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DOI: 10.1039/C8CC00938D

N-Aryltrifluoromethanesulfonimides as new trifluoromethylating agents for the (photo)catalyst-free functionalization of (hetero)aromatics

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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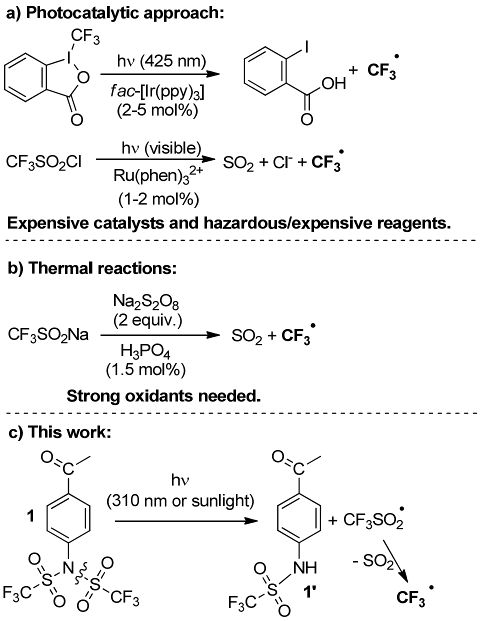
The photoinduced (by UV or sunlight) catalyst-free radical trifluoromethylation of (hetero)aromatics (up to 87% yield) has been succeeded by using *N*-aryltrifluoromethanesulfonimides as the trifluoromethylating agents. The process likewise occurred under continuous flow conditions.

The trifluoromethyl (CF_3) group is a key substituent in medicinal chemistry, since it often enhances the lipophilicity, bioavailability and metabolic stability of bioactive molecules.[1] Indeed, trifluoromethylated aromatics are core building blocks in both pharmaceuticals (including, among others, nilutamide, fluoxetine and leflunomide) and in drug candidates. For this aim, the incorporation of a -CF_3 moiety into aromatic rings is a crucial challenge in organic synthesis and impressive efforts have been carried out to develop new trifluoromethylating protocols.[2] Most of the recent strategies rely on the (photo)generation of trifluoromethyl radicals (Scheme 1). Photoredox catalysis is an elegant approach for the formation of these species from a suitable redox active precursor.[3] However, the widespread use of expensive catalysts such as iridium and ruthenium complexes and harmful reactants like CF_3I, CF_3SO_2Cl or the Umemoto's and the Togni's reagents (Scheme 1a) prompts for the development of cheaper and safer synthetic alternatives.

Accordingly, both thermal[4] and photochemical[5] catalyst-free strategies have been reported, but in most cases the use of strong oxidants (e.g. persulfate ion, Scheme 1b),[4a,b,d,e] gaseous CF_3I[5a,c-f,h-j] and moisture sensitive trifluoroacetic anhydride[4b,d] were mandatory for the process. Furthermore, the developed photochemical methodologies usually made use of undesirable UVC radiation (λ = 254 nm) to take place.[5d-f,h-j] We reasoned that *N*-aryltrifluoromethanesulfonimides could be successfully exploited as simple, cheap and easy to handle reagents for trifluoromethylations since compound **1** (or **1'** from it) was reported to release $F_3C^\bullet$ radicals upon irradiation (Scheme 1c).[6]



Scheme 1. Typical approaches for the generation of the trifluoromethyl radicals.

The functionalization of 1,4-dimethoxybenzene (**2a**) in the presence of **1**[7] as trifluoromethylating agent was investigated as a model reaction. Deaerated solutions of the two reagents in different solvents were irradiated in a multi-lamp reactor equipped with 10 phosphor coated lamps (15 W) emitting at 310 nm until no reagent **1** or photogenerated sulfonamide **1'** were present. The wavelength used was selected according to the absorption properties of **1** and **1'** (see Fig. S2-S5 in Supporting Information). A molar ratio of **1**/**2a** = 0.8 was used to have a reasonable excess of the $F_3C^\bullet$ radical that could be released. The consumption of **2a** and the yield of

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†Electronic Supplementary Information (ESI) available: it contains syntheses and full characterization of compounds, optimization of reaction conditions, flow experiments, UV-vis and NMR spectra. See DOI: 10.1039/x0xx00000x

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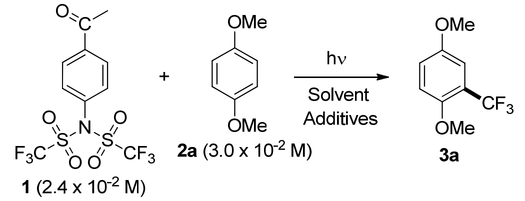
trifluoromethylated compound **3a** are listed in Table 1. The reaction took place efficiently in acetonitrile and dichloromethane (ca. 70-80% yields of **3a**, according to GC analyses) but not in in ethyl acetate, methanol and diethyl ether. Notably, omitting water was beneficial for the overall yield (compare entries 6 and 7). Lowering the concentration of **1** down to 0.015 M (entry 8) caused the formation of **3a** in only 58% yield, whereas when adopting a large excess of the trifluoromethylating agent (0.03 M), the desired product was obtained in 84% yield (18 h irradiation, entry 9). Since compound **1** photoreleases huge amounts of HF and H_2SO_3,[6] we found convenient to perform the irradiation in the presence of a buffering agent. The presence of a buffering agent Cs_2CO_3 (entry 10) was however detrimental as it was the use of persulfate anion[8] (entry 11).

Table 1. Optimization of the reaction conditions for the trifluoromethylation of 1,4-dimethoxybenzene **2a**.[a]



Entry	Solvent	Additives	Irradiation conditions	**2a** Conv. [%][b]	**3a** yield [%][b]
1	CH_2Cl_2	-	310 nm, 12h	90	81
2	AcOEt	-	310 nm, 12h	62	55
3	CH_3OH	-	310 nm, 12h	23	16
4	CH_3CN	-	310 nm, 12h	83	74
5	Et_2O	-	310 nm, 12h	7	0
6	dry CH_3CN	-	310 nm, 12h	88	81
7	**dry CH_2Cl_2**	**-**	**310 nm, 12h**	**100**	**87**
8[c]	dry CH_2Cl_2	-	310 nm, 6h	65	58
9[d]	dry CH_2Cl_2	-	310 nm, 18h	100	84
10[e]	dry CH_2Cl_2	Cs_2CO_3, 0.12 M	310 nm, 16h	84	76
11[e]	dry CH_2Cl_2	$K_2S_2O_8$, 0.048 M	310 nm, 12h	86	79
12[f]	dry CH_2Cl_2	-	310 nm, 12h	91	83
13[g]	dry CH_2Cl_2	-	Sunlight, 18h	100	86
14[h]	dry CH_2Cl_2	-	dark, 12h	0	0
15[i]	dry CH_2Cl_2	-	310 nm, 72h	80	69

[a] **2a** (3.0×10^{-2} M), **1** (2.4×10^{-2} M). Reagents and additives were dissolved in 3.0 mL of the chosen medium and irradiated in quartz tubes under deaerated conditions. The best reaction conditions are given in bold. [b] Gas Chromatography (GC) yields referred to the initial amount of **2a**. α,α,α-Trifluorotoluene was used as internal standard. [c] **1** (1.5×10^{-2} M). [d] **1** (3.0×10^{-2} M). [e] Irradiation performed under stirring. [f] Under air equilibrated conditions. [g] Irradiation performed in a Pyrex vessel exposed to sunlight (3 days, 6 h/day) in July 2017, Pavia (Italy). [h] Blank experiment performed in the absence of light by covering the reaction tube with an aluminum foil and placing the sample in the 310 nm reactor, as done for entries 1-12. [i] **1'** (4.8×10^{-2} M) used as the trifluoromethylating agent.

The presence of molecular oxygen in the samples had a marginal effect on the photoreaction (entry 12). Noteworthy, **3a** was formed roughly in the same yield when using sunlight as the radiation source (entry 13). No reaction was observed when keeping the starting reaction mixture in the dark (entry 14). Lastly, **1'** (4.8×10^{-2} M) was tested as the trifluoromethylating reagent (entry 15) but **3a** was obtained in only 69% yield after 72 h irradiation, showing that **1** performed better, despite the amount of triflamide **1'** employed could in principle release the same equivalents of $F_3C^\bullet$ radicals.

The presence of an electron-withdrawing substituent on the sulfonamide ring, is mandatory for the reaction in order to avoid a possible attack of the $F_3C^\bullet$ radical onto the starting sulfonamide.[6] However, the use of a cyano-substituted sulfonimide (**1a**, see the Supporting Information) gave a lower amount of **3a** when adopting the conditions of entry 7, Table 1. We then extended the scope of the reaction by applying the trifluoromethylation to a range of aromatic and heteroaromatic derivatives (Table 2) adopting the conditions described in Table 1, entry 7. The irradiation of **1** in the presence of arenes **2a-f** led to the formation of **3a-f** in satisfactory yields (60-85%). In the case of mesitylene **2e** a minor amount of 1,3-bis(trifluoromethyl) derivative (**3e-bis**, 12% yield) was formed along with the desired **3e**. The present methodology appears to be suitable also for aromatics having electron-withdrawing substituents, as pointed out by the functionalization of 2',4',6'-trimethylacetophenone **2g**, which gave **3g** in 74% yield, (3.2 equiv. of **1** used). The scope was further extended to heterocycles. Irradiation of 3,4-ethylenedioxythiophene **2h** resulted in the formation of bis-trifluoromethylated **3h-bis** (59% yield).[3g,9] However, when decreasing the concentration of **1** (down to 0.015 M), compound **3h** became the major product. Further decrease of **1** below 0.010 M concentration gave no isolated trifluoromethylated compound (data not shown). Moving to nitrogen based heterocycles, pyridines **2i**,**j** gave **3i**,**j** in satisfactory amounts, whereas derivative **3k** was the only product isolated starting from 2-methylimidazole **2k**, via N-C bond formation. This result is striking since radical trifluoromethylation of imidazoles usually brings to the formation of C-CF_3 bonds[5b,e,f,h,i,10] and *N*-CF_3 imidazoles are otherwise difficult to prepare.[11] Bioactive methylxanthines such as caffeine and theophylline were selectively functionalized and **3l**,**m** were obtained in 58% and 67% yield, respectively. In each reaction performed no byproducts arising from the addition of the $F_3C^\bullet$ radical onto **1** has been detected by GC/MS analysis. Pyrex vessels containing selected reaction mixtures were exposed to natural sunlight for three days (6 h for day) and compounds **3a**, **3d**, **3j**, **3l** were isolated in yields comparable to those observed when using phosphor coated lamps as the light sources (Scheme 2). Continuous-flow conditions were likewise explored in order to develop an experimental scalable setup.[12]

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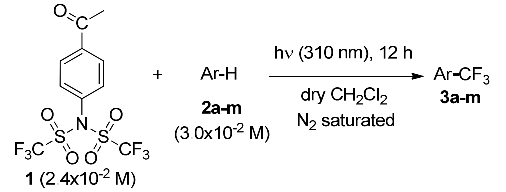
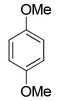
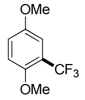
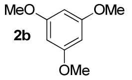
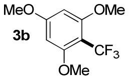
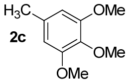
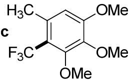
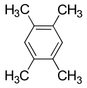
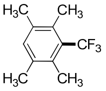
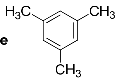
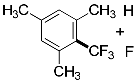
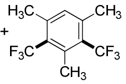
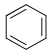
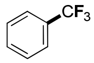
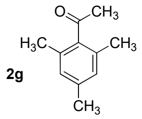
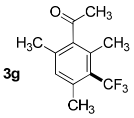
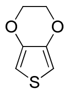
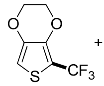
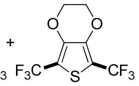
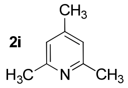
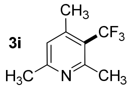
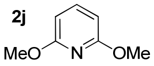
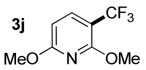
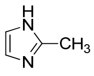
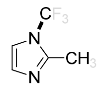
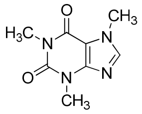
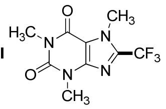
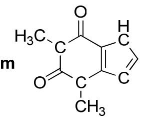
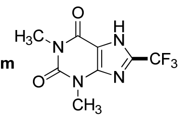
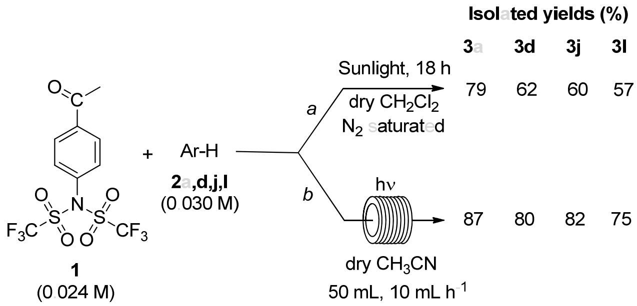
Table 2. Trifluoromethylation of aromatics and heteroaromatics.[a]



Substrates	Products	**3a-m** yields [%]
2a 	**3a** 	81
2b 	**3b** 	85
2c 	**3c** 	79
2d 	**3d** 	61
2e 	 +  **3e** **3e-bis**	**3e**, 60; **3e-bis**, 12
2f 	**3f** 	73[b]
2g 	**3g** 	74[c]
2h 	 +  **3h** **3h-bis**	**3h-bis**, 59 - - - - - - - **3h**[d], 26; **3h-bis**[d], 18
2i 	**3i** 	59
2j 	**3j** 	64
2k 	**3k** 	69
2l 	**3l** 	58
2m 	**3m** 	67[e]

[a] Yields of products isolated by distillation or by column chromatography. [b] Yield obtained by means of a GC calibration curves by using *n*-dodecane as internal standard. [c] [**1**] = 0.048 M (irradiation time: 42 h). [d] [**1**] = 0.015 M (irradiation time: 6 h). [e] Irradiation performed in CH_3CN/H_2O 5:1.

The reactions were carried out in a photoreactor consisting in coils of UV-transparent FEP tubing wrapped around a traditional water cooled 500 W medium pressure mercury lamp.[13] Dry acetonitrile, however, was the best reaction medium in this case (see the Supporting Information for further details).



Scheme 2. Photochemical trifluoromethylation of **2a,d,j,l** under (a) solar irradiation and (b) flow conditions (see the Supporting Information for details).

The solution was circulated at a rate of 10 mL hour^{-1}. As depicted in Scheme 2, for all the reactions tested, products **3** were obtained in higher yields (up to 30%) and in a shorter time (5 h irradiation) than those performed under batch experiments (compare data reported in Table 2 and Scheme 2).

The proposed mechanism is described in Scheme 3. Compound **1** undergoes photoinduced homolysis of one of the N-S bonds (*path a*)[6] to afford radicals **I** and **II**. Loss of SO_2 from **II** gives $F_3C^•$ radical (**III**, *path b*) that is in turn trapped by the (hetero)aromatic **2**, to give intermediate **IV** (*path c*). Compound **3** is then formed via hydrogen atom transfer by the reactive sulfonamido radical **I** (*path d*). Hydrogen abstraction by the $F_3C^•$ radical from **IV** (*path d'*)[3f,14] or from the reaction medium[6,15] had a role since CHF_3 was detected by headspace FT-IR analysis of the photolyzed solution of **1** in the presence (or in the absence)[6,15a,16] of **2f** in CH_2Cl_2 (see the Supporting Information). Nonetheless, the overall efficiency of the process is satisfactory thanks also to the photoinduced release of another equivalent of $F_3C^•$ radical from sulfonamide **1'** (*path a'*), to give 4'-aminoacetophenone **1''**.[6]

We propose that **3k** may be formed from **2k** by the coupling between **III** and the radical cation generated from oxidation of **2k** by intermediate **I**. Related radical couplings had some precedents in the literature[17] and in this case it is supported by electrochemical measurements carried out on sulfonamide anion (see section 9 in the Supporting Information).

Summing up, we demonstrated that *N*-aryltrifluoromethanesulfonimide **1** is a simple and cost-effective reagent for the photoinduced, catalyst-free

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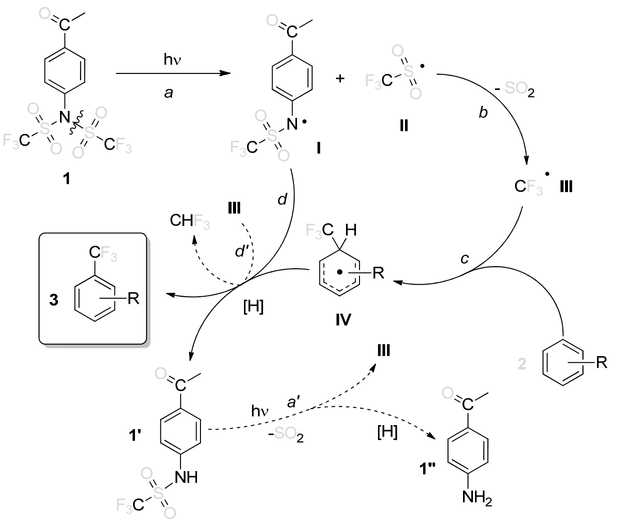
trifluoromethylation of differently substituted (hetero)aromatics, including bioactive molecules.



Scheme 3. Proposed pathways involved in the photochemical trifluoromethylation of (hetero)arenes by **1**.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support by the Fondazione Cariplo (grant no. 2012-0186) is gratefully acknowledged. We also thank Dr. Daniele Merli (University of Pavia) for the electrochemical measurements.

Notes and references

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