Generation of Trifluoromethyl Thiolsulphonate Through One-pot Reaction of Sulfonyl Chloride and Trifluoromethanesulfonanylamides

Yuewen Li, Guanyinsheng Qiu, Hailong Wang, Jie Sheng

PII: S0040-4039(17)30030-8
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.01.018
Reference: TETL 48521

To appear in: *Tetrahedron Letters*

Received Date: 31 December 2016
Accepted Date: 6 January 2017

Please cite this article as: Li, Y., Qiu, G., Wang, H., Sheng, J., Generation of Trifluoromethyl Thiolsulphonate Through One-pot Reaction of Sulfonyl Chloride and Trifluoromethanesulfonanylamides, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.01.018

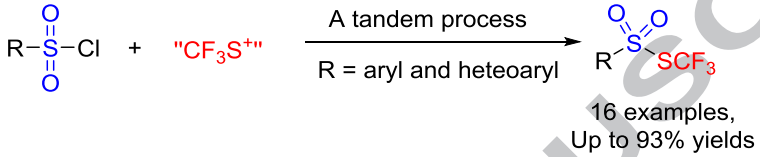
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Generation of Trifluoromethyl thiolsulphonates Through One-pot Reaction of Sulfonyl Chloride and Trifluoromethanesulfanylamide

Leave this area blank for abstract info.

Yuewen Li, Guanyinsheng Qiu*, Hailong Wang, and Jie Sheng*



16 examples,
Up to 93% yields

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Generation of Trifluoromethyl Thiolsulphonate Through One-pot Reaction of Sulfonyl Chloride and Trifluoromethanesulfonanylamides

Yuewen Li,[a] Guanyinsheng Qiu,[a]* Hailong Wang,[a] and Jie Sheng,[b]*

[a] *College of Biological, Chemical Science and Engineering, Jiaxing University, 118 Jiahang Road, Jiaxing 314001, China.*
[b] *College of Food Sciencee and Technology, Shanghai Ocean University, 999 Huchenghuan Road, Shanghai, China.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Sulfinate
Electrophilic trifluoromethylthiolation
Trifluoromethanesulfanylamide
Trifluoromethyl thiolsulphonate
Tandem reaction

ABSTRACT

A novel and efficient tandem reaction of sulfonyl chloride and trifluoromethylsulfanylamide is described here for the synthesis of various trifluoromethyl thiolsulphonates with a broad functional group tolerance. In the process, it is believed that sulfinate generated from sulfonyl chloride is a critical intermediate and the additive 4-methylbenzenesulfonic acid (*p*-TsOH) facilitates the formation of "CF_3S^+". Electrophilic trifluoromethylthiolation of *in situ* generated sulfinate and "CF_3S^+" provides the final products.

It was generally accepted that organic fluorine chemistry was one of the hottest fields in organic chemistry.[1-5] Consequently, tremendous efforts were made on introducing fluoro-containing building blocks into final products, and an unprecedented progress on fluorine chemistry (especially, synthetic fluorine chemistry) has been achieved so far.[2] Among these established achievements, it's well-known that trifluoromethylthiolation could be reached through three major pathways, which were generally concluded as electrophilic trifluoromethylthiolation,[3] nucleophilic trifluoromethylthiolation,[4] and radical trifluoromethylthiolation,[5] respectively. Interestingly, a particular emphasis was put on incorporating "CF_3S" motif into organic molecules by electrophilic trifluoromethylthiolation, probably attributing to its abundant accessibility of trifluoromethylthiolating reagents (Figure 1).

As a privileged core, trifluoromethyl thiolsulphonate was a kind of important compounds in medicinal chemistry due to its potential bioactivity against fungal infections.[6] According to the findings from Weidner and co-workers, trifluoromethyl thiolsulphonate showed much higher antifungal activity than that of alkyl, aryl, and trichloromethyl thiolsulphonates, respectively.[6a] Traditionally, synthesis of this useful architecture resorted to the use of moisture-sensitive zinc sulfinate and toxic "CF_3S" reagents (such as CF_3SCl).[6b] Its generality and application on synthetic chemistry was thus restricted, perhaps because the availability of sulfinates was commercially inadequate and the nature of trifluoromethylthiolating reagent was toxic. To date, it remained rare that the synthesis of trifluoromethyl thiolsulphonate was realized from simple substrates under mild conditions. Considering its great application potential, it's highly desirable to develop a mild procedure for the synthesis of trifluoromethyl thiolsulphonate with high efficiency.

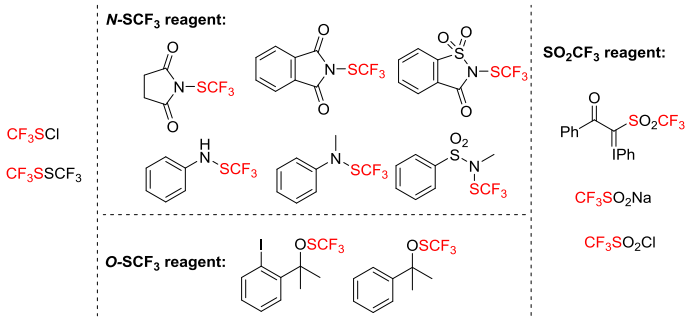
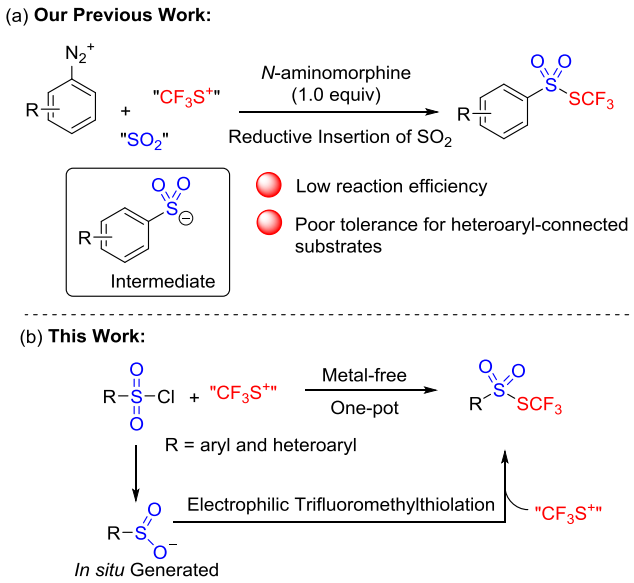


Figure 1 Electrophilic trifluoromethylthiolating reagents

* G. Qiu, Tel.: +86-0573-83642057; fax: +86-0573-83642057; e-mail: 11110220028@fudan.edu.cn
* J. Sheng, Tel.: +86-021-88120380; fax: +86-021-88120380; e-mail: jsheng@shou.edu.cn



Scheme 1 Proposed route for the synthesis of trifluoromethyl thiolsulphonates via electrophilic trifluoromethylthiolation

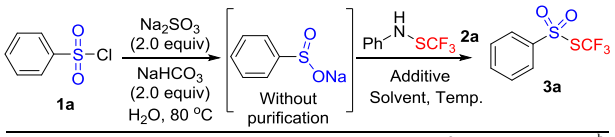
Starting from aniline, an elegant protocol was highlighted by our group for the preparation of trifluoromethyl thiolsulphonate (Scheme 1a).[7] Distinctively, sulfonyl group in trifluoromethyl thiolsulphonate was installed through reductive insertion of sulfur dioxide. In the process, a tandem pathway involving diazotization of aniline, radical sulfur dioxide fixation, and electrophilic trifluoromethylthiolation contributed to providing trifluoromethyl thiolsulphonate. Based on the results from control experiments, sulfinate was postulated as a critical intermediate. Unfortunately, our methodology mentioned above always suffered from relatively low reaction efficiency, thus producing trifluoromethyl thiolsulphonate in moderate yields. Besides, heteroaryl-connected trifluoromethyl thiolsulphonate was not achieved by this strategy. As a consequence, to modify this protocol is highly desirable for improving reaction efficiency and widening reaction scope (especially for heteroaryl-substituted substrate). As a part of our program on constructing a library of potential bioactive molecules with privileged structural core through tandem reaction[8] and in light of rich commercial availability of sulfonyl chloride, we would like to explore preparation of trifluoromethyl thiolsulphonate from sulfonyl chloride by a tandem reaction strategy.

From our previous result and Shen's work, it's well-known that the sulfinate-based electrophilic trifluoromethylthiolation can produce trifluoromethyl thiolsulphonate with high efficiency. Acceptably, sulfonyl chloride could offer sulfinate by means of a Na_2SO_3-based reduction.[9] Therefore, it seemed rationally reliable that *in situ* generation of sulfinate from sulfonyl chloride and electrophilic trifluoromethylthiolation could be combined in an one-pot fashion for the synthesis of trifluoromethyl thiolsulphonate (Scheme 1b). Compared to our previous findings described in Scheme 1a, this projected protocol avoided the use of Lewis acid (bismuth chloride) and reaction operation was relatively practical. More importantly, this tandem process was herein performed with an aim to address the two unsettled issues (reaction efficiency and reaction scope) mentioned in Scheme 1a for the synthesis of trifluoromethyl thiolsulphonate. Considering our continuous interests in smuggling "CF_3S" group in the final product using *N*-SCF_3 reagent,[7,10] we employed *N*-phenyl-*S*-(trifluoromethyl) thiohydroxylamine **2a** as the electrophilic trifluoromethylthiolating reagent in this paper.

To verify possibility of this tandem process, the reaction of phenyl sulfonyl chloride **1a** and *N*-phenyl-*S*-(trifluoromethyl) thiohydroxylamine **2a** was selected as model reaction. To the best of our knowledge, sulfinate salt could be derived from sulfonyl chloride and sodium sulfite (Na_2SO_3) in water at 80 °C with extremely high efficiency. As a result, herein *in situ* generation of sulfinate was not optimized. After evaporation of the solvent H_2O, the *in situ* generated sulfinate was directly employed into the sequential step without further purification. During the reaction optimization, we were pleased to find that the reaction of *in situ* generated sulfinate and **2a** gave rise to a desired product **3a** in 48% isolated yield when the reaction was treated with an additive bismuth chloride ($BiCl_3$, 2.5 equiv) at 80 °C in acetonitrile (entry 1, table 1). Change of the additive to $FeCl_3$ and $BF_3{\cdot}Et_2O$ was not favorable for the formation of **3a** (entries 2-3, table 1). According to the previous findings from Shen's group, it seemed that protonic acid could promote electrophilic trifluoromethylthiolation of sulfinate. Consequently, acetic acid and 4-methylbenzenesulfonic acid (*p*-TsOH) were used as the additive. To our delight, the use of *p*-TsOH greatly improved the reaction efficiency, leading to the final product **3a** in 70% yield (entry 5, table 1). A control experiment without the additive implied that the additive was pivotal for the formation of the final product **3a** (entry 1, table 1). We then explored the solvent effect. Pleasingly, the use of 1, 2-dichloroethane improved the yield to 79% (entry 7, table 1). Other solvents such as toluene, *N*, *N*-dimethylamide, tetrahydrofuran, and dimethyl sulfoxide did not provide better results (entries 8-11, table 1). Decrease of reaction temperature facilitated the reaction. For example, the reaction afforded the final product **3a** in 85% yield when the reaction proceeded at 50 °C (entry 12, table 1). Further reduction of temperature to room temperature offered the desired product **3a** in 90% yield (entry 13, table 1). The reactions were retarded when loading of either *p*-TsOH or $PhNHSCF_3$ was decreased (entries 14-15, table 1).

To the best of our knowledge, Shen's group employed Shen's trifluoromethylthiolating reagent (a stable and easy-to- handle O-

Table 1 Initial studies for electrophilic trifluoromethylthiolation of sodium sulfinate **1a** with trifluoromethanesulfanylamide **2a** [a]



Entry	Additive	Solvent	Temp. (°C)	Yield (%)[b]
1	$BiCl_3$	MeCN	80	48
2	$FeCl_3$	MeCN	80	32
3	$BF_3{\cdot}Et_2O$	MeCN	80	42
4	HOAc	MeCN	80	56
5	*p*-TsOH	MeCN	80	70
6	-	MeCN	80	N.R.
7	*p*-TsOH	DCE	80	79
8	*p*-TsOH	Toluene	80	72
9	*p*-TsOH	DMF	80	36
10	*p*-TsOH	THF	80	61
11	*p*-TsOH	DMSO	80	49
12	*p*-TsOH	DCE	50	85
13	***p*-TsOH**	**DCE**	**rt**	**90**
14[c]	*p*-TsOH	DCE	rt	79
15[d]	*p*-TsOH	DCE	rt	87

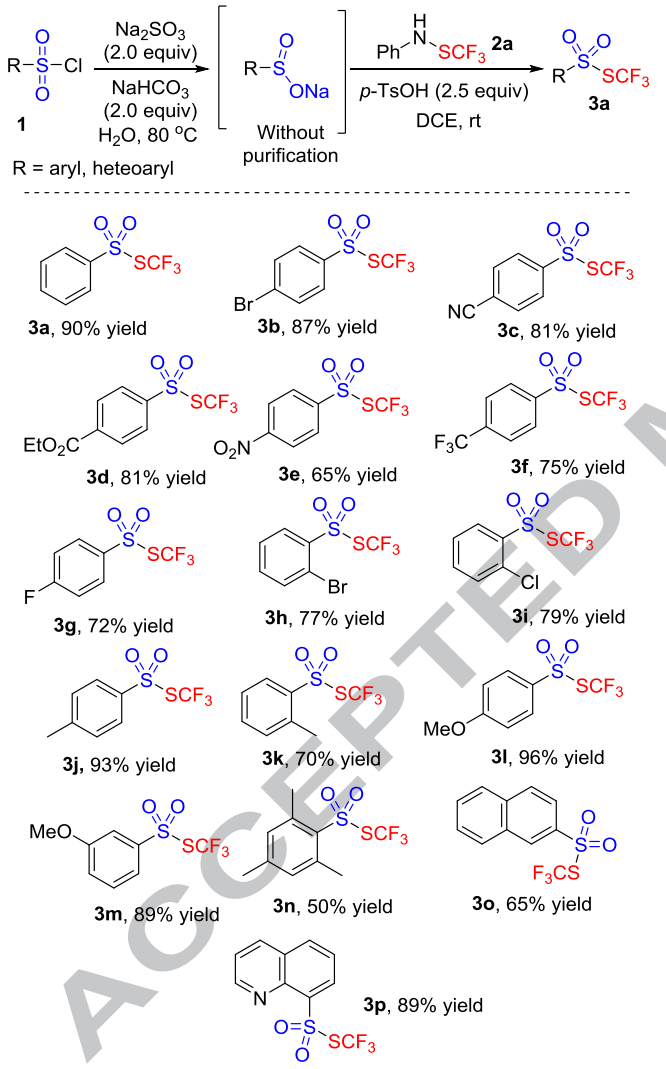
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), additive (2.5 equiv), 8 hrs. [b] Isolated yield based on sulfinate **1a**. [c] 1.5 equiv *p*-TsOH. [d] 1.3 equiv $PhNHSCF_3$. *p*-TsOH: 4-methylbenzenesulfonic acid; DCE = 1,2-dichlorethane; N. R. = no reaction

SCF_3 reagent) to prepare trifluoromethyl thiolsulphonate as well.[11a] Different from the traditional protocol,[6] Shen's methodology avoided the use of gaseous and toxic CF_3SCl as a trifluoromethylthiolating reagent, and employed bench-stable sodium sulfinate as a reaction partner.

Our method described here served as a supplementary of Shen's work and our previous result, and relatively simple reaction operation and easy substrate's accessibility of our method were impressive.

With the above conditions in hand, we then examined the scope. The results were illustrated in Table 2. A series of

Table 2 Synthesis of trifluoromethyl thiolsulphonate through electrophilic trifluoromethylthiolation of sodium sulfinate 1 with trifluoromethanesulfanylamide 2a a



a Isolated yield based on sulfinate 1.

trifluoromethyl thiolsulphonate **3** were constructed as expected. For example, the substrates with methyl, methoxyl, fluoro, chloro, bromo, cyano, and trifluoromethyl were compatible for the reactions, producing corresponding trifluoromethyl thiolsulphonate **3** in 70-96% yields. The ester group was also tolerated, and the corresponding thiolsulphonate **3d** was obtained in 81% yield, while that of 4-nitro-connected substrate produced the desired product **3e** in 65% yield. Interestingly, the reaction of 4-toluenesulfonyl chloride afforded the desired sulphonate **3j** in 93% yield, while the reaction of 2-toluenesulfonyl chloride was greatly suppressed, leading to the corresponding product **3k** in 70% yield. This result is probably attributed to the effect of steric hindrance in the substrate. To support this conclusion, the reaction of 2, 4, 6-trimethylbenzenesulfonyl chloride was carried out under standard conditions. As expected, the reaction yield was decreased to 50%. Additionally, the substrates with naphthalene and heterocycles were also tested accordingly. To our delight, the corresponding products **3o** and **3p** were achieved in good yields. The reaction using *N*-methyl-*N*-phenyl-S-(trifluoromethyl)thiohydroxylamine was conducted as well, and **3a** was observed in a similar yield.

In conclusion, we have developed an alternative route for the generation of trifluoromethyl thiolsulphonate from sulfonyl chloride. The reaction proceeded smoothly under mild reaction conditions and an array of trifluoromethyl thiolsulphonate was achieved with high efficiency and excellent functional group tolerance. A tandem process comprised by *in situ* generation of sulfinate and electrophilic trifluoromethylthiolation was involved in the reaction.

Acknowledgments

Financial supports from the Natural Science Foundation of China (No: 21502069), the Natural Science Foundation of Zhejiang Province (No: LQ15B020006) and the Ph.D. Scientific Research Starting Foundation of Jiaxing University (No: 70515015) and Shanghai Ocean University (No. A2-0203-00-100338) are gratefully acknowledged. Generous support of human resources from Prof. Jie Wu (Fudan University, China) is very gratefully acknowledged.

References and notes

1. For the selected examples, see: (a) Preshlock, S.; Tredwell, M.; Gouverneur, V. *Chem. Rev.*, **2016**, *116*, 719; (b) Buckingham, F.; Gouverneur, V. *Chem. Sci.*, **2016**, *7*, 1645; (c) Serguchev, Y.; Ponomarenko, M.; Ignat'ev N. *J. Fluorine, Chem.*, **2016**, *185*, 1; (d) Yerien, D.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem.*, **2016**, *14*, 8398; (e) Kirsch, P. *J. Fluorine Chem.*, **2015**, *177*, 29; (f) O'Hagan, D.; Deng, H. *Chem. Rev.*, **2015**, *115*, 634; (g) Pace, C.; Gao, J. *Acc. Chem. Res.*, **2013**, *46*, 907; (h) Merkel, L.; Budisa, N. *Org. Biomol. Chem.*, **2012**, *10*, 7241; (i) Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J. *Chem. Soc. Rev.*, **2011**, *40*, 3496;

2. For the selected reviews, see: (a) Chatalova-Sazepin, C.; Hemelaere, R.; Paquin, J.-F.; Sammis, G. *Synthesis*, **2015**, *47*, 2554; (b) Chen, P.; Liu, G. *Eur. J. Org. Chem.*, **2015**, 4295; (c) Champagne, P.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.*, **2015**, *115*, 9073; (d) Neumann, C.; Ritter, T. *Angew. Chem., Int. Ed.*, **2015**, *54*, 3216; (e) Besset, T.; Poisson, T.; Pannecoucke, X. *Chem.-Eur. J.*, **2014**, *20*, 16830; (f) Hennecke, U. *Angew. Chem., Int. Ed.*, **2012**, *51*, 4532; (g) Qiu, X.-L.; Qing, F.-L. *Eur. J. Org. Chem.*, **2011**, 3261; (h) Grushin, V. V. *Acc. Chem. Res.*, **2010**, *43*, 160; (i) Gao, P.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. *Chem.-Eur. J.*, **2015**, *21*, 7648; (j) Chu, L.; Qing, F.-L. *Acc. Chem. Res.*, **2014**, *47*, 1513; (k) Egami, H.; Sodeoka, M. *Angew. Chem. Int. Ed.*, **2014**, *53*, 8294; (l) Studer, A. *Angew. Chem., Int. Ed.*, **2012**, *51*, 8950; (m) Wu, X.-F.; Neumann, H.; Beller, M. *Chem.-An Asian J.*, **2012**, *7*, 1744; (n) Furuya, T.; Kamlet, A. S.; Ritter T. *Nature*, **2011**, *473*, 470; (o) Ma, J.-A.; Cahard, D.; *Chem. Rev.*, **2004**, *104*, 6119;

3. For selected examples, see:(a) Barata-Vallejo, S.; Bonesi, S.; Postigo, A. *Org. Biomol. Chem*. **2016**, *14*, 7150; (b) Toulgoat, F.; Alazet, S.; Billard, T. *Eur. J. Org. Chem*. **2014**, 2415; (c) Ni, C.; Hu, M.; Hu, J. *Chem. Rev*. **2015**, *115*, 765; (d) Xu, X.-H.; Matsuzaki, K.; Shibata, N. *Chem. Rev*. **2015**, *115*, 731; (e) Yang,

X.; Wu, T.; Phipps, R. J.; Toste, F. D. *Chem. Rev*. **2015,** *115*, 826; (f) Shao, X.; Xu, C.; Lu, L.; Shen, Q. *Acc. Chem. Res*. **2015**, *48*, 1227; (g) Sheng, J.; Li, S.; Wu, J.; *Chem. Commun*. **2014**, *50*, 578; (h) Chen, D.-Q.; Gao, P.; Zhou, P-X.; Song, X.-R.; Qiu, Y.-F.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun*. **2015**, *51*, 6637.

4. For examples, see: (a) Teverovskiy, G.; Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2011**, *50*, 7312; (b) Zhang, C.-P.; Vicic, D. A.; *J. Am. Chem. Soc*. **2012**, *134*, 183; (c) Adams, D. J.; Clark, J. H. *J. Org. Chem*. **2000**, *65*, 1456; (d) Xu, J.-X.; Mu, X.; Chen, P.-H.; Ye, J.-X.; Liu, G.-S. *Org. Lett*. **2014**, *16*, 3942; (f) Hu, M.-Y.; Rong, J.; Miao, W.-J.; Ni, C.-F.; Han, Y.-X.; Hu, J.-B. *Org. Lett.* **2014**, *16*, 2030; (g) Yin, G.; Kalvet, I.; Englert, U.; Schoenebeck, F. *J. Am. Chem. Soc*. **2015**, *137*, 4164; (h) Huang, Y.; Ding, J.; Wu, C.; Zheng, H.; Weng, Z. *J. Org. Chem*. **2015**, *80*, 2912; (i) Chen, C.; Xu, X.-H.; Yang, B.; Qing, F.-L. *Org. Lett*. **2014**, *16*, 3372; (j) Zhu, X.-L.; Xu, J.-H.; Cheng, D.-J.; Zhao, L.-J.; Liu, X.-Y.; Tan, B. *Org. Lett*. **2014**, *16*, 2192.
5. (a) Yin, F.; Wang, X.-S. *Org. Lett*. **201**4, *16*, 1128; (b) Fuentes, N.; Kong, W.; Fernàndez-Sànchez, L.; Merino, E.; Nevado, C. *J. Am. Chem. Soc*. **2015**, *137*, 964.
6. (a) Block, S. S.; Weidner, J. P. *Nature*, **1967**, *214*, 478; (b) Weidner, J. P.; Block, S. S. *J. Med. Chem*. **1967**, *10*, 1167
7. Sheng, J; Li, Y.; Qiu, G. *Org. Chem. Front.*, **2017**, *4*, 95.
8. (a) Liu, T.; Ding, Q.; Qiu, G.; Wu, J. *Tetrahedron*, **2016**, *72*, 279; (b) Song, J.; Fan, C.; Liu, G.; Qiu, G. *Org. Chem. Front.*, **2014**, *1*, 1045; (c) Liu, T.; Ding, Q.; Zong, Q.; Qiu, G. *Org. Chem. Front.*, **2015**, *2*, 670; (d) Qiu, G.; Liu, T.; Ding, Q. *Org. Chem. Front.*, **2016**, *3*, 510.
9. For selected examples, see: (a) Doumont, J. M; Rumf, P. *Bulletin De La Soc. Chimique De France*, **1962**, 1213; (b) Whirmore, F. C.; Hamilton, F. H. *Org. Synth*. II, **1922**, 89.
10. Liu, T.; Qiu, G.; Ding, Q.; Wu, J. *Tetrahedron*, **2016**, *72*, 1472.
11. (a) Shao, X.; Xu, C.; Lu, L.; Shen, Q. *J. Org. Chem*. **2015**, *80*, 3012; (b) Yagupolskii, L. M.; Matsnev, A. V.; Orlova, R. K.; Deryabkin, B. G.; Yagupolskii, Y. L. *J. Fluorine Chem*. **2008**, *19*, 131; (c) Jereb, M.; Dolenc, D. *RSC Adv*., **2015**, *5*, 58292

Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights

Research Highlights:

- A tandem reaction of sulfonyl chloride and trifluoromethylsulfanylamide is described here for the synthesis of various trifluoromethyl thiolsulphonates.
- This tandem reaction includes *in situ* reduction of sulfonyl chloride and electrophilic trifluoromethylation.
- Sulfinate was postulated as a key intermediate.
- This tandem process worked efficiently with a broad functional tolerance.