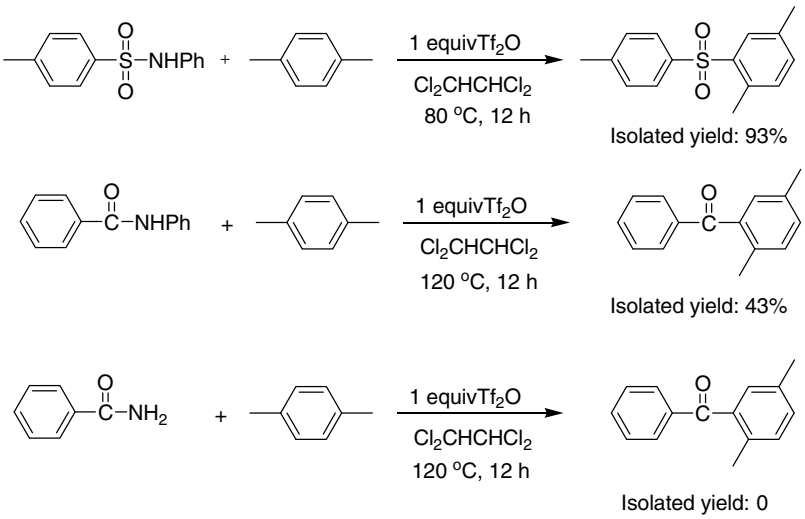
Entry	Aryl	Arene	Product	Yield[b] (%)
8			 β:α=18:74[d]	92
9				85
10				89
11				83
12				95
13				84[e]
14			 *p*:*o*=68:7[c]	75[e]
15				42[e]
16				86[f]
17				58

[a] Reaction conditions: sulfonamides 0.5 mmol, arene 1 mmol, triflic anhydride 0.5 mmol, $CHCl_2CHCl_2$ 3 mL, 120 °C, 12 h.
[b] Isolated yield.
[c] Determined by GC–MS.
[d] Determined by ^1H NMR.
[e] Reaction temperature was 140 °C.
[f] Reaction temperature was 80 °C.

biphenyl was used as the substrate, the ratio of *para*-substituted product was increased and only trace of the *ortho*-substituted isomer was isolated (Table 2, entry 7), *m*-isomer was not observed. In the case of naphthalene, the dynamically stable isomer was preferentially generated (Table 2, entry 8). The deactivated aromatic halides such as chlorobenzene, bromobenzene and iodobenzene, could be easily converted to the corresponding sulfones with excellent *para*-selectivity (Table 2, entries 9–11). It is important to note that the arylsulfonamides with deactivated substitutes in the phenyl ring such as –Cl and $–NO_2$ could carry out the desired **FC** sulfonylation reactions at higher temperature and gave in moderate to good yields (Table 2, entries 13–15). 2-Thiophenyl sulfon-



Scheme 1. The plausible mechanism.



Scheme 2. The acylation reactivity of *N*-phenyl amide.

amide also showed good reactivity and delivered the desired sulfonylation product in good yield (Table 2, entry 16). The alkylsulfonamide was less active with respect to arylsulfonamide (Table 2, entry 17).

Because sulfonamides were used as the acylation substrates, the sulfiminium salt intermediate **1** via a Vilsmeier-Haack process[10] is possibly formed in the presence of triflic anhydride, which should be a potential agent for the **FC** sulfonylation and generates the **FC** sulfonylation product **2** with arene (Scheme 1).[11] The subsequent hydrolysis gives the desired sulfone product. Concerning the intermediate, **1** and **2**, their stability should be enhanced by the substitution of phenyl on amide and hence their reactivity should be higher. Indeed, we found that *N*-phenyl-*p*-toluenesulfonamide showed much higher activity to give the sulfonylation product in 93% yield at 80 °C (Scheme 2), indicating that the phenyl on the amide facilitates the reaction. The similar results were observed in the cases of benzamide and *N*-phenylbenzamide, where benzamide did not react with *p*-xylene, and a 43% yield of acylation product was obtained for *N*-phenylbenzamide under the reaction conditions (Scheme 2).

In conclusion, we have described an unusual process of arenes with sulfonamides to produce arylsulfones in the presence of triflic anhydride.[12] The method provides a direct process for the synthesis of arylsulfones. The transformation has been shown to be high yielding and constitutes a useful alternative to the commonly accepted sulfonylation procedures.

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References and notes

1. (a) Sturino, C. F.; O'Neill, G.; Lachance, N.; Boyd, M.; Berthelette, C.; Labelle, M.; Li, L.; Roy, B.; Scheigetz, J.; Tsou, N.; Aubin, Y.; Bateman, K. P.; Chauret, N.; Day, S. H.; Levesque, J.-F.; Seto, C.; Silva, J. H.; Trimble, L. A.; Carriere, M.-C.; Denis, D.; Greig, G.; Kargman, S.; Lamontagne, S.; Mathieu, M.-C.; Sawyer, N.; Slipetz, D.; Abraham, W. M.; Jones, T.; McAuliffe, M.; Piechuta, H.; Nicoll-Griffith, D. A.; Wang, Z.; Zamboni, R.; Young, R. N.; Metters, K. M. *J. Med. Chem.* **2007**, *50*, 794–806; (b) Trost, B. M.; Shen, H. C.; Surivet, J.-P. *J. Am. Chem. Soc.* **2004**, *126*, 12565–12579; (c) Adams, C. M.; Ghosh, I.; Kishi, Y. *Org. Lett.* **2004**, *6*, 4723–4726; (d) Artico, M.; Silvestri, R.; Pagnozzi, E.; Bruno, B.; Novellino, E.; Greco, G.; Massa, S.; Ettorre, A.; Loi, A. G.; Scintu, F.; La Colla, P. *J. Med. Chem.* **2000**, *43*, 1886–1888; (e) Michaely, W. J.; Krattz, G. W. U.S. Patent 4,780,127, **1988**; *Chem. Abstr.* **1989**, *111*, 129017; (f) Kochi, T.; Noda, S.; Yoshimura, K.; Nozaki, K. *J. Am. Chem. Soc.* **2007**, *129*, 8948–8949; (g) Wei, X.-L.; Wang, Y. Z.; Long, S. M.; Bobeczko, C.; Epstein, A. J. *J. Am. Chem. Soc.* **1996**, *118*, 2545–2555.
2. (a) Neamati, N.; Mazumder, A.; Zhao, H.; Sunder, S.; Burke, T. R., Jr.; Schultz, R. J.; Pommier, Y. *Antimicrob. Agents Chemother.* **1997**, *41*, 385–393; (b) Artico, M.; Silvestri, R.; Massa, S.; Loi, A. G.; Corrias, S.; Piras, G.; La Colla, P. *J. Med. Chem.* **1996**, *39*, 522–530; (c) McMahon, J. B.; Gulakowsky, R. J.; Weislow, O. S.; Schultz, R. J.; Narayanan, V. L.; Clanton, D. J.; Pedemonte, R.; Wassmundt, F. W.; Buckheit, R. W., Jr.; Decker, W. D.; White, E. L.; Bader, J. P.; Boyd, M. R. *Antimicrob. Agents Chemother.* **1993**, *37*, 754–760.
3. Williams, T. M.; Ciccarone, T. M.; MacTough, S. C.; Rooney, C. S.; Balani, S. K.; Condra, J. H.; Emini, E. A.; Goldman, M. E.; Greenlee, W. J.; Kauffman, L. R.; O'Brien, J. A.; Sardana, V. V.; Schleif, W. A.; Theoharides, A. D.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 1291–1294.
4. Répichet, S.; Le Roux, C.; Hernandez, P.; Dubac, J.; Desmurs, J.-R. *J. Org. Chem.* **1999**, *64*, 6479–6482.
5. (a) Kar, A.; Sayyed, I. A.; Lo, W. F.; Kaiser, H. M.; Beller, M.; Tse, M. F. *Org. Lett.* **2007**, *9*, 3405–3408; (b) Kuwano, R.; Kondo, Y.; Shirahama, T. *Org. Lett.* **2005**, *7*, 2973–2975; (c) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M.; Bernini, R. *J. Org. Chem.* **2004**, *69*, 5608–5614; (d) Baskin, J. M.; Wang, Z.-Y. *Org. Lett.* **2002**, *4*, 4423–4425; (e) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 4719–4721.
6. (a) Jensen, F. R.; Goldman, G. In *Friedel–Crafts and Related Reactions*; Olah, G. A., Ed.; Wiley-Interscience: New York, 1964; Vol. III, pp 1319–1367; (b) Taylor, R. In *Comprehensive Chemical Kinetics*; Banford, C. H., Tipper, C. F. H., Eds.; Elsevier: New York, 1972; pp 77–83; (c) Alexander, M. V.; Khandekar, A. C.; Samant, S. D. *J. Mol. Catal. A: Chem.* **2004**, *223*, 75–83.
7. (a) Ono, M.; Nakamura, Y.; Sato, S.; Itoh, I. *Chem. Lett.* **1988**, *17*, 395–398; (b) Effenberger, F.; Huthmacher, K. *Chem. Ber.* **1976**, *109*, 2315–2326.
8. (a) Alizadeh, M.; Khodaei, M. M.; Nazari, E. *Tetrahedron Lett.* **2007**, *48*, 6805–6808; (b) Khodaei, M. M.; Alizadeh, A.; Nazari, E. *Tetahedron Lett.* **2007**, *48*, 4199–4202; (c) Corey, E. J.; Tian, Y. *Org. Lett.* **2005**, *7*, 5535–5537.
9. Répichet, S.; Le Roux, C.; Dubac, J. *Tetrahedron Lett.* **1999**, *40*, 9233–9237.
10. (a) Lellouche, J.-P.; Koeller, S. *J. Org. Chem.* **2001**, *66*, 693–696; (b) Pan, W.; Dong, D.; Wang, K.; Zhang, J.; Wu, R.; Xiang, D.; Liu, Q. *Org. Lett.* **2007**, *9*, 2421–2423; (c) Ermili, A.; Castro, A. J.; Westfall, P. A. *J. Org. Chem.* **1965**, *30*, 339–343.
11. (a) Effenberger, F.; Epple, G. *Angew. Chem., Int. Ed.* **1972**, *11*, 299–300; (b) Effenberger, F.; Huthmacher, K. *Angew. Chem., Int. Ed.* **1974**, *13*, 409–410.
12. *General procedure for sulfonylation:* A mixture of sulfonamides (0.5 mmol), arenes (1 mmol), triflic anhydride (1 mmol) in 3 mL $Cl_2CHCHCl_2$ was stirred at 120 °C for 12 h. Afterward, the reaction solution was cooled to room temperature and the solvent was removed under reduced pressure. The further purification of the product was achieved by flash chromatography on a silica gel column. Selected spectroscopic data: 4-(4-nitrophenylsulfonyl)biphenyl. White solid; mp 187–188 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) 8.36 (d, J = 8.4 Hz, 2H), 8.17 (d, J = 8.4 Hz, 2H), 8.03 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 6.8 Hz, 2H), 7.41–7.49 (m, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, TMS) 150.6, 147.7, 147.4, 139.0, 138.6, 129.4, 129.2, 129.1, 128.8, 128.5, 127.6, 124.8 ppm; MS (ESI) m/z 362 (100%) $[M+Na]^+$. HRESIMS: m/z calcd for $[M+Na]^+$ $C_{18}H_{13}NSO_4$, 362.0457, found 362.0452.
2-(2,5-Dimethylphenylsulfonyl)thiophene. White solid; mp 129–131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz, TMS) 7.98 (s, 1H), 7.685 (d, J = 3.6 Hz, 1H), 7.63 (d, J = 4.8 Hz, 1H), 7.285 (d, J = 7.2 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.08 (t, J = 4.6 Hz, 1H), 2.55 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, TMS) 143.4, 139.5, 136.9, 135.1, 134.7, 133.5, 133.4, 132.9, 129.5, 127.6, 21.1, 20.0 ppm; MS (ESI) m/z 253 (100%) $[M+H]^+$. HRESIMS: m/z calcd for $[M+Na]^+$ $C_{12}H_{12}S_2O_2$, 275.0171, found 275.0176.