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N-Difluoromethylation of Imidazoles and Benzimidazoles Using the Ruppert–Prakash Reagent under Neutral Conditions

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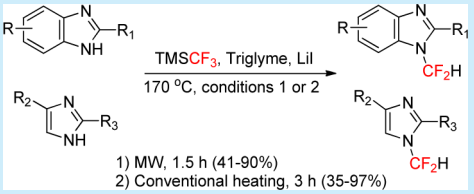
Supporting Information

ABSTRACT: Direct *N*-difluoromethylation of imidazoles and benzimidazoles has been achieved using TMS-CF_3 (the Ruppert–Prakash reagent) under neutral conditions. Difluoromethylated products were obtained in good-to-excellent yields. Inexpensive, commercially available starting materials, neutral conditions, and shorter reaction times are advantages of this methodology. Reactions are accessible through conventional as well as microwave irradiation conditions.



Selective fluorination and fluoroalkylation of organic compounds result in products that have significantly altered electronic and skeletal features. Such fluorinated compounds are greatly utilized in the areas of medicines, agrochemicals, materials chemistry, and catalysis.[1] Among the fluoroalkyl groups, the difluoromethyl group is of key interest as it resembles conventional hydrogen bond donors (N–H, O–H). However, it exhibits enhanced lipophilicity. Moreover, it can serve as a nonconventional hydrogen bond donor (F_2C–H) and a weak hydrogen bond acceptor (C–F) through fluorine. Difluoromethylation has attracted significant attention[2] in the pharmaceutical industry as the CF_2H moiety, when introduced, appreciably affects the pharmacokinetic properties, namely membrane permeability, bioavailability, binding affinity, metabolic stability, and lipophilicity of drug candidates.[3] Consequently, the CF_2H moiety is notably considered in isostere-based drug design.[4] The commercial pharmaceuticals Eflornithine,[5] Pantaprazole,[6] and Garenoxacin,[7] the marketed agrochemicals Sulfentrazone[8] and Carfentrazone-ethyl,[9] and related potential drug candidates[10] all have CF_2H functionality (Figure 1). Imidazoles and benzimidazoles are key structural units, prevalent in biological systems, and have wide applications in medicine,[11] material sciences,[12] and catalysis.[13] Furthermore, fluorinated alkyl and arylated imidazoles and related structures are studied for the preparation of novel imidazolium salts, which can be used as ionic liquids,[14] and as precursors for the preparation of *N*-heterocyclic carbenes, which are useful organocatalysts and ligands for transition metal catalyzed reactions.[15] In this context, selective introduction of the difluoromethyl group onto the imidazole and benzimidazole nitrogen is of great interest.

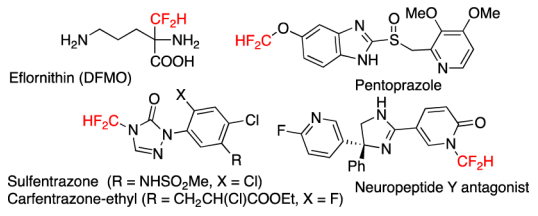


Figure 1. Bioactive compounds containing the difluoromethyl group.

There are several methods in the literature to obtain 1-difluoromethylimidazoles and benzimidazoles using different reagents. Ozone-depleting chlorodifluoromethane is one of the frequently used reagents.[16] The others are sodium trifluoroacetate,[17] methyl chlorodifluoroacetate,[18] chlorodifluoromethyl phenyl sulfone,[19] *N*-tosyl-*S*-difluoromethyl-*S*-phenylsulfoximine,[20] and the more recent sodium chlorodifluoroacetate[21] and $TMSCF_2Br$.[22,23] Hu et al., in their recent work, demonstrated the versatility of $TMSCF_2Br$ in the difluoromethylation of heteroatom nucleophiles. However, when they used $TMSCF_3$ in place of $TMSCF_2Br$, they found no product formation. Although effective and versatile, the lack of commercial availability of $TMSCF_2Br$ and the strongly basic conditions put limitations on the method. Moreover, in their procedure $TMSCF_2Br$ is derived either from $TMSCF_3$ using BBr_3 or $TMSCF_2H$ with NBS.

Previously, the Hu and Prakash groups reported the generation of difluorocarbene from the Ruppert–Prakash reagent[24] ($TMSCF_3$) and successfully added it across alkenes, alkynes,[25a] and Sn–H bonds[25b] under neutral conditions using metal halides and nonmetallic fluorides (CaI_2, NaI, TBAT, TMAF) as initiators. Now, we report the one-step difluoromethylation of imidazoles and benzimidazoles in triglyme using $TMSCF_3$ and LiI as the initiator under neutral conditions. 1*H*-Benzimidazole was chosen as the model substrate for the reaction screening (Table 1; details in the Supporting Information). Screening for optimized conditions using previously reported carbene generation and addition methods

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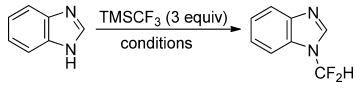
Table 1. Solvent and Initiator Screening[a]

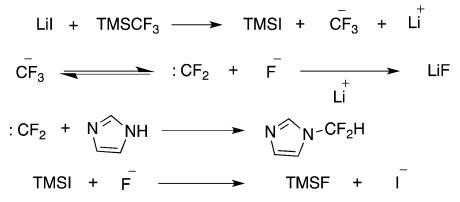


entry	solvent	MX (equiv)	temp (°C)	time (h)	conv[b] (%)
1	DMA	CaI_2 (0.15)	100	0.67	20
2	DMA	K_2CO_3 (1.0)	80	12	23
3	DMA	TBAT (0.1)	rt	2	54
4	DMA	KF (0.5)	rt	2	56
5	THF	LiHMDS (1.2)	−78	21	50
6	HMPA	KF (0.5)	40	14	14
7	THF	LiI (0.5)	90	24	45
8	THF	t-BuOLi (1.2)	−78	7	8
9	THF	LiI (1.5)	140	72	63
10	triglyme	LiI (1.2)	140	8	70
11	triglyme	LiI (1.2)	170 (MW)	1	72

[a]Reactions were carried out on a 0.25 mmol scale with 3 equiv of $TMSCF_3$. [b]The conversion was determined by ^{19}F NMR spectroscopy using trifluorotoluene as internal standard. Entries 6 and 7 were brought to rt from −78 °C. Entry 11 was further optimized (see the Supporting Information for details).

led to low conversions. For example, with CaI_2 in DMA gave 20% (Table 1, entry 1), whereas NaI (THF) produced 30% conversion. Use of fluoride initiators such as TBAT and KF in DMA or LiHMDS in THF resulted in 50% conversion (Table 1, entries 3−5) with most of the $TMSCF_3$ consumed. However, our attempts to optimize the conditions met with little success. Interestingly, lithium iodide in THF produced 45% conversion after 24 h at 90 °C (Table 1, entry 7) but still unreacted $TMSCF_3$ was left behind. It was postulated that the generation of insoluble LiF during the course of the reaction would help to push the carbene generation reaction forward, thereby resulting in an increased yield of the difluoromethylated product (Scheme 1). At the same time, the fluoride generated during

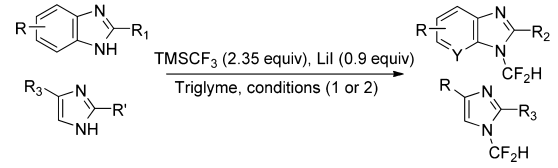
Scheme 1. Proposed Mechanism

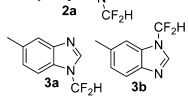
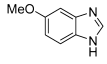
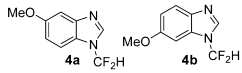
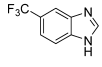
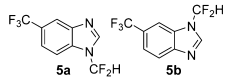
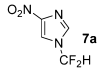
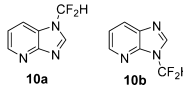


carbene formation would be trapped by Li(I) cation preventing a runaway reaction with the silyl group. Higher boiling ethereal solvents like triglyme enabled the reactions to be performed safely at higher temperatures. Reactions carried out with KF, NaF resulted in complete consumption of $TMSCF_3$ with no product formation probably due to rapid decomposition of $TMSCF_3$ to CF_3H, carbene oligomers and other undesired side products. Control reactions carried out in triglyme (a) without LiI (metal salt initiator) and (b) with LiF both resulted in no product formation. However, an equal amount of unreacted $TMSCF_3$ was left behind (details in the Supporting Information). These results prompted us to postulate that Li(I) cation plays a key role in controlling the availability of fluoride in the reaction mixture, which otherwise will undergo runaway reaction with $TMSCF_3$. Hence, LiI was chosen to optimize the reaction conditions.

We optimized the reactions with 1*H*-benzimidazole (Table 2, entry 1), LiI, and triglyme under microwave conditions, and the

Table 2. Substrate Scope



entry	substrate	product	1) microwave (%) conversion[f] (yield)[g]	2) conventional (%) conversion[f]
1		 1a	90 (80)	82
[a]2		 2a	86 (81)	70
[b,c]3		 3a 3b	77 (73)	77
[b]4		 4a 4b	75 (50)	85
[a,b]5		 5a 5b	77 (71)	78
6		 6a	89 (81)	96
7		 7a	88 (75)	97
[d]8		 8a	76 --	41
9		 9a	44 (22)	46
[e]10		 10a 10b	41 (17)	35

Conditions 1: 0.25 mmol, microwave heating, 170 °C, 1.5 h. Conditions 2: conventional heating, 170 °C, 3 h. [a]Heated for 120 min. [b]Formed two isomers in a 1:1 ratio (based on ^{19}F NMR). [c]Eluted together as a mixture. [d]Product not isolated. [e]Isomers formed MW (34:7); thermal (29:6), only the major isomer was isolated (**10b**). [f]Conversions were determined by ^{19}F NMR spectroscopy using trifluorotoluene as an internal standard. [g]Isolated yield.

amounts of $TMSCF_3$ and LiI were varied to achieve an optimum conversion. It was observed that higher amounts of $TMSCF_3$ or LiI and longer reaction times resulted in lower yields. This is probably due to decomposition of the difluoromethylated product to CF_2HI. The optimized conditions and the substrate scope are shown in Table 2. The reactions can also be carried out under conventional heating conditions *albeit* with longer reaction times (∼3 h).

Imidazoles and benzimidazoles showed similar reactivity with electron-donating and -withdrawing substituents, whereas triazole and 4-azabenzimidazole produced the desired products in lower yields. Substituted imidazole and benzimidazoles produced both of the regioisomers (Table 2, entries 3−5 and 10). In the case of 4-nitroimidazole, only one isomer was observed because of stereoelectronic constraints. Diphenylamine, acetanilide, *N*-methylbenzenesulfonamide, and indole failed to give products under these conditions.

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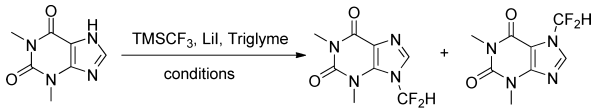
We decided to showcase the application of this methodology by introducing the CF_2H group into biologically active molecules. Caffeine has been known to influence cell cycle function, bringing about programmed cell death and also affecting important regulatory proteins, for instance, the tumor suppressor protein.[26] Difluoromethylation of theophylline (Scheme 2) gave the difluoromethylated analogue of caffeine

Scheme 2. *N*-Difluoromethylation of Theophylline*,[a,b]



11	11a	11b
[a]MW	34%	58%
[a]Conventional	38%	48%
[b]Gram Scale (Conventional)	27%	40%

*MW: 0.25 mmol, 170 °C, 1.5 h. Conventional heating: 170 °C, 3 h. Gram scale: 10 mmol, 170 °C 2 h. [a]Conversions were determined by ^{19}F NMR spectroscopy using trifluorotoluene internal standard. [b]Isolated yield (see the Supporting Information for further details).

(**11b**) and isocaffeine (**11a**) in 3:2 ratio.[27,28] Single-crystal X-ray diffraction (Figure 2) showed the presence of weak

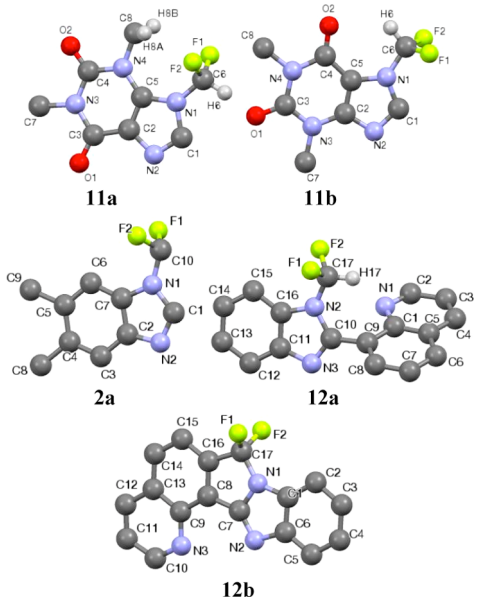
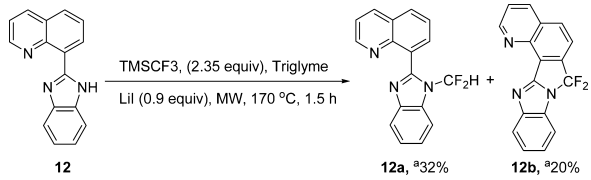


Figure 2. Single-crystal X-ray structures of **11a**,**b**, **2a**, and **12a**,**b** (only a few protons are shown for clarity).

hydrogen-bonding interactions in both the isomers.[29] In **11a**, the fluorine atoms are disposed toward the C8 carbon, which was also evident from throughspace coupling of the C8 protons with C6 fluorines in the ^1H and ^{19}F NMR, whereas the fluorine atoms in **11b** are positioned away from the oxygen atom (O2).[30]

Another extension of this methodology is in the synthesis of difluoromethylated analogues of 8-(1*H*-benzoimidazol-2-yl)-quinoline (8-BQ). Pt-based 8-BQ complexes are known to inhibit amyloid β-peptide in vivo studies.[31] During the synthesis, we obtained the desired product (**12a**) in 32% yield along with an interesting fluoroscent byproduct (**12b**) in 20% yield (Scheme 3), which probably formed by intra-

Scheme 3. Synthesis of *N*-Difluoromethylated Ligand for Amyloid β-Peptide Inhibitor Pt Complex[a]



12 **12a**, [a]32% **12b**, [a]20%

[a]Isolated yield.

molecular nucleophilic substitution of *N*-difluoromethyl carbanion on the quinoline ring. The optimization and investigation of the mechanistic aspects of these applications are currently underway.

In summary, we have successfully demonstrated the difluoromethylation of imidazoles, benzimidazoles, and related molecules using $TMSCF_3$ and LiI under neutral conditions. The difluoromethylated products were obtained in good-to-excellent yield in relatively short reaction times.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and spectroscopic data of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(28) In ref 27, difluorocaffeine (**11b**) was claimed to have been made; however, clear characterization details were not provided. In ref 21, compounds **11a** and **11b** were reported to be a white solid and a yellow liquid, respectively. But in our work we found that **11a** and **11b** as yellow and white solids, respectively, and were able to characterize them by single-crystal X-ray diffraction (Figure 2).
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(30) Through-space coupling details between C8 protons and C6 fluorines in **11a** (Figure 2.): ^{1}H 3.59 ppm (t, $^{6}J_{F-H}$ = 1.6 Hz), ^{19}F −89.28 ppm (dd, $^{2}J_{F-H}$ = 58.7 Hz; $^{6}J_{F-H}$ = 1.6 Hz) ^{13}C NMR, C1 (t, ^{3}J = 2.8 Hz), C5 (s) and C8 (t, ^{5}J = 4.8 Hz). Single-crystal X-ray diffraction details (bond distances and bond angles): C8−F1 = 3.020 Å; C8−F2 = 3.053 Å; F2−H8B = 2.340 Å; F1−H8A = 2.478 Å; C8−H8A−F1 = 114.60°; C8−H8B−F2 = 128.97°. For **11b**, the distances H6−O2 and C6−O2 and the angle C6−H6−O2 are 2.418 Å, 3.146 Å, and 129.04°, respectively, which falls in the range of weak hydrogen bonding interaction (refs 1a and 29).
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