Journal Pre-proofs

Practical and efficient synthesis of aryl trifluoromethyl sulfones from arylsulfonyl chlorides with Umemoto's reagent II

Xiaocong Zhou, Dufen Hu, Xinyi He, Yuanqiang Li, Youqun Chu, Yuanbin She

PII: S0040-4039(19)31264-X
DOI: https://doi.org/10.1016/j.tetlet.2019.151465
Reference: TETL 151465

To appear in: *Tetrahedron Letters*

Received Date: 18 September 2019
Revised Date: 13 November 2019
Accepted Date: 28 November 2019

Please cite this article as: Zhou, X., Hu, D., He, X., Li, Y., Chu, Y., She, Y., Practical and efficient synthesis of aryl trifluoromethyl sulfones from arylsulfonyl chlorides with Umemoto's reagent II, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.151465

Tetrahedron Letters
journal homepage: www.elsevier.com

Practical and efficient synthesis of aryl trifluoromethyl sulfones from arylsulfonyl chlorides with Umemoto's reagent II

Xiaocong Zhou[a,b], Dufen Hu[b], Xinyi He[b], Yuanqiang Li[b], Youqun Chu [a*], Yuanbin She [a*]

[a] College of Chemical Engineering, Zhejiang University of Technology, Hangzhou, Zhejiang 310014, China
[b] Zhejiang Jiuzhou Pharmaceutical Co. Ltd, Waisha Road 99, Taizhou, Zhejiang 318000, China
E-mail: chuyq@zjut.edu.cn (Y. Chu), sheyb@zjut.edu.cn (Y. She)

ARTICLE INFO

Trifluoromethylation
Sulfonyl chloride
Umemoto's reagent II
Aryl trifluoromethyl sulfones

ABSTRACT

A practical and efficient method for the synthesis of aryl trifluoromethyl sulfones has been developed by a tandem reaction of arylsulfonyl chlorides with Umemoto's reagent II. The advantageous features of this method are simple operation, mild reaction conditions, wide scope of substrates, high yield of products, and easy scalability.

1. Introduction

Aryl trifluoromethyl sulfones are important structural motifs, which are frequently found in bioactive compounds (Figure 1) [1], chiral catalysts [2], and functional materials [3]. Therefore, a series of organic compounds with the structure of aryl trifluoromethyl sulfone have been designed and synthesized as frequent targets of recent synthetic organic chemistry efforts [4]. Many approaches for the preparation of aryl trifluoromethyl sulfones have been reported, such as oxidation of aryl trifluoromethyl sulfides [5], Friedel-Crafts triflylation [6], aryl Grignard reaction to $(CF_3SO_2)_2O$ [7], and nucleophilic trifluoromethylation reaction [8]. Unfortunately, these approaches have several shortcomings such as low yields, narrow substrate scope, use of expensive reagents, and formation of isomeric products, which restrict their extensive application opportunities in multiple industry fields.

To overcome these drawbacks, new Pd- or Cu-catalyzed cross-coupling reactions of diaryliodonium salts [9a], aryldiazonium tetrafluoroborates [9b] or aryl triflates [9c] with $NaSO_2CF_3$ have been developed. However, the low chemoselectivity [9a] and the use of explosive reactants [9b] and toxic and expensive transition metal catalysts [9c] may hinder their development in pharmaceutical and agrochemical industries. Alternative methods based on the trifluoromethylation of sodium arylsulfinates using Yagupolskii's reagent [9d], Togni's reagents [9e] or Umemoto's reagent II [9f] have also been reported. But they still suffer from such disadvantages as high temperature reaction [9d, e], potentially explosive reagents [9e], very narrow substrate application [9d,f], and limited availability of sodium arylsulfinates [9d-f]. Therefore, a practical and efficient synthetic approach for the trifluoromethyl sulfones from readily available arylsulfinyl sources and safe trifluoromethylating agents with broad substrate scope under transition-metal-free and mild conditions is highly desirable.

Arylsulfonyl chlorides are easily commercially available. In the past twenty years, various sulfonylation reactions using arylsulfonyl chlorides have been reported employing Zn [10a-c], In [10d], Fe [10e], Mg [10f] or Na_2SO_3 [10g-i] as a reducing reagent. Among the methods, the sodium sulfite-reduction method is considered as a simple and practical protocol, which shows potential development in pharmaceutical field [10g]. Recently, Qiu's group developed a method for preparation of trifluoromethyl thiolsulphonates from sulfonyl chlorides by a tandem reaction strategy [11]. To the best of our knowledge, the preparation of aryl trifluoromethyl sulfones from sulfonyl chlorides by the tandem reaction method has not been reported. As a continuation of our eager interest into synthetic pathways to trifluoromethylated compounds using Umemoto's reagent [12], we herein report a practical and efficient approach for the synthesis of aryl trifluoromethyl sulfones from inexpensive and readily available arylsulfonyl chlorides and safe Umemoto's reagent II (**2a**) that is commercially easily available at a large scale.

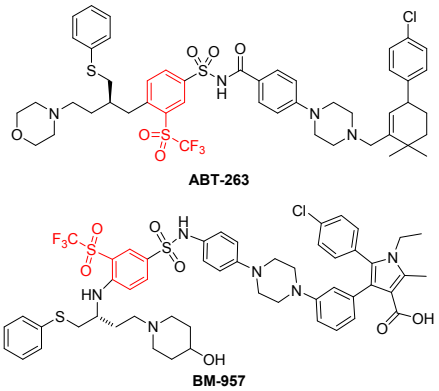
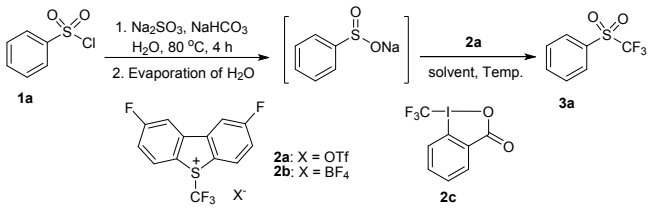


Figure 1. Structures of biologically active aryl trifluoromethyl sulfones.



Scheme 1. Synthesis of phenyl trifluoromethyl sulfone **3a**

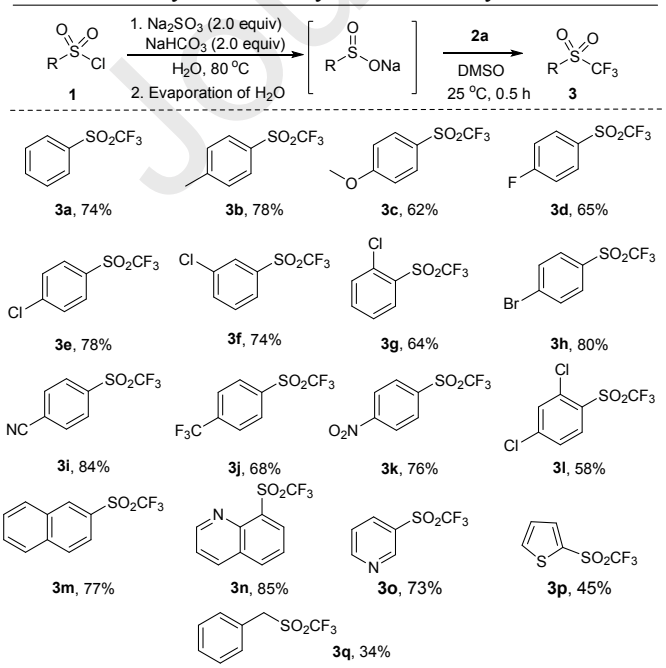
Initially, we began our investigation with phenylsulfonyl chloride **1a** and CF_3^+ reagent **2a**, Umemoto's reagent II, as the model reaction, in which DMSO was used as a solvent for the trifluoromethylation step (**Scheme 1**). To our delight, the formation of the desired sulfone **3a** (68% yield) could be evidenced by the ^{1}H and ^{19}F NMR spectroscopic analysis of the crude reaction mixture-(**Table 1**, entry 1). **2.** the trifluoromethylation was investigated (**Table** 1, entries 1-5). DMSO was found to be the best choice, while other solvents such as DMF, DMA, DCM and toluene were less effective. Next, different CF_3^+ reagents **2b** and **2c** (Togni's reagent) were investigated (entries 6-7). **2a** and **2b** were almost the same yields, but **2c** was low yield. Thus, **2a** was the best reagent since **2a** was directly prepared by the one-pot method [9f]. Furthermore, the molar ratios of **1a**/Na_2SO_3/$NaHCO_3$/**2a** were investigated (entries 6-9). Increasing the loading of **2a** from 1.0 equiv to 1.5 equiv did not show any improvement. A molar ratio of **1a**/Na_2SO_3/$NaHCO_3$/**2a** = 1.5:3:3:1 provided 81% yield (entry 10). Furthermore, by the examination of the reaction temperature and reaction time (entries 12-15), it was found that 82% yield could be achieved at 25°C in a short time (30 min) (entry 14).

Table 1. Optimization of reaction conditions.[a]

Entry	Solvent	Molar Ratio **1a**/Na_2SO_3/$NaHCO_3$/**2a**	T (°C)	Time	^{19}F NMR yield [b] (%)
1	DMSO	1:2:2:1	25	1 h	68
2	DMF	1:2:2:1	25	1 h	55
3	DMA	1:2:2:1	25	1 h	50
4	DCM	1:2:2:1	25	1 h	n.d.
5	toluene	1:2:2:1	25	1 h	n.d.
6[c]	DMSO	1:2:2:1	25	1 h	66
7[d]	DMSO	1:2:2:1	25	1 h	48
8	DMSO	1:2:2:1.5	25	1 h	70
9	DMSO	1.3:2.6:2.6:1	25	1 h	76
10	DMSO	1.5:3:3:1	25	1 h	81
11	DMSO	2:4:4:1	25	1 h	81
12	DMSO	1.5:3:3:1	50	1 h	60
13	DMSO	1.5:3:3:1	80	1 h	32
14	DMSO	1.5:3:3:1	25	30 min	82 (74)
15	DMSO	1.5:3:3:1	25	15 min	79

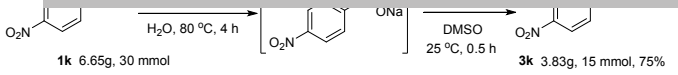
[a] Reaction conditions: a mixture of **1a**, Na_2SO_3, $NaHCO_3$ in 5 mL of H_2O was stirred at 80 °C for 4 h in a *Schlenk tube* and the H_2O was evaporated, and then 5 mL of a solvent and 1 mmol of **2a** were added.
[b] Yields were determined by ^{19}F NMR using *p*-$ClC_6H_4CF_3$ as an internal standard. The isolated yield is reported in parentheses.
[c] Tetrafluoroborate **2b** was used.
[d] Togni's reagent **2c** was used as a CF_3 reagent.

Table 2. Synthesis of aryl trifluoromethyl sulfones.



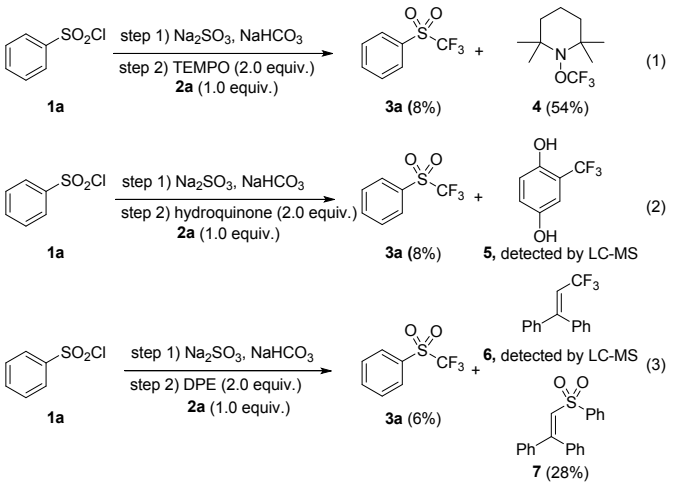
[a] Reaction conditions: a mixture of **1a**, Na_2SO_3, $NaHCO_3$ in 5 mL of H_2O was stirred at 80 °C for 4 h in a *Schlenk tube* and the H_2O was evaporated, and then 5 mL of DMSO and 1 mmol of **2a** were added.
[b] Isolated yield.

Under the optimized reaction conditions, the scope of arylsulfonyl chlorides was investigated (**Table 2**). The sulfonyl chlorides possessing electron-donating and electron-withdrawing groups afforded the corresponding products in moderate to excellent isolated yields. Halogens on the sulfonyl chlorides were well tolerated, providing good yields of desired products (**3e**−**h**), which may be suitable for further functionalization. However, the chlorine substituent on the *ortho*-position resulted in a lower yield than that on the *para*- and *meta*-positions, which may be attributed to the effect of steric hindrance. Disubstituted arylsulfonyl chloride **1l** was also compatible under the standard reaction conditions. It should be noted that heteroarylsulfonyl chlorides such as quinoline-8-sulfonyl chloride, pyridine-3-sulfonyl chloride and thiophene-2-sulfonyl chloride afforded the appropriate products (**3n, 3o, 3p**) in 85, 73, and 45% isolated yields, respectively. In addition, aliphatic sulfonyl chloride **3q** was also able to afford the desired product (34%).



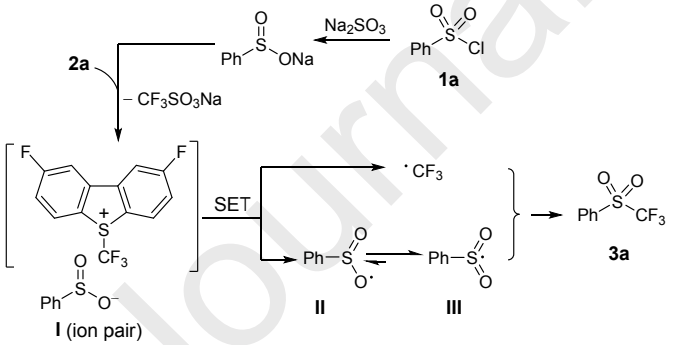
Scheme 2. Gram-scale synthesis of **3k**.

To demonstrate the practicability and scalability of our method, a gram-scale reaction was performed with **1k** and **2a** under the optimized conditions. To our delight, the present reaction provided 4-nitrophenyl trifluoromethyl sulfone **3k** in 75% yield (3.83 g), indicating an excellent potential application for large scale synthesis (**Scheme 2**).



Scheme 3. Experiment for mechanistic study.

To gain an insight into the reaction mechanism, several control experiments were carried out **(Scheme 3**). When 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and hydroquinone were added as radical scavengers, CF_3 radical was trapped and the trifluoromethylation reaction was greatly retarded **(Scheme 3**, eq. 1 and eq. 2) [13]. Significantly, when 1,1-diphenylethylene (DPE) was added, phenylsulfonyl-coupling product **7** [14] was isolated in 28% yield (**Scheme 3**, eq. 3). This strongly indicated that phenylsulfonyl radical was generated in the reactions in addition to the CF_3 radical.



Scheme 4. Proposed mechanism.

Based on the above results, a possible reaction pathway can be proposed as seen in **Scheme 4**. Sodium benzenesulfinate resulting from **1a** [15] undertakes counteranion-replacement with **2a** to give ion pair **I** [16], since the sulfinate anion is much more nucleophilic than triflate anion. Then, **I** provides a CF_3 radical and benzenesulfinate radical **II** through single electron transfer (SET). As benzenesulfinate radical **II** turns into sulfonyl radical **III** [17], radical cross-coupling between **III** and CF_3 radical takes place to form **3a** [16].

In summary, we have developed a simple and effective procedure for the practical preparation of aryl trifluoromethyl sulfones from readily available arylsulfonyl chlorides and safe Umemoto's reagent II under mild conditions. By means of this, a series of aryl trifluoromethyl sulfones could be synthesized in high yields. Thus, this approach may lead to many aryl trifluoromethyl sulfones which are important structural motifs of biologically active, chiral catalysts, and functional materials. The exploration of further applications of this method is ongoing in our lab.

Conflicts of interest

There are no conflicts to declare.

Acknowledgments

These investigations were supported by Zhejiang Jiuzhou Pharmaceutical Co. Ltd. We thank Dr. Teruo Umemoto for technical instruction for the reaction with his Umemoto's reagent and for reviewing the manuscript.

References and notes

1. (a) Park, C. -M.; Bruncko, M.; Adickes, J.; Bauch, J.; Ding, H.; Kunzer, A.; Marsh, K. C.; Nimmer, P.; Shoemaker, A. R.; Song, X.; Tahir, S. K.; Tse, C.; Wang, X.; Wendt, M. D.; Yang, X.; Zhang, H.; Fesik, S. W.; Rosenberg, S. H.; Elmore, S. W. *J. Med. Chem*. **2008**, *51*, 6902. (b) Chen, J.; Zhou, H.; Aguilar, A.; Liu, L.; Bai, L.; McEachern, D.; Yang, C.-Y.; Meagher, J. L.; Stuckey, J. A.; Wang, S. *J. Med. Chem*. **2012**, *55*, 8502. (c) Tanaka, Y.; Aikawa, K.; Nishida, G.; Homma, M.; Sogabe, S.; Igaki, S.; Hayano, Y.; Sameshima, T.; Miyahisa, I.; Kawamoto, T.; Tawada, M.; Imai, Y.; Inazuka, M.; Cho, N.; Imaeda, Y.; Ishikawa, T. *J. Med. Chem*. **2013**, *56*, 9635.
2. (a) Kargbo, R.; Takahashi, Y.; Bhor, S.; Cook, G. R.; Lloyd-Jones, G. C.; Shepperson, I. R. *J. Am. Chem. Soc*. **2007**, *129*, 3846. (b) Barta, K.; Franciò, G.; Leitner, W.; Lloyd-Jones, G. C.; Shepperson, I. R. *Adv. Synth. Catal*. **2008**, *350*, 2013.
3. (a) Porrès, L.; Mongin, O.; Katan, C.; Charlot, M.; Pons, T.; Mertz, J.; Blanchard-Desce, M. *Org. Lett*. **2004**, *6*, 47. (b) Le Droumaguet, C. L.; Mongin, O.; Werts, M. H. V.; Blanchard-Desce, M. *Chem. Commun*. **2005**, 2802. (c) Mongin, O.; Porrès, L.; Charlot, M.; Katan, C.; Blanchard-Desce, M. *Chem. - Eur. J*. **2007**, *13*, 1481.
4. (a) Xu, X. -H.; Matsuzaki, K.; Shibata, N. *Chem. Rev*. **2015**, 115, 731. (b) Zhao, X.; Huang, Y.; Qing, F.-L.; Xu, X. -H. *RSC Adv*. **2017**, *7*, 47.
5. (a) Chen, Q.-Y.; Duan, J.-X. *J. Chem. Soc., Chem. Commun*. **1993**, 918. (b) Liang, X.; Cheng, J.; Trudell, M. L. *J. Org. Chem*. **2003**, *68*, 5388−5391. (c) Su, W. *Tetrahedron Lett*. **1994**, *35*, 4955. (d) Kirsch, P.; Lenges, M.; Kühne, D.; Wanczek, K.-P. *Eur. J. Org. Chem*. **2005**, 797.
6. Hendrickson, J. B.; Bair, K. W. *J. Org. Chem*. **1977**, *42*, 3875.
7. Creary, X. *J. Org. Chem*. **1980**, *45*, 2727.
8. (a) Movchun, V. N.; Kolomeitsev, A. A.; Yagupolskii, Y. L. *J. Fluorine Chem*. 1995, *70*, 255. (b) Singh, R. P.; Cao, G.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem*. **1999**, *64*, 2873. (c) Chang, Y.; Cai, C. *J. Fluorine Chem*. **2005**, *126*, 937.
9. (a) Cullen, S. C.; Shekhar, S.; Nere, N. K. *J. Org. Chem*. **2013**, *78*, 12194−12201. (b) Zhang, K.; Xu, X.-H.; Qing, F.-L. *J. Org. Chem*. **2015**, *80*, 7658. (c) Smyth, L. A.; Phillips, E. M.; Chan, V. S.; Napolitano, J. G.; Henry, R.; Shekhar, S. *J. Org. Chem*. **2016**, *81*, 1285. (d) Yagupolskii, L. M.; Matsnev, A. V.; Orlova, R. K.; Deryabkin, B. G.; Yagupolskii, Y. L. *J. Fluorine Chem*. **2008**, *129*, 131. (e) Lin, X.; Wang, G.; Li, H.; Huang, Y.; He, W.; Ye, D.; Huang, K.-W.; Yuan, Y.; Weng, Z. *Tetrahedron* **2013**, *69*, 2628. (f) Umemoto, T.; Zhang, B.; Zhu, T.; Zhou, X.; Zhang, P.; H, Song.; Li, Y. *J. Org. Chem.* **2017**, *82*, 7708.
10. (a) Sun, P. P.; Wang, L.; Zhang, Y. M. Tetrahedron Lett. **1997**, *38*, 5549. (b) Chumachenko, N.; Sampson, P. *Tetrahedron* **2006**, *62*, 4540−4548. (c) Bao, P.; Wang, L.; Liu, Q.; Yang, D.; Wang, H.;

Sun, X.-H.; Wang, L.; Zhang, Y.-M. *Synth. Commun.* **1998**, *28*, 1785. (e) Saikia, P.; Laskar, D. D.; Prajapati, D.; Sandhu, J. S. *Chem. Lett.* **2001**, 512. (f) Fu, Y.; Xu, Q.-S.; Li, Q.-Z.; Du, Z.; Wang, K.-H.; Huang, D.; Hu, Y. *Org. Biomol. Chem*., **2017**, *15*, 2841. (g) Chen, J. J.; Nugent, T. C.; Lu, C. V.; Kondapally, S.; Giannousis, P.; Wang, Y.; Wilmot, J. T. *Org. Proc. Res. Dev*. **2003**, *7*, 313. (h) Antane, S.; Bernotas, N.; Li, Y.; McDevitt, R.; Yan, Y. *Synth. Commun*. **2004**, *34*, 2443. (i) Ragni, R.; Orselli, E.; Kottas, G. S.; Omar, O. H.; Babudri, F.; Pedone, A.; Naso, F.; Farinola, G. M.; De Cola, L. *Chem. Eur. J*. **2009**, *15*, 136.

11. Li, Y.; Qiu, G.; Wang, H.; Sheng, J. *Tetrahedron* **2017**, *58*, 690.
12. Zhou, X.; Li, G.; Shao, Z.; Fang, K.; Gao, H.; Li, Y.; She, Y. *Org. Biomol. Chem.* **2019,** *17*, 24.
13. The reactions using 1,4-dinitrobenzene and BHP as radical scavengers were carried out. With these scavengers, mild inhibition of the product ($PhSO_2CF_3$) was observed (see the supporting information).
14. (a) Gao, Y.; Mei, H.; Han, J. L.; Pan, Y. *Chem. - Eur. J*. **2018**, *24*, 17205. (b) Gao, Y.; Wu, W.-Q.; Huang, Y.-B.; Huang, K.-F; Jiang, H.-F. *Org. Chem. Front*. **2014**, *1*, 361.

Chem - Eur. J. **2011**, *17*, 1996. (b) Wei, W.; Liu, C.; Yang, D.; Wen, J.; You, J.; Wang, H. *Adv. Synth. Catal*. **2015**, *357*, 987.

16. Gietter-Burch, A. A. S.; Devannah, V.; Watson, D. A. *Org. Lett.* **2017**, *19,* 2957.
17. (a) Lu, Q.; Zhang, J.; Wei, F.; Qi, Y.; Wang, H.; Liu, Z.; Lei, A. W. *Angew. Chem., Int. Ed*. **2013**, *52*, 7156. (b) Lu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H.; Lei, A. W. *J. Am. Chem. Soc.* **2013**, *135*, 11481.

Supplementary Material

Supplementary Material

Supplementary data (general information and experimental procedures) associated with this article can be found.