Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6805–6808

Rapid and mild sulfonylation of aromatic compounds with sulfonic acids via mixed anhydrides using Tf_2O

Abdolhamid Alizadeh,* Mohammd Mehdi Khodaei* and Ehsan Nazari

Department of Chemistry, Faculty of Science, Razi University, Kermanshah 67149, Iran

Received 6 May 2007; revised 5 July 2007; accepted 12 July 2007
Available online 21 July 2007

Abstract—An efficient and direct sulfonylation of aromatic compounds with sulfonic acids is described via mixed anhydrides in short reaction times using Tf_2O in nitromethane at room temperature.

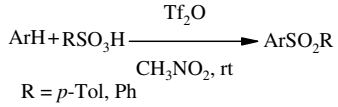
Aryl sulfones are important compounds in industry and organic synthesis.[1] Diaryl sulfones are especially important intermediates for synthesizing pharmaceutical compounds[2] and are potent anti-HIV-1 agents.[3] In addition, they are active against malaria, leishmaniasis, and infections in patients with discoid lupus erythematosus.[4] There are several methods for preparing these compounds, which include the oxidation of sulfides,[5] sulfonylation of arenes using an aryl sulfonyl halide in the presence of Lewis acids,[6] and reaction of sulfonyl fluorides with organometallic reagents.[7] Recently, Olah et al. reported the sulfonylation of aromatic compounds using sulfonic acids in the presence of Nafion-H.[8] Sulfonylation of aromatic compounds with sulfonic acids using Montmorillonite clay,[9] P_2O_5/SiO_2[10] and under microwave irradiation[11] has also been reported. However, there are only a few reports[8–11] in the direct sulfonylation of arenes with sulfonic acids whilst sulfonylation of arenes via mixed anhydrides prepared in situ from a sulfonic acid to the best of our knowledge has not been reported. Therefore, the development of more efficient activating agents, especially those not requiring a catalyst are highly desirable.

In continuation of our studies on electrophilic aromatic substitution,[12] we report the use of triflic anhydride (Tf_2O) for the direct sulfonylation of arenes using sulfonic acids in nitromethane at room temperature (Scheme 1).

We found that Friedel–Crafts type acylation of aromatic compounds with carboxylic acids in the presence of Tf_2O afforded the corresponding ketones in good yields[13] which prompted us to test the efficiency of Tf_2O in the direct sulfonylation of arenes. Mesitylene and *p*-toluenesulfonic acid (*p*-TSA) were chosen as a model arene and sulfonic acid. The reaction of an equimolar (1 mmol, each) mixture of mesitylene and *p*-TSA in the presence of Tf_2O (0.25 ml, 1.5 mmol) proceeded via an exothermic reaction and afforded 2,4,6-trimethylphenylsulfonyl-*p*-methylbenzene in 83% yield, in 10 min at room temperature in nitromethane (Table 1).

Encouraged by this initial success, Friedel–Crafts type sulfonylation reactions were then performed between a variety of arenes and *p*-toluenesulfonic acid to produce symmetrical and unsymmeterical aromatic sulfones. The results summarized in Table 1 highlight the general applicability of this reaction. The reactions of arenes with sulfonic acids yielded the desired sulfonylated products rapidly (5–15 min) and in 32–89% yields.

Anisole reacted with *p*-toluenesulfonic acid under the same reaction conditions to give the corresponding aryl

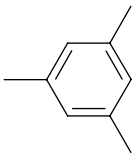
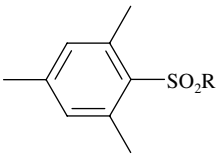
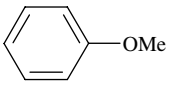
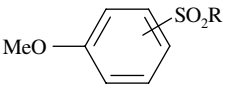
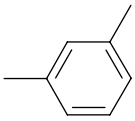
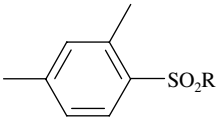
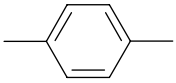
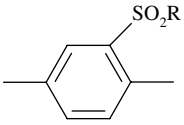
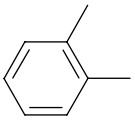
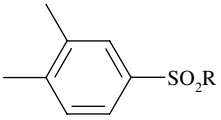
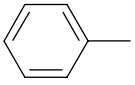
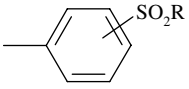
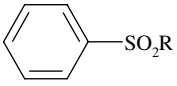


Scheme 1.

Keywords: Sulfonylation; Sulfones; Sulfonic acids; Tf_2O; Aromatic compounds.
* Corresponding authors. Tel.: +98 831 4279296; fax: +98 831 4274559; e-mail addresses: ahalizadeh2@yahoo.com; mmkhoda@razi.ac.ir

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.081

Table 1. Sulfonylation of aromatic compounds with sulfonic acids using Tf_2O in nitromethane

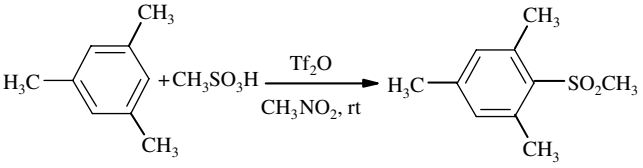
Entry	ArH	R	Product[a]	Time (min)	Yield[b] (%)
1		Tol		10	83
2		Ph		10	75
3		Tol		10	89 *o*:*m*:*p* = 4:2:94
4		Ph		10	80 *o*:*m*:*p* = 4:0:96
5		Tol		10	78
6		Ph		10	70
7		Tol		13	75
8		Ph		15	68
9		Tol		10	74
10		Ph		10	70
11		Tol		5[c]	67 *o*:*m*:*p* = 15:0:85
12		Ph		5[c]	63 *o*:*m*:*p* = 8:0:92
13		Tol		5[c]	38
14		Ph		5[c]	32

[a] The products were characterized by comparison of their spectroscopic data with those reported in the literature.
[b] Isolated yields.
[c] Reaction was carried out at 60 °C.

sulfone as a mixture of isomers in 89% yield. The *p*-isomer was 94% of the product mixture. In the absence of Tf_2O reaction did not proceed, implying that Tf_2O is the promoter.

The reactions of various aromatic compounds with benzenesulfonic acid in the presence of Tf_2O were studied to examine the scope and limitations of the reaction. The results in Table 1 showed that the reactions with less reactive sulfonic acids (benzenesulfonic acid) proceed less well. The reaction of mesitylene with methanesulfonic acid (MsOH) under the same reaction conditions was also studied and the corresponding sulfone was obtained in 45% yield after 30 min (Scheme 2).

A competitive experiment was carried out to assess the selectivity of the reaction. Thus, a mixture of *p*-TsOH and MsOH (1:1) was reacted with mesitylene in the presence of Tf_2O in nitromethane at room temperature. The diaryl sulfone was obtained as the sole product in 82%



Scheme 2.

yield indicating a high selectivity between MsOH and *p*-TsOH. Also, a mixture of anisole and toluene (1:1) was reacted with *p*-TsOH using Tf_2O in nitromethane at room temperature. The results showed that only the corresponding sulfone of anisole was obtained (Table 2).

The yields of the corresponding sulfones from the reactions of benzenesulfonic acid with benzene and toluene were low (32% and 63%) due to insufficient activation of Tf_2O under the relatively mild reaction conditions

Table 2. Competitive reactions on selective sulfonylation

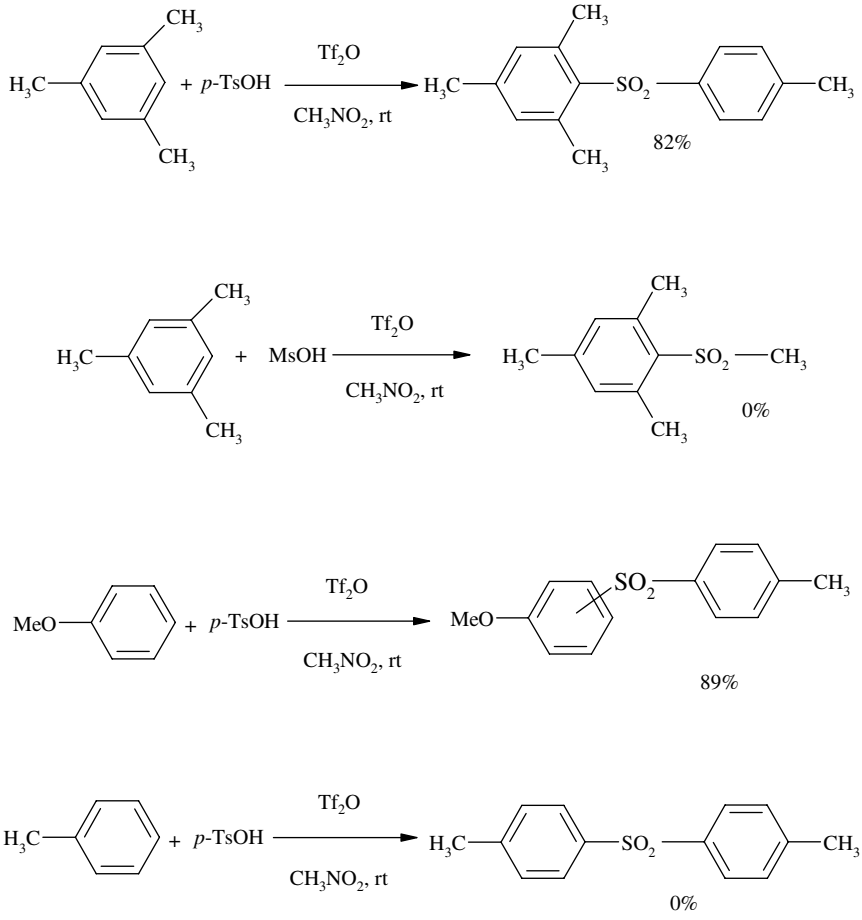


Table 3. Comparison of this method (entry 6) with reported methods for the sulfonylation of aromatic compounds with sulfonylating agent (1 mmol)

Entry	Aromatic compound	Conditions	Time	Yield (%)
1	*p*-Xylene	Nafion H, *p*-TsOH, dry *p*-xylene (8 ml), reflux[8]	8 h	78
2	*p*-Xylene	*p*-TsCl, [bmim]Cl-$AlCl_3$, 30 °C[15]	3 h	87
3	*o*-Xylene	*p*-TsCl, $NaIO_4$, *o*-xylene (2 ml), reflux[16]	4.5 h	82
4	Aniline	H_2SO_4, MW[11]	4 min	93
5	Mesitylene	*p*-TsOH, P_2O_5/SiO_2,mesitylene (1.6 ml), reflux[10]	30 min	85
6	*p*-Xylene	*p*-TsOH, *p*-xylene (1 mmol), nitromethane (2 ml), rt	13 min	75

used. In addition, the boiling point of benzene is low and it may evaporate under the reaction conditions. Sulfonylation of toluene and anisole gave *para* substituted sulfones as the major products indicating that the reaction occurs via electrophilic aromatic sulfonylation. The present method is simple and uses readily available aromatic compounds and sulfonic acids instead of sulfonyl halides. In contrast to other reported methods, no excess of arene was required.

In conclusion, we have described an easy, fast and selective approach to sulfones under mild reaction conditions without any by-product formation.[14] The advantages of Tf_2O over reported reagents for sulfonylation of aromatic compounds are shown in Table 3.

Acknowledgment

The authors thank the Razi University Research Council for financial assistance.

References and notes

1. Roy, K. M. In *Ullmann's Encyclopedia of Industrial Chemistry*; Gerhartz, W., Ed.; VCH: Weinheim, 1985; A25, pp 487–501.
2. McMahan, J. B.; Gulakowsky, R. J.; Weislow, O. S.; Schoktz, 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. (a) Willams, 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.; Brien, J. A.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 1291–1294; (b) Artico, M.; Silvestri, R.; Pagnozzi, E.; Bruno, B.; Novellino, E.; Greco, G.; Massa, S.; Ettorre, A.; Loi, G.; Scintu, F.; La Colla, P. *J. Med. Chem.* **2000**, *43*, 1886–1891.
4. (a) Hastings, R. C.; Franzblau, S. G. *Ann. Rev. Pharmacol. Toxicol.* **1966**, *28*, 231–250; (b) Wozel, G. *Int. J. Dermatol.* **1989**, *28*, 17–21; (c) Lo, J. S.; Berg, R. E.; Tomecki, K. J. *Int. J. Dermatol.* **1989**, *28*, 497–507.
5. Schank, K. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. M. J., Eds.; Wiley: New York, 1998, Chapter 7.
6. (a) Truce, W. E.; Klinger, T. C.; Brand, W. W. In *Organic Chemistry of Sulfur*; Oae, S., Ed.; Plenum Press: New York, 1977; (b) Ueda, M.; Uchiyama, K.; Kano, T. *Synthesis* **1984**, *4*, 323–324; (c) Graybill, B. M. *J. Org. Chem.* **1967**, *32*, 2931–2933.
7. (a) Shirota, Y.; Nagai, T.; Tokura, N. *Tetrahedron* **1969**, *25*, 3193–3204; (b) Frye, L. L.; Sullivan, E. L.; Cusack, K. P.; Funaro, J. M. *J. Org. Chem.* **1992**, *57*, 697–701.
8. Olah, G. A.; Mathew, T.; Parakash, G. K. S. *Chem. Commun.* **2001**, 1696–1697.
9. Choudary, B. M.; Chowdari, N. S.; Kantam, M. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2689–2694.
10. Mirjalali, B. M.; Zolfigol, M. A.; Bamoniri, A.; Khazdooz, L. *Bull. Korean Chem. Soc.* **2003**, *24*, 1009–1010.
11. Li, H.-Z.; Xiao, L.-W.; Li, H.-Y.; Wang, K.-F.; Li, X. *J. Chem. Res. (S)* **2003**, 493–494.
12. (a) Salehi, P.; Khodaei, M. M.; Zolfigol, M. A.; Sirouszadeh, S. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1863–1864; (b) Salehi, P.; Khodaei, M. M.; Zolfigol, M. A.; Zeinoldini, S. *Synth. Commun.* **2003**, *33*, 1367–1373.
13. Khodaei, M. M.; Alizadeh, A.; Nazari, E. *Tetahedron Lett.* **2007**, *48*, 4199–4202.
14. *General procedure for sulfonylation*: To a solution of aromatic compound (1 mmol) and sulfonic acid (1 mmol) in nitromethane (2 ml), Tf_2O (0.25 ml, 1.5 mmol) was added. The reaction was stirred magnetically at room temperature and monitored by TLC. On completion of the reaction, the solvent was evaporated and then aqueous saturated $NaHCO_3$ (20 ml) was added to destroy the unreacted sulfonic acid and Tf_2O. The resulting precipitated crude product was purified by recrystallization from a mixture of dichloromethane and *n*-hexane (1:2) or water and ethanol. Selected spectroscopic data: (2,4,6-Trimethylphenyl)tolylsulfone. White solid; mp 114–116 °C (lit.[17] 117 °C); IR (KBr): 1142, 1299 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.33 (s, 3H), 2.44 (s, 3H), 2.63 (s, 6H), 6.98 (s, 2H), 7.3 (d, $J = 7.9$ Hz, 2H), 7.71 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.9, 21.4, 22.7, 125.9, 126.2, 129.4, 132.1, 139.8, 140.6, 143.1, 143.3. (2,4,6-Trimethylphenyl)phenylsulfone. White solid; mp 78–80 °C (lit.[18] 78–79 °C); IR (KBr): 1152, 1305 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.34 (s, 3H), 2.63 (s, 6H), 6.98 (s, 2H), 7.47–7.58 (m, 3H), 7.83 (d, $J = 7.7$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.9, 21.3, 125.8, 126.1, 128.8, 132.1, 132.5, 133.7, 140.0, 143.3. (2,4,6-Trimethylphenyl)methylsulfone. White solid; mp 122–124 °C (lit.[19] 122–124 °C); IR(KBr): 1136, 1292 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.28 (s, 3H), 2.64 (s, 6H), 3.01 (s, 3H), 6.95 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.6, 22.4, 43.9, 131.8, 134.0, 139.0, 142.8.
15. Nara, S. J.; Harjani, J. R.; Salunkhe, M. M. *J. Org. Chem.* **2001**, *66*, 8616–8620.
16. Bandgar, P. B.; Kamble, V. T. *Chem. Lett.* **2002**, 1066–1067.
17. Graybill, B. M. *J. Org. Chem.* **1967**, *32*, 2931–2933.
18. Jin, T.; Yang, M.; Feng, G.; Li, T. *J. Chem. Res. (S)* **2003**, 721–723.
19. Singh, P. S.; Kamble, R. M.; Chandra, K. L.; Saravanan, P.; Singh, V. K. *Tetrahedron* **2001**, *57*, 241–247.