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Metal-free, Initiator-free Graphene Oxide Catalyzed Trifluoromethylation of Arenes

Jingyu Zhang, Yun Yang, Jingxian Fang, Guo-Jun Deng and Hang Gong*

Abstract: The direct C–H trifluoromethylation of arenes catalyzed by graphene oxide (GO) under safe conditions is described. This strategy is metal free, initiator free, safe, and scalable. It employs a readily available CF_3 source and could easily control the reaction to obtain a mono-trifluorinated product. This method opened a new field for GO-catalyzed chemistry.

Arene trifluoromethylation is attractive because of the special effects of trifluoromethyl (CF₃) on parent molecules. These effects include improvements in stability, solubility, polarity, dipole moment, lipophilicity, and catabolic stability.^[1] Although rare in nature, synthetic trifluorinated aromatics have been widely applied in various fields, especially in pesticides and pharmaceuticals (Fig. 1).^[2] Thus, developing synthetic strategies for the selective trifluoromethylation of arenes is of great interest among scientists. Many functionalized molecules, such as aryl halides or pseudohalides, aryl boronic derivatives, and aromatic acids, were used as substrates for the trifluoromethylation of arenes (Scheme 1, A and B).^[3] These methods often use poisonous fluorinating reagents, pre-synthesized functional substrates, as well as stoichiometric metal salts. With the development of transition metal-catalyzed chemistry, the metalcatalyzed direct C-H bond trifluoromethylation of arene was also developed thoroughly (Scheme 1, C).^[3,4] These methods reduced the number of reaction steps and improved the atomic economic efficiency and synthesis efficiency. However, the metal residue remains a continuous concern in pharmaceuticals and materials fields.^[5]

Recently, a metal-free procedure for direct aromatic trifluoromethylation was developed by our group^[6] and other researchers^[3,7] (Scheme 1, D). Nevertheless, the preparation and use of concentrated peroxides or persulfides leads to exposure to certain dangerous chemicals. Thus, developing metal-free and initiator-free direct C–H trifluoromethylation of arenes under safe conditions is desirable.



Figure 1. Examples of the application of arene trifluoromethylation.

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Scheme 1. Examples of the application of arene trifluoromethylation.

Given our recent research on trifluoromethylation^[6] and graphene oxide (GO)-catalyzed reactions,^[8] the current work describes the GO-catalyzed trifluoromethylation of arenes in the absence of metal and initiator under safe conditions. Despite the extensive use of this strategy in catalytic reactions,^[9] to the best of our knowledge, GO-catalyzed trifluoromethylation has not been reported.

The trifluoromethylation reaction was commenced by using sym-trimethoxybenzene as template substrate (0.1 mmol), GO (10 mg) as catalyst, and NaSO₂CF₃ (Langlois' reagent, 3.0 equiv.)^[10] as CF₃ source in various solvents (1.0 mL) at 100 °C under air (Table 1, Entries 1-6; Table S1, Entries 1-13). When ethyl chloroacetate was used as solvent, a moderate yield (60%) of the desired product was achieved (Table 1, Entry 5). Increasing or reducing the reaction temperature is not beneficial to this reaction (Table 1, Entries 7-8; Table S1, Entries 14-19). This reaction could be finished within 12 h. Prolonging the reaction time does not also aid the transformation (Table 1, Entries 9-10; Table S1, Entries 20-24). To augment the yield of this reaction, we examined several additives (Table 1, Entries 11-15; Table S1, Entries 25-33). When 10 mol% NH₄NO₃ was used, an improved yield of 65% was achieved (Table 1, Entry 15). When the amount of NH₄NO₃ was increased to 20 mol%, a good yield of 73% was achieved (Table 1, Entry 17). Particularly, this transformation showed good selectivity; almost no ditrifluoromethylated product was detected when NH4NO3 was employed as additive (Table 1, Entries 15-18). Moreover, increasing the amount of GO catalyst did not increase the yield (Table 1, Entries 19-20). Further experiments indicated that increasing the CF₃SO₂Na amount did not benefit the reaction (Table 1, Entries 21-22; Table S1, Entries 39-41). Finally, we checked the reaction atmosphere and observed that the transformation could be conducted more effectively under air than in other conditions (Table 1, Entries 17, 23-24). Furthermore, the influence of metal impurities in GO was investigated (please see Scheme S1 in Supporting

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Table 1. Selected optimization results.ª

MeO la	H GO(10 mg), CF ₃ additive10 mol% 100 °C, 12 OMe	SO ₂ Na(3 equiv) , solvent(1 mL) 2 h, Air MeO	$\begin{array}{c} OMe \\ CF_3 \\ OMe \\ 2a \end{array} \begin{array}{c} F_3C \\ HeO \\ BeO \\ 3a \end{array} \begin{array}{c} OMe \\ OMe \\ OMe \\ BeO \\ CF_3 \\ OMe \\ OMe \\ CF_3 \\ OMe \\ CF_3 \\ OMe \\ OMe \\ CF_3 \\ OMe \\ OMe$
Entry	Solvent	Additive	Yield/% (2a:3a)
1	H ₂ O	_	0
2	THF	_	7 (7:0)
3	CH₃CN	_	35 (35:0)
4	EtOAc	—	35 (35:0)
5	CICH ₂ CO ₂ Et	—	60 (60:0)
6	BrCH ₂ CO ₂ Et	—	36 (35:1)
7 ^b	CICH ₂ CO ₂ Et	_	55 (55:0)
8 ^c	CICH ₂ CO ₂ Et	_	39 (39:0)
9 ^d	CICH ₂ CO ₂ Et	_	25 (25:0)
10 ^e	CICH ₂ CO ₂ Et	_	56 (53:3)
11	CICH ₂ CO ₂ Et	I ₂	0
12	CICH ₂ CO ₂ Et	iPr₂NEt	43 (43:0)
13	CICH ₂ CO ₂ Et	H ₃ PO ₄	38 (38:0)
14	CICH ₂ CO ₂ Et	KHCO ₃	42 (42:0)
15	CICH ₂ CO ₂ Et	NH ₄ NO ₃	65 (65:0)
16 ^f	CICH ₂ CO ₂ Et	NH ₄ NO ₃	58 (58:0)
17 ^g	CICH ₂ CO ₂ Et	NH ₄ NO ₃	73 (73:0)
18 ^{g,h}	CICH ₂ CO ₂ Et	NH ₄ NO ₃	74 (74:0)
19 ^{g,i}	CICH ₂ CO ₂ Et	NH ₄ NO ₃	65 (65:0)
20 ^{g,j}	CICH ₂ CO ₂ Et	NH ₄ NO ₃	74 (74:0)
21 ^{g,k}	CICH ₂ CO ₂ Et	NH4NO3	43 (43:0)
22 ^{g,I}	CICH ₂ CO ₂ Et	NH ₄ NO ₃	69 (69:0)
23 ^{g,m}	CICH ₂ CO ₂ Et	NH ₄ NO ₃	51 (51:0)
24 g,n			60 (60:0)

^a Unless otherwise noted, all reactions were conducted at 0.1 mmol scale with CF₃SO₂Na (3 equiv), GO (10 mg), and additive (10 mol%) in a sealed tube in 1 mL solvent under air atmosphere for 12 h. Yields are detected by GC-MS using naphthalene as internal standard. All other optimization reaction results please see **Table S1** in *Supporting Informations*; ^b Reaction temperature is 110 °C; ^c reaction temperature is 90 °C; ^d Reaction time is 6 h; ^e Reaction time is 18 h; ^f 5 mol% NH₄NO₃ was added; ^g 20 mol% NH₄NO₃ was added; ^h 30 mol% NH₄NO₃ was added; ⁱ 5 mg GO was added; ^k 2 equiv of CF₃SO₂Na was used; ⁱ Under argon atmosphere; ⁿ Under oxygen atmosphere.

Information), and the catalytic activity of GO was found to be unrelated to metal impurities.

The scope of the substrate was examined using the reliable trifluoromethylation protocol (Table 2). Generally, this transformation depends highly on the electronic degree of the substrate. Nearly all of the arenes substituted with three electron-rich groups were converted into the desired trifluoromethylation product at good yields (Table 2, 2a-e). However, when the electronic effect of the substituents are inconsistent, or less electron-donating groups are observed in the arene, trifluoromethylation yield diminishes. In this case, only a moderate yield could be achieved (Table 2, 2f-h). This reaction is also compatible with ester, ketone, and halogen. However, only moderate yields could be achieved because of the negative inductive effect of these groups (Table 2, 2i-l). Alkoxy-substituted thiophene also improved this transformation, as shown by the obtained moderate to good yield (Table 2, 2mn). Unfortunately, almost none of the desired product or only poor yield was attained when less electron-rich or electron-poor arenes were used as substrates (Table 2, 20-v).





 a Unless otherwise noted, all reactions were conducted at 0.2 mmol scale with CF₃SO₂Na (3 equiv), GO (20 mg), and NH₄NO₃ (20 mol%) in a sealed tube in 1 mL CICH₂CO₂Et under air atmosphere for 12 h. Yields are detected by GC-MS using naphthalene as internal standard. The isolated yields were presented.

This transformation can be easily scaled up to the gram level by using GO (100 mg, 20 wt%) as catalyst, 1b (0.5 gram, 2.38 mmol) as the substrate, CF_3SO_2Na (1.1 g, 3.0 equiv.) as CF_3 source, and NH_4NO_3 (38 mg, 20 mol%) as additive in $CICH_2CO_2Et$ (5 mL). The mixture was stirred in a sealed tube under air at 100 °C for 72 h. A good yield of 73% was achieved; this yield is comparable to that of the template reaction (Scheme 2).

The radical inhibition experiment was conducted using TEMPO as blocker (Scheme 3). Only a trace amount of the desired product was detected and thus indicated that the transformation is probably achieved through a radical process.

Loh's work demonstrated that the unpaired electrons of porous GO plays a critical role in the aerobic oxidative reaction of amine. In this reaction, tandem single-electron transfer (SET) of amine to the GO shell and further to oxygen could occur and gather the superoxide radical.^[11] Given the current investigation and our previous work,⁶ a reasonable mechanism was proposed (Scheme 4). The trifluoromethyl radical and superoxide radical were formed through a tandem SET process. Subsequently, a radical



Scheme 2. Gram-scale reaction.



Scheme 3. Radical inhibition experiment.

addition of trifluoromethyl radical to arene occurred and accessed the intermediate phenyl radical (I). The hydrogen atom of phenyl radical was abstracted by the superoxide radical to accomplish the aromatization reaction, and the target molecule (T.M.) was achieved. Additionally, we thought that the alkoxy group also benefits this transformation because of the stabilization of radical intermediate (I).



Scheme 4. Proposed mechanism for the GO-catalyzed trifluoromethylation of arenes

In conclusion, a metal-free and initiator-free GO-catalyzed direct C-H trifluoromethylation of arenes under safe conditions is described. The initial-free process radical of trifluoromethylation is promising. This strategy possesses several advantages, such as being metal free, initiator free, safe, and scalable. The other benefits include the use of readily available CF3 source and the easy control of the reaction to obtain the mono-trifluorinated product. Therefore, the proposed method introduced a new field for GO-catalyzed chemistry.

Experimental Section

A typical experimental procedure: A solution of arene (0.2 mmol), GO (20 mg), CF₃SO₂Na (3.0 equiv), and NH₄NO₃ (20 mol%) in CICH₂CO₂Et (1 mL) was stirred in a sealed tube under air atmosphere at 100 °C for 12 h. The reaction mixture was then filtered and washed with ethyl acetate. Afterwards, the solvent was evaporated in vacuo. The residue was purified by preparative thin-layer chromatography on silica gel with petroleum ether and ethyl acetate to yield the pure product.

Acknowledgements

We are grateful to the National Natural Science Foundation of China (No. 21402168), Scientific Research Foundation of Hunan Provincial Education Department (No. 15B232) and Hunan 2011 Collaborative Innovation Center of Chemical Engineering & Technology with Environmental Benignity and Effective Resource Utilization for their support of our research.

Keywords: trifluoromethylation • graphene oxide • metal-free • initiator-free

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