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Electrophilic Aromatic Trifluoromethylthiolation with the Second Generation of Trifluoromethanesulfenamide

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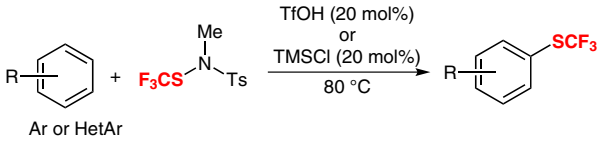

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Abstract Direct trifluoromethylthiolation of various aromatic and heteroaromatic compounds, variously substituted, can be performed with the second generation of trifluoromethanesulfenamide via a 'Friedel–Crafts-like reaction'. This reaction requires mild conditions with a catalytic amount of protic or Lewis acid. Good results have been obtained, even with aromatic compounds bearing deactivating substituents.

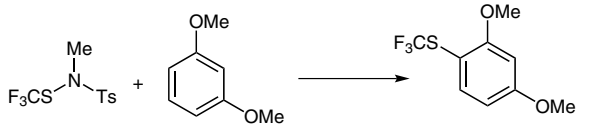
Key words trifluoromethylthiolation, fluorine, arenes, heterocycles, trifluoromethanesulfenamide

Because of the intrinsic properties of the fluorine atom, fluorinated compounds have known these last years an increasing interest in a large panel of applications, from materials to life sciences.[1] In this last field, the introduction of fluorinated group generally contributes to better physicochemical properties.[2] In particular, the CF_3S group, because of its high lipophilicity (Hansch parameter π_R = 1.44),[3] can favor the transmembrane permeation and, consequently, increase the biodisponibility of molecules.[4]

A lot of methods have been described in literature to synthesize compounds bearing this specific group.[5] However, these methods are essentially indirect methods which could require aggressive reagents. The most efficient, and elegant, way to easily access the trifluoromethylthiolated molecules is the direct introduction of the CF_3S moiety. Recently, some elegant solutions have emerged to enable one to propose an efficient toolbox to organic chemists. Thus, various reagents for nucleophilic or electrophilic reactions are now available for a large panel of reactions.[5a,b,6] Nevertheless, only a few classic electrophilic aromatic substitutions have been described.

If we exclude the CF_3SCl chemistry, because of the high toxicity of this gaseous compound,[7] the first generation of trifluoromethanesulfenamide has been the first reagent able to perform 'Friedel–Crafts-like reaction'.[8] However, these reactions were limited to electron-rich aromatic compounds such as indoles. Later, a trifluoromethanesulfonyl hypervalent iodonium ylide reagent was also successfully employed to trifluoromethylthiolate indoles.[9] Shen et al. have also published lately the trifluoromethylthiolation of indoles in mild conditions with their trifluoromethanesulfenate reagent.[10] Very recently, *N*-trifluoromethylthiosaccharin has been developed and a larger panel of aromatics could be trifluoromethylthiolated with this new reagent.[11] Nevertheless, to this day, it appears that the electrophilic aromatic trifluoromethylthiolation is still in progress and further methods are expected to extend the investigations.

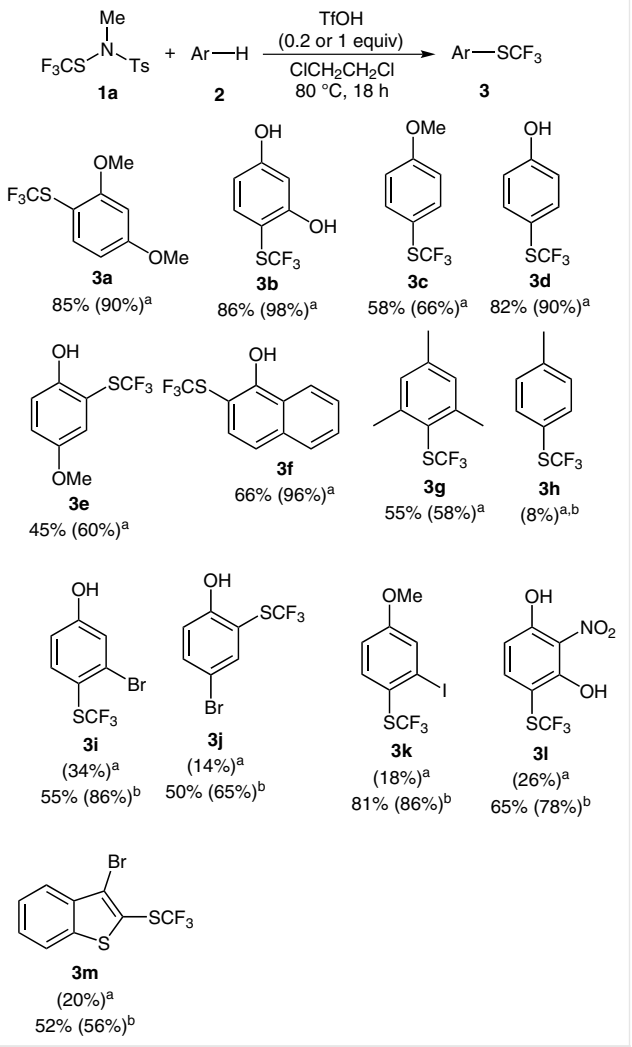
Table 1 Trifluoromethylthiolation of **2a** with **1a**



1a **2a** **3a**

Entry	Catalyst (equiv)	Solvent	Temp (°C)	Time (h)	**3a** (%)[a]
1	$BF_3{\cdot}Et_2O$ (2.5)	CH_2Cl_2	20	18	0
2	$BF_3{\cdot}Et_2O$ (2.5)	CH_2Cl_2	50	18	16
3	TMSCl (1)	CH_2Cl_2	50	18	0
4	TfOH (1)	CH_2Cl_2	20	18	92
5	TfOH (1)	CH_2Cl_2	50	18	88
6	TfOH (1)	$ClCH_2CH_2Cl$	80	18	88
7	TfOH (0.2)	CH_2Cl_2	20	18	25
8	TfOH (0.2)	CH_2Cl_2	50	18	40
9	TfOH (0.2)	$ClCH_2CH_2Cl$	80	18	90
10	TfOH (0.2)	$ClCH_2CH_2Cl$	80	5 min	22
11	TfOH (0.2)	$ClCH_2CH_2Cl$	80	1	40
12	TfOH (0.2)	$ClCH_2CH_2Cl$	80	6	68
13	TfOH (0.2)	$ClCH_2CH_2Cl$	80	36	90
14	TMSCl (1)	MeCN	80	18	90
15	TMSCl (0.2)	MeCN	80	18	86

[a] Crude yield was determined by ^{19}F NMR using $PhOCF_3$ as an internal standard.



Scheme 1 Electrophilic aromatic trifluoromethylthiolation with **1a**, catalyzed by TfOH. [a] The reaction was carried out with 0.2 equiv of TfOH. [b] The reaction was carried out with 1 equiv of TfOH. Isolated yields (in parentheses, crude yields determined by ^{19}F NMR titration with $PhOCF_3$ as internal standard).

Recently, we have developed a second generation of trifluoromethanesulfenamide (**1a**) that is more reactive and which has been successfully used to carry out reactions that were impossible to realize with the first-generation reagent.[12] In this context, to continue the exploration of the reactivity of this new reagent and, also, to propose new tools for electrophilic aromatic trifluorometylthiolation, we decided to study 'Friedel–Crafts-like reactions' with **1a**.

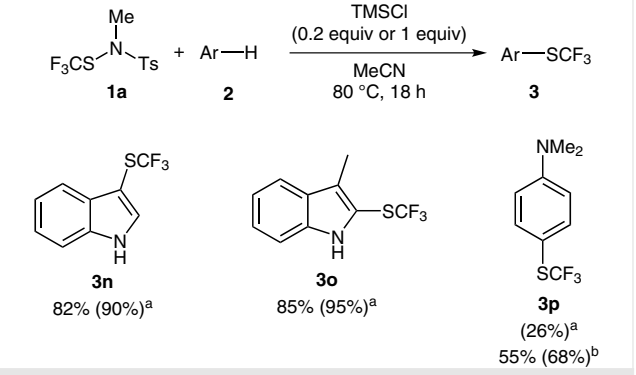
To determine the optimal conditions, *m*-dimethoxybenzene has been chosen as the model substrate (Table 1).

If Lewis acids were not efficient to favor this reaction in dichloromethane (Table 1, entries 1–3), Brönsted acid, such as triflic acid, was very efficient to catalyze this reaction (Table 1, entries 4–6). With one equivalent of TfOH, no temperature effect on the yield was observed (Table 1, entries 4–6). Given the mechanism of the S_EAr, the required proton amount should be catalytic. Indeed, only 0.2 equivalent of TfOH appeared to be sufficient. Nevertheless, in this case, heating to 80 °C was required to favor the kinetics (Table 1, entries 7–9). A solvent effect was observed for the TMSCl catalysis since good results were obtained in acetonitrile, with stoichiometric or catalytic amount, (Table 1, entries 14 and 15) whereas nothing happened with one equivalent in CH_2Cl_2. In term of kinetics, the optimal reaction time was determined to be around 18 hours (Table 1, entries 9–13).

With the optimal conditions in hand (Table 1, entry 9), various aromatic compounds were engaged in this reaction (Scheme 1).[13–15]

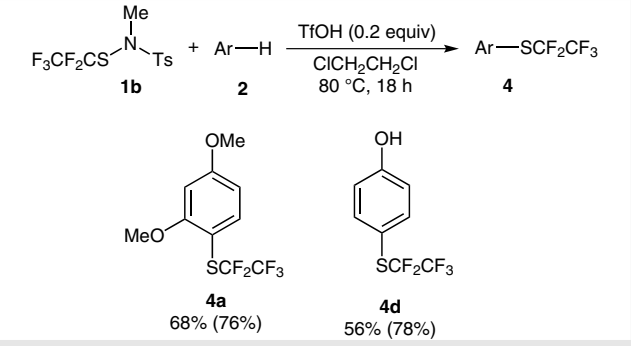
The reaction gave, in general, good yields with various aromatic compounds. The trifluoromethylation of toluene remained unsatisfactory, which is certainly because it is not sufficiently electron-rich. On the contrary, mesitylene was trifluoromethylated with satisfactory yield (**3g**). When the trifluoromethylthiolation was difficult, the use of one equivalent of TfOH was, generally, beneficial and good yields could be then obtained, even in the case of nitro compounds (**3l**).

In the case of protic acid sensitive compounds, such as nitrogenated molecules, catalysis with TMSCl was considered (Scheme 2). Good yields were then obtained. Again, the use of one equivalent of TMSCl was required to increase the obtained yields.



Scheme 2 Electrophilic aromatic trifluoromethylthiolation with **1a**, catalyzed by TMSCl. [a] The reaction was carried out with 0.2 equiv of TMSCl. [b] The reaction was carried out with 1 equiv of TMSCl. Isolated yields (in parentheses, crude yields determined by ^{19}F NMR titration with $PhOCF_3$ as internal standard).

Since the superior homologue of **1a** is also easily available, a few examples of pentafluoroethylthiolation were also performed (Scheme 3). Good yields were observed also for this reaction.



Scheme 3 Electrophilic aromatic pentafluoroethylthiolation with **1a**, catalyzed by TfOH. Isolated yields (in parentheses, crude yields determined by ^{19}F NMR titration with $PhOCF_3$ as internal standard).

To conclude, the second generation of trifluoromethanesulfenamide, which we have recently developed, confirms its higher reactivity, compared to its first-generation counterpart. With this new reagent, electrophilic aromatic trifluoromethylthiolations can be performed in mild conditions (catalytic amount of acid) with various aromatic compounds. For the first time, aromatics bearing alkyl or nitro compounds have been successfully trifluoromethylthiolated. Furthermore, the extension of these reactions to pentafluoroethylthiolation has been initiated. Therefore, this family of reagent confirms its effectiveness and its place into the toolbox of trifluoromethylthiolating reagents.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379501.

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(13) **Typical Procedure**: A 10 mL sealed tube equipped with a magnetic stirrer was charged with the arene (0.50 mmol, 1.0 equiv) and $TsNMeSCF_3$ (**1a**) or $TsNMeSCF_2CF_3$ (**1b**; 1.2 equiv) in anhyd DCE. The reaction was stirred at r.t. for 1 min and triflic acid was added slowly (0.2 equiv) and the reaction was stirred at 80 °C for 18 h. The progress of the reaction was checked by ^{19}F NMR with $PhOCF_3$ as internal standard. After completion, the reaction was warmed to r.t. and the solvent was removed under vacuum and the residue was purified by flash chromatography to give the desired product.

(14) **4-[(Trifluoromethyl)sulfanyl]benzene-1,3-diol** (**3b**): brown solid; mp <50 °C. ^1H NMR: δ = 7.41 (d, $^3J_{H,H}$ = 8.6 Hz, 1 H), 6.56 (d, $^3J_{H,H}$ = 2.7 Hz, 1 H), 6.85 (dd, $^3J_{H,H}$ = 8.6, 2.7 Hz, 1 H), 4.50–6.10 (br, 2 H). ^{13}C NMR: δ = 161.1, 159.5, 139.6, 128.8 (q, $^1J_{C,F}$ = 315 Hz), 109.9, 103.0, 99.62 (q, $^3J_{C,F}$ = 1.7 Hz). ^{19}F NMR: δ = –44.52 (s, 3 F). Anal. Calcd for $C_7H_5F_3O_2S$: C, 40.00; H, 2.40; S, 15.26. Found: C, 40.12; H, 2.29; S, 15.47.

(15) **Synthesis of 2,4-Dimethoxy-1-[(pentafluoroethyl)sulfanyl]benzene** (**4a**): ^1H NMR: δ = 7.51 (d, $^3J_{H,H}$ = 8.5 Hz, 1 H), 6.50–6.52 (m, 2 H), 3.87 (s, 3 H), 3.83 (s, 3 H). $^{13}C\{^{19}F\}$ NMR: δ = 164.3, 162.7, 141.0, 120.0 (CF_2), 118.9 (CF_3), 105.7, 101.7 (t, $^3J_{C,F}$ = 2 Hz), 99.3, 56.1, 55.62. ^{19}F NMR: δ = –82.94 (t, $^3J_{F,F}$ = 3.4 Hz, 3 F), –93.06 (q, $^3J_{F,F}$ = 3.5 Hz, 2 F). Anal. Calcd for $C_{10}H_9F_5O_2S$: C, 41.67; H, 3.15; S, 11.12. Found: C, 41.79; H, 2.91; S, 11.4.