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Trifluoromethyl aryl sulfonates (TFMS): an applicable trifluoromethoxylation reagent

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ABSTRACT

Fluorine is probably another favorite hetero-atom for incorporation into small molecules after nitrogen. Among many fluorine-containing groups, trifluoromethyl aryl ethers ($ArOCF_3$) have unique properties in drug design and are difficult to be synthesized, and many different methods were developed to prepare them. A novel one-pot synthesis of *o*-iodine-aryl trifluoromethyl ethers ($ArOCF_3I$) was described by the reaction of trifluoromethoxylation and iodination with trifluoromethyl aryl sulfonates (TFMS) in this manuscript. The reaction conditions were optimized by screening different solvents, crown ethers, substrates and the ratios and the yields of products were in moderate to high yields (up to 86%).

Keywords: Organofluorine compounds; Trifluoromethylation; Arenes

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Introduction

In recent years, fluorinated organic compounds had played increasingly important roles in pharmaceuticals, materials and other scientific fields.[1] One or more fluorine atoms substituted at a particular position in an organic compound could significantly alter their chemical and biological properties, such as solubility, metabolism and oxidative stability, lipophilicity and bioavailability. [1c,2] Fluorination of organic compounds had become a new method for the design of novel drugs, which attracted many interests of research on the synthesis of fluorine-containing compounds and made the methodology of organic fluorine a very popular field of organic synthesis. Among many fluorine-containing groups, trifluoromethyl aryl ethers ($ArOCF_3$) had unique properties[1c,3] and were difficult to be synthesized. Thus, the reactions to prepare these molecules had become focus for the development of synthetic methods. However, despite this particular interest, the synthesis of $ArOCF_3$ compounds was challenging. Several strategies for the preparation of trifluoromethyl aryl ethers had been published.[4] However, the one-pot synthesis of *o*-iodine trifluoromethyl ethers with functional iodine atoms was rarely reported.[5]

Traditional methods for the synthesis of trifluoromethyl ethers, such as chlorine/fluorine exchange of chlorinated precursors[6] and deoxyfluorination of fluoroformates,[7] were restricted by few substrates and reaction conditions. Recently, Ngai and co-workers developed intramolecular OCF_3 migration to prepare trifluoromethylation products.[8] Ritter and co-workers reported a silver-mediated cross coupling of aryl stannanes and aryl boronic aids with tris(dimethylamino)sulfonium trifluoromethoxide ($TASOCF_3$),[9] which was a method of generating trifluoromethyl ethers from transition metals. In addition, chemists also developed a series of trifluoromethylation reagents for the synthesis of trifluoromethoxy compounds, but these reagents also had various problems. Fluoroxytrifluoromethane (FMT) was used for trifluoromethylation through free radical reaction, but it was toxic and was difficult to be operated.[10] Trifluoromethyl triflate (TFMT) had been known since its preparation by Noftle and Cady, but it was a volatile liquid with the boiling point of only 19 °C, which limited its applications.[11] The 2,4-dinitrotrifluoromethoxybenzene (DNTFB)

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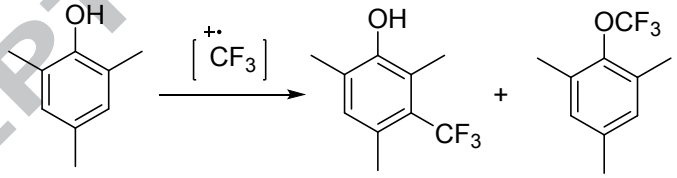
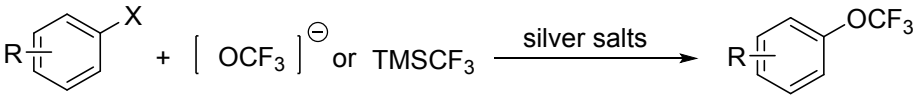
developed by Langlois showed poor reactivity and narrow substrate ranges.[12] In 2017, Tang group developed a new trifluoromethoxylation reagent, trifluoromethyl aryl sulfonates (TFMS).[13] Hu and co-workers reported the trifluoromethyl benzoate (TFBz) in 2018.[5] However, the synthesis of this compound required the application of COF_2, which was a highly toxic reagent.[5] In 2018, Ngai and co-workers reported the direct C-H aryl trifluoromethylation by the OCF_3 radical mechanism under photocatalysis or redox-active catalyst.[14] Togni and co-workers designed highly electrophilic N-O pyridinium reagents capable of undergoing facile single-electron reduction to afford trifluoromethoxyl radicals under catalytic conditions in 2018.[15] Up to now, only several methods for the synthesis of trifluoromethoxylated aromatics had been reported in the past decades (Scheme 1). Compared with other trifluoromethoxyl reagents, TFMS was much easier to be prepared and operated. Furthermore, TFMS had good thermal stability and reactivity. In this manuscript, we reported one-pot synthesis of *o*-iodine trifluoromethyl ethers in moderate to high yields with functional iodine atoms by the employment of benzene-acetylene precursor as a substrate and TFMS as a trifluoromethoxyl reagent.

Togni (2008) - direct, electrophilic radical *o*-trifluoromethylation of phenols:

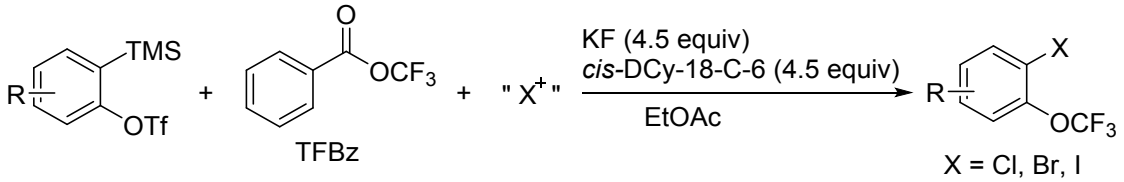


Ritter (2011) - silver-mediated synthesis of trifluoromethoxylated arynes:



X=OH, $B(OH)_2$, or $SnBu_3$

Hu (2018) –trifluoromethoxylation-halogenation of arynes:



X = Cl, Br, I

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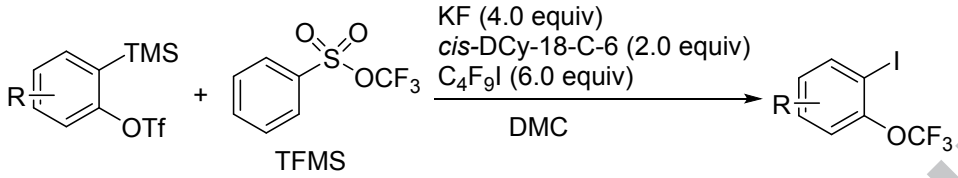
This work-one pot synthesis of *o*-iodine trifluoromethyl ethers:

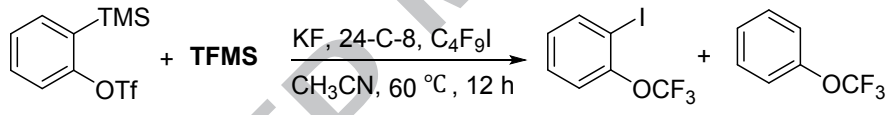


Scheme 1. Synthesis of trifluoromethoxylation reagents and related trifluoro-methoxylated aryl ethers.

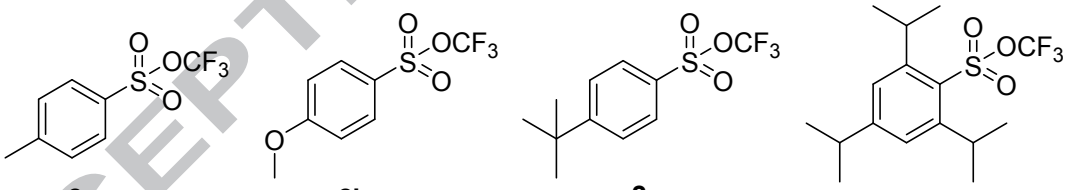
Results and discussion

We initiated our investigation with 2-(trimethylsilyl)phenyl trifluoromethane-sulfonate **1** as model substrate to screen different trifluoromethyl *p*-toluenesulfonates (TFMS) **2** (Table 1), which were trifluoromethoxyl reagents.

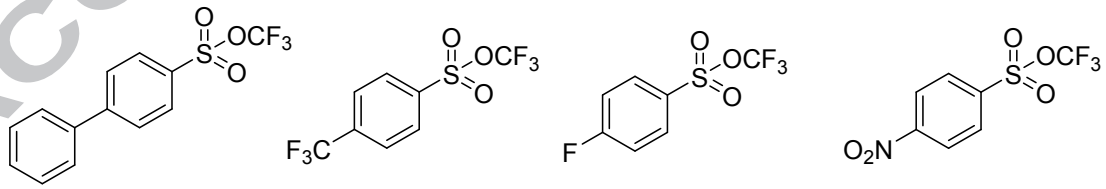
Table 1. Investigation of different substituted trifluoromethyl aryl sulfonates (TFMS)



1 **2** **3** **4**



2a **2b** **2c** **2d**



2e **2f** **2g** **2h**

Entry	**2**	Yield (**3**, %)	Yield (**4**, %)
1	**2a**	48	10
2	**2b**	40	6
3	**2c**	38	7

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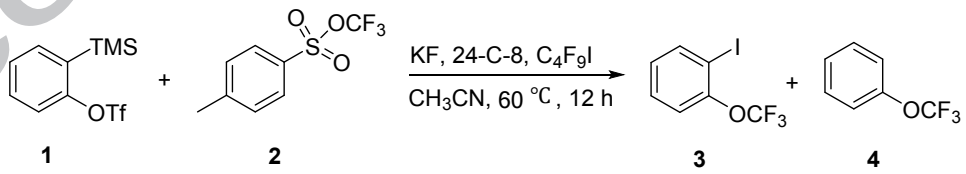
4	**2d**	40	7
5	**2e**	45	9
6	**2f**	35	4
7	**2g**	40	9
8	**2h**	41	6

Conditions: **1** (0.05 mmol), **2** (2.0 equiv), KF (4.0 equiv), 24-crown-8 (24-C-8, 2.0 equiv), C_4F_9I (6.0 equiv), CH_3CN (0.3 mL), 60 °C, 12 h. Yields were determined by ^{19}F NMR with $PhCF_3$ as the internal standard.

It was interestingly found that all the reactions produced **3** in moderate yields and by-products **4** in low yields. Trifluoromethoxyl reagent **2a** gave final product **3** in the highest yield (Table 1, entry 1). Other trifluoromethoxyl reagents with electron withdrawing groups (phenyl of **2e**, trifluoromethyl of **2f**, fluoro of **2g**, nitro of **2h**) and substituents with steric hindrance (**2c** and **2d**) give products **3** in lower yields, which showed that there were stereo and electronic effects on this reaction. Then we checked the effects of different ratios of **2**/**1** and it showed that the yields of **3** were nearly the same when the ratio of **2**/**1** was varied from 2 to 4 equivalents (Table 2, entries 1-3). However, when the ratio of **2** was increased to 5 and 6 equivalents, the yields of **3** were greatly decreased (Table 2, entries 4-5), which was probably due to more $-OCF_3$ to attack the arynes intermediate to give other byproducts.

Table 2. Investigation of different ratios of trifluoromethyl aryl sulfonate reagents



1 **2** **3** **4**

Entry	Ratio (**2**/**1**)	Yield (**3**, %)	Yield (**4**, %)
1	2	42	5
2	3	40	7
3	4	42	4

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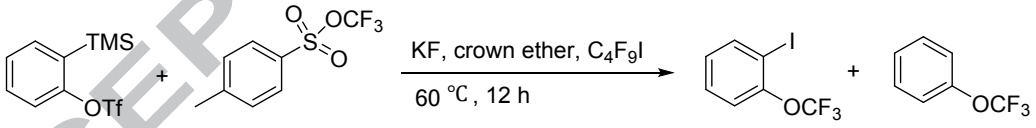
4	5	25	1
5	6	11	1

Conditions: **1** (0.05 mmol), KF (4.0 equiv), 24-C-8 (2.0 equiv), C_4F_9I (6.0 equiv), CH_3CN (0.3 mL), 60 °C, 12 h. Yields were determined by ^{19}F NMR with $PhCF_3$ as the internal standard.

Crown ethers were good phase-transfer catalysts (PTC) in the presence of metal ions.[16] We investigated the effect of different types of crown ethers on the formation of **3** and found that 18-crown-6 (18-C-6) was more favorable to the yield of **3** than 24-C-8 (Table 3, entries 1-2). As to different solvents in the presence of 18-C-6, the highest yield was obtained in ethyl acetate (EA) and byproducts **4** were not determined in EA and dimethyl carbonate (DMC) (Table 3, entries 3-4). Finally, the reaction was carried out in EA, dimethoxy ethane (DME) and DMC, respectively with the *cis*-dicyclohexano-18-C-6 (*cis*-Dcy-18-C-6) as the PTC, and the results showed that high yields of **3** were obtained without byproducts **4** in EA and DMC (Table 3, entries 5-6). However, DME only gave **3** in 21% yield (Table 3, entry 7). As can be found in Table 3, hydrophilic solvent CH_3CN resulted in the formation of by-product **4,** while hydrophobic solvents, such as EA, DMC and DME only gave products **3**.

Table 3. Effects of different crown ethers and solvents



1 **2** **3** **4**

Entry	Additives	Solvents	Yield (**3**, %)	Yield (**4**, %)
1	24-C-8	CH_3CN	37	5
2	18-C-6	CH_3CN	44	2
3	18-C-6	EA	60	0
4	18-C-6	DMC	54	0
5	*cis*-DCy-18-C-6	EA	62	0
6	*cis*-DCy-18-C-6	DMC	64	0

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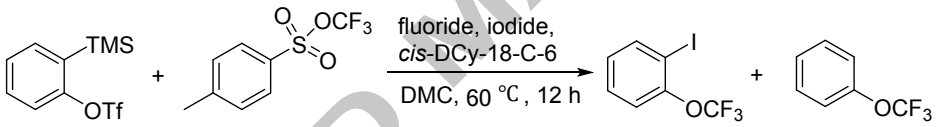
7	*cis*-DCy-18-C-6	DME	21	0

Conditions: **1** (0.05 mmol), **2** (2.0 equiv), additives (2.0 equiv), KF (4.0 equiv), C_4F_9I (6.0 equiv), solvents (0.3 mL), 60 °C, 12 h. Yields were determined by ^{19}F NMR with $PhCF_3$ as the internal standard.

How did different fluorides and iodides affect the reaction? The results showed that only KF could produce **3** in the presence of C_4F_9I (Table 4, entry 1). However, NaF, AgF and no fluoride did not give expected products **3** (Table 4, entries 2-4), which was probably due to lack of proper crown ethers. Finally, we investigated the effect of different iodides on the yields of **3** in the presence of KF. The results showed that I_2, NIS and CsI did not give expected products **3** (Table 4, entries 5-7). In contrast, product **3** could be obtained in 58% of yields in the presence of tetrabutylazanium iodide (Table 4, entry 8).

Table 4. Investigation of different fluoride salts and iodides



1 **2a** **3** **4**

Entry	Fluoride salts	Iodide	Yield (**3**, %)	Yield (**4**, %)
1	KF	C_4F_9I	64	0
2	NaF	C_4F_9I	0	0
3	AgF	C_4F_9I	0	0
4	-	C_4F_9I	0	0
5	KF	I_2	0	0
6	KF	NIS	0	0
7	KF	CsI	0	0
8	KF	tetrabutylazanium iodide	58	0

Conditions: **1** (0.05 mmol), fluoride salts (4.0 equiv), *cis*-DCy-18-C-6 (2.0 equiv), Iodide (6.0 equiv), DMC (0.3 mL), 60 °C, 12 h. Yields were determined by ^{19}F NMR with $PhCF_3$ as the internal standard.

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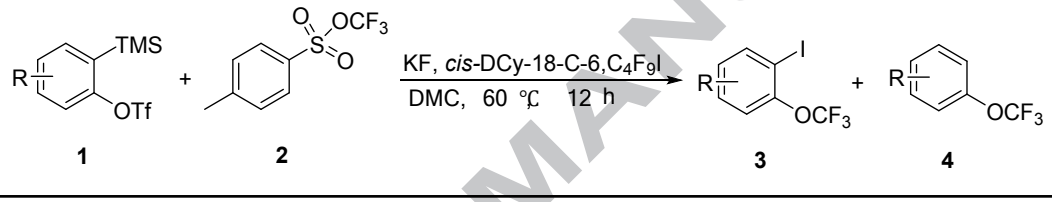
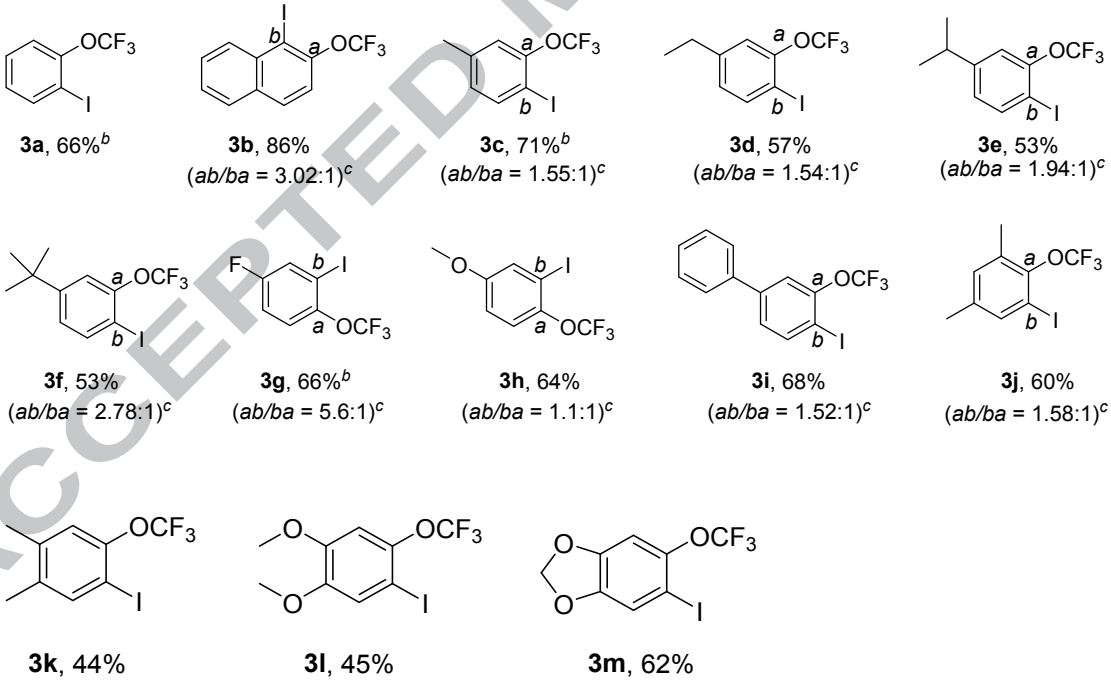
With the optimized conditions, we explored the scope of substrates with different substituents on the aryl rings. Substituted phenyl rings (**3a-3m**) smoothly underwent trifluoromethoxylation and iodination to give the corresponding products in moderate to high yields (Table 5). In all cases, no byproducts of fluorination, trifluoromethoxylation-protonated and **4** were observed. In cases of unsymmetrical aryls with 4-substituent, low to moderate regioselectivities were observed, which might be dependent on the electronic characteristics of the substituents (**3b-3j**). Functional groups such as methoxyl (**3h**, **3l**, **3m**), fluoride (**3g**), phenyl (**3i**) and alkyl (**3c-3f**, **3j**, **3k**) were well tolerated in this reaction.

Table 5. Investigation of different substrates[a]





3a, 66%[b]

3b, 86% (*ab/ba* = 3.02:1)[c]

3c, 71%[b] (*ab/ba* = 1.55:1)[c]

3d, 57% (*ab/ba* = 1.54:1)[c]

3e, 53% (*ab/ba* = 1.94:1)[c]

3f, 53% (*ab/ba* = 2.78:1)[c]

3g, 66%[b] (*ab/ba* = 5.6:1)[c]

3h, 64% (*ab/ba* = 1.1:1)[c]

3i, 68% (*ab/ba* = 1.52:1)[c]

3j, 60% (*ab/ba* = 1.58:1)[c]

3k, 44%

3l, 45%

3m, 62%

[a] Conditions: **1** (0.5 mmol), **2** (2.0 equiv), iodides (6.0 equiv), *cis*-DCy-18-C-6 (2.0 equiv), KF (4.0 equiv), DMC (0.3 mL), 60 °C, 12 h. Unless otherwise noted, isolated yields were given. For structures of **1**, see SI. [b] Yields were determined by ^{19}F NMR with $PhCF_3$ as the internal standard. [c] The ratio of regioisomers was determined by ^{19}F NMR spectroscopy prior to isolation.

In conclusion, we developed a useful method of one-pot synthesis of *o*-iodine aryl trifluoromethyl ethers with functional iodine atoms in moderate to high yields through

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the reaction of trifluoromethoxylation and iodination with TFMS. The functional building blocks could be used in drug design and synthesis.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the SI file.

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Highlights:

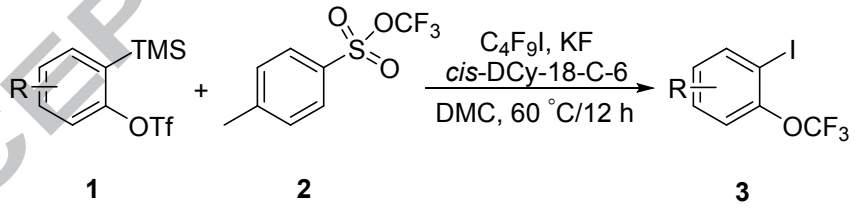
(1) A novel one-pot synthesis of *o*-iodine-aryl trifluoromethyl ethers ($ArOCF_3I$) with an excellent handle (the iodine atom).

(2) A benzene-acetylene precursor was used as a substrate and a high performance TFMS was used as a trifluoromethyloxy reagent.

(3) The reaction was carried out in mild and robust conditions and gave the expected products in moderate to high yields.

17.

A new one-pot synthesis of trifluoromethyl ethers with an excellent handle (the iodine atom) in moderate to high yields was developed.



1 **2** **3**

18.

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