

The Direct C–H Difluoromethylation of Heteroarenes Based on the Photolysis of Hypervalent Iodine(III) Reagents That Contain Difluoroacetoxy Ligands

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Supporting Information

ABSTRACT: In this letter, an efficient method for the photolytic generation of difluoromethyl radicals from [bis(difluoroacetoxy)iodo]benzene reagents is described. The present approach enables the introduction of difluoromethyl groups into various heteroarenes under mild conditions in the absence of any additional reagents or catalysts.



T he preparation of organofluorine compounds is an area of considerable importance in pharmaceutical, agrochemical, and materials science, as the introduction of fluoro substituents into organic molecules has a profoundly positive impact on their physical properties, including metabolic stability, solubility, and lipophilicity.^{1–3} Among various fluoroalkyl groups, the difluoromethyl group has attracted particular attention in medicinal chemistry, due to the fact that the CF₂H moiety is isosteric and isopolar to the hydroxyl and thiol groups and may also act as a lipophilic hydrogen donor.⁴ Thus, considerable research efforts have been devoted to the efficient introduction of difluoromethyl groups into organic compounds. However, compared to the well-established trifluoromethylations remain scarce and challenging.⁶

Classically, difluoromethylated compounds are prepared by the deoxyfluorination of aldehydes with SF_4 or dialkylaminosulfur trifluorides such as *N*,*N*-dimethylaminosulfur trifluoride (DAST) or bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor) (Figure 1).⁷ These methods, however, often



Figure 1. Commonly used difluoromethylating agents and strategies to generate difluoromethyl radicals.

suffer from functional (in)compatibility and the need for expensive and/or toxic fluorinating agents. In recent years, the development of radical-based difluoromethylation methods has been the subject of intensive research. In 2013, Baran and coworkers reported zinc bis(difluoromethanesulfinate) as a useful difluoromethylating agent that generates a difluoromethyl radical in the presence of the oxidant tert-butyl hydroperoxide (TBHP).⁸ Sodium difluoromethanesulfinate may also act as a source for a difluoromethyl radical.9 Alternatively, photoredox radical difluoromethylations have recently been realized by using difluoromethanesulfonyl chloride,¹⁰ difluoromethylphosphonium salts,¹¹ and difluoromethylsulfone¹² or -sulfoximine¹³ as difluoromethyl radical sources. The synthetic utility of these methods still remains counterbalanced by the difficulties associated with the handling of some of the expensive and/or gaseous starting materials required to prepare these agents, as well as the necessity for high temperatures, additional oxidants, and/or transition-metal catalysts for the generation of the difluoromethyl radicals. Therefore, alternative strategies that generate mild, efficient, and cost-effective difluoromethyl radicals should be highly desirable.

Difluoroacetic acid is an inexpensive and commercially available reagent that is easy handled, and we envisioned that this acid could be used as a source of difluoromethyl substituents. However, to the best of our knowledge, difluoromethylations using the acid as a difluoromethyl radical source remain elusive. The generation of alkyl radicals from the corresponding carboxylic acids via decarboxylation generally requires strong oxidants, transition-metal catalysts, and/or high temperatures.¹⁴ Therefore, we were interested in using hypervalent iodine(III) reagents with carboxylic acid ligands, as these are highly susceptible to photodecomposition upon exposure to weak UV or visible light to furnish carboxyl radicals that generate the corresponding alkyl radicals upon decarbox-

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ylation.¹⁵ Herein, we report the photolytically induced direct C–H difluoromethylation of heteroarenes using hypervalent iodine(III) reagents (1) that contain difluoroacetoxy ligands. The easily prepared iodine(III) reagents 1 smoothly generate difluoromethyl radicals upon irradiation with visible light (λ = 400 nm) in the absence of any additional reagents or catalysts (Scheme 1).





To test its utility as a difluoromethyl radical source, 1 was subjected to photolysis conditions in the presence of caffeine as a model substrate (Table 1). When the reaction was conducted

Table 1. Optimization of the Reaction Conditions for the Transformation of Caffeine into Difluoromethylated Caffeine $(2a)^a$

Me N O N Me	Ме N N – н –	I(III) (2.0 equiv) hv (λ = 400 nm) solvent (0.2 M) rt, 24 h	$\begin{array}{c} 0 & Me \\ Me & N & N \\ 0 & N & N \\ 0 & N & N \\ Me & 2a \end{array} CF_2H$
entry	I(III)	solvent	2a yield (%) ^b
1	1a	CH_2Cl_2	37
2^{c}	1a	CH_2Cl_2	34
3^d	1b	CH_2Cl_2	53
4^d	1c	CH_2Cl_2	43
5	1d	CH_2Cl_2	41
6	1e	CH_2Cl_2	49
7^d	1b	CDCl ₃	54
8 ^d	1b	CHCl ₃	22
9 ^{<i>d</i>,<i>e</i>}	1b	CDCl ₃	56

^{*a*}Unless otherwise specified, reactions were conducted in the specified solvent (0.2 M) in the presence of caffeine (0.2 mmol) and **1** (0.4 mmol) under irradiation with visible light ($\lambda = 400$ nm). ^{*b*}The yield was determined by ¹H NMR spectroscopy using 1,1,2,2-tetrachloro-ethane as an internal standard. ^{*c*}The reaction was conducted under irradiation with UV light ($\lambda = 365$ nm). ^{*d*}t = 14 h. ^{*e*}c = 0.4 M.

I(OCOCF ₂ H) ₂	1a (R = H)
\downarrow $$	1b (R = 4- <i>t</i> Bu)
	1c (R = 3,5-di- <i>t</i> Bu)
	1d ($R = 4 - CF_3$)
∼R	1e (R = 3,5-di-CF ₃)

with [bis(difluoroacetoxy)iodo]benzene (1a) under exposure to visible light ($\lambda = 400$ nm), difluoromethylated caffeine 2a was obtained in 37% yield (entry 1), while an almost equimolar amount of caffeine (37%) remained unchanged. Changing the wavelength from 400 to 365 nm afforded similar results (entry 2). Subsequently, we tested substituted iodine(III) reagents (1b-e), which afforded the products in slightly improved yields (entries 3-6). While the electronic nature of the substituents had virtually no effect on the product yields (entries 3 and 4 vs entries 5 and 6), the presence of electron-donating *tert*-butyl substituents (**1b** and **1c**) reduced the reaction time (14 h). A screening of solvents revealed that the use of deuterated chloroform (CDCl₃) slightly improved the product yield (entry 7).¹⁶ On the other hand, the reaction in chloroform decreased the yield of **2a**, due to the formation of a large amount of unknown byproducts, which might be derived from the abstraction of hydrogen atoms from chloroform (entry 8).¹⁷ Finally, increasing concentration afforded the best product yield for **2a** (entry 9).

With the optimized conditions in hand, we subsequently investigated the generality of this reaction (Scheme 2). The





^{*a*}Unless otherwise specified, reactions were conducted in CDCl₃ (0.4 M) in the presence of heterocycle (0.2 mmol) and **1b** (2**a**–**d**) or **1c** (2**e**–**n**) (0.4 mmol) under irradiation with visible light (λ = 400 nm). ^{*b*}Isolated yield. ^{*c*}NMR yield.

introduction of difluoromethyl groups on pentoxifylline afforded 2b in 47% yield. The reactions involving uracile derivatives proceeded well, and the corresponding difluoromethylated uraciles (2c and 2d) were obtained in moderate yield. In the case of pyridines, 1c furnished better results than 1b, and the difluoromethyl groups were introduced mainly at the 2position of the pyridines (2e-h).¹⁸ In the case of 2e and 2g, only small amounts of bis-difluoromethylated products were obtained. The reactions with pyrimidines, pyridazine, pyrazine, triazine, and pyrazole also afforded the corresponding products (2i-n) in moderate to good yields.

The utility of the present approach was further demonstrated by the introduction of other fluoroalkyl groups into caffeine (Scheme 3).¹⁹ The reaction of caffeine with iodine(III) reagent Scheme 3. Scope with Respect to the Carboxylic Acid Ligands in the Fluoroalkylation Reagents, Using Caffeine as a Model Substrate



3a, which contains chlorodifluoroacetoxy groups, afforded **4a** in 60% yield. The use of iodine(III) reagents **3b** and **3c** successfully transferred the corresponding difluoroalkyl substituents onto caffeine, affording **4b** and **4c** in acceptable yields. Unfortunately, the introduction of a trifluoromethyl group using **3d** was relatively inefficient, and trifluoromethylated caffeine **4d** was obtained in only 20% yield.

The reaction of caffeine with the *in situ* generated iodine(III) agent **1c** also proceeded well and furnished **2a** in moderate yield (Scheme 4). It should be noted that generation of

Scheme 4. Difluoromethylation of Caffeine by *in Situ* Generated 1c



methylated caffeine 5, which would be potentially formed by the reaction of caffeine with a methyl radical derived from acetoxy radicals, was not observed.

Finally, we conducted several control experiments (Scheme 5). When the difluoromethylation of caffeine with 1a was conducted in the dark, the formation of 2a was not observed (Scheme 5a). A similar reaction under an atmosphere of oxygen significantly reduced the product yield of 2a (Scheme 5b). Moreover, the generation of difluoromethyl radicals was

Scheme 5. Control Experiments



ascertained by radical trapping experiments. When a reaction mixture containing caffeine and **1a** was irradiated with visible light ($\lambda = 400$ nm) in the presence of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), the formation of the difluoromethyl adduct **6** was observed (Scheme 5c).²⁰ On the basis of these results, we tentatively concluded that the present reaction should proceed by a radical mechanism that involves the generation of difluoromethyl radicals induced by the photodecomposition of iodine(III) reagent **1** (Figure 2).



Figure 2. Plauisible reaction mechanism.

First, the photolysis of hypervalent iodine(III) reagents 1 would generate a carboxyl radical 7 and an iodanyl radical 8. Then, the decarboxylation of 7 would afford a difluoromethyl radical, while iodanyl radical 8 would degrade to provide 7 and iodoarene. The difluoromethyl radical subsequently would react with heteroarenes to generate a radical intermediate 9. The oxidation of 9 by 1 or iodanyl radical 8 would give a carbocation intermediate 10. Finally, the deprotonation of 10 would furnish a desired product.

In summary, we have developed a method for the photolytically induced direct C–H difluoromethylation of heteroarenes using hypervalent iodine(III) reagents that contain difluoroacetoxy ligands. The iodine(III) reagents used in this study can be easily prepared from convenient starting materials and are easy to handle. Further applications of the photoreaction presented herein are currently under investigation in our laboratory.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b02416.

Experimental procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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