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PII: S0040-4039(18)30733-0
DOI: https://doi.org/10.1016/j.tetlet.2018.06.003
Reference: TETL 50041

To appear in: *Tetrahedron Letters*

Received Date: 7 April 2018
Revised Date: 25 May 2018
Accepted Date: 1 June 2018

Please cite this article as: Mao, T., Zhao, L., Huang, Y., Lou, Y-G., Yao, Q., Li, X-F., He, C-Y., N-Difluoromethylation of Imidazoles and Pyrazoles Using $BrCF_2PO(OEt)_2$ under Mild Condition, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.06.003

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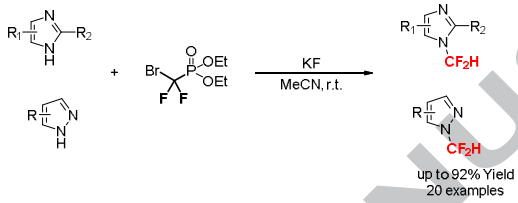

Tetrahedron Letters
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Difluoromethylation
Difluorocarbene
Benzimidazoles
Imidazoles
Pyrazoles

ABSTRACT

A simple and efficient protocol for the direct N-difluoromethylation of imidazoles and pyrazoles has been developed. The reaction makes use of commercially available, non-ozone-depleting and easy handling $BrCF_2PO(OEt)_2$ as difluorocarbene precursor, and provides a cost-efficient and environmentally benign access to some difluoromethylated biologically relevant molecules.

The introduction of a fluorine-containing group into organic molecules has been well recognized as a general strategy in structure-based pharmaceutical research and drug discovery.[1] Specifically, as one of the most omnipresent fluorinated moieties, difluoromethyl (CF_2H) group has attracted much attention because this group can act as a lipophilic hydrogen-bond donor (CF_2-H) and a weak hydrogen-bond acceptor (C-F). Moreover, the introduced CF_2H group can appreciably affect the metabolic stability, lipophility, bioavailability, membrane permeability, and binding affinity of pharmaceutically relevant compounds.[2] Consequently, the CF_2H moiety has been used as bioisostere in drug discovery and considerable efforts have been made in order to develop new and improved strategies for incorporating this important group into a wide scope of compounds. [3]

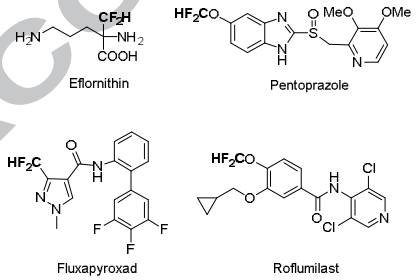
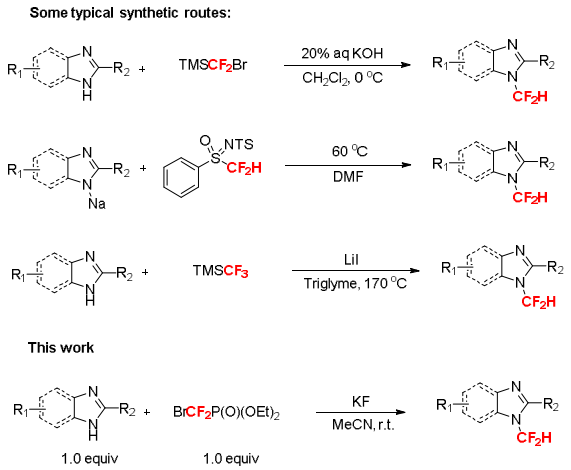


Figure 1. Bioactive compounds containing the difluoromethyl group.

Imidazole derivatives play an important role in chemical and biological systems.[4] Recently, the introduction of fluorinated alkyl onto the imidazole and benzimidazole nitrogen attracted much attention, because this kind of structure can be used as precursors for the preparation of ionic liquids,[5] N-heterocyclic carbenes [6] and as important intermediates in drug discovery. [7]

Until now, there are several methods to access to N-difluoromethylated imidazole. Chlorodifluoromethane, an ozone-depleting chlorofluorocarbon gas, is the frequently used reagent.[8] Over the past few years, some impressive non-ozone-depleting and bench-stable sources to generate difluorocarbene intermediate have been developed (Scheme 1). [9] Hu et al., in their recent works, used $TMSCF_2Br$ [9a] and N-tosyl-S-difluoromethyl-S-phenylsulfox [9b] in the difluoromethylation of heteroatom nucleophiles. Prakash's group reported difluoromethylation of imidazoles using commercial available $TMSCF_3$ under neutral conditions. [9c] However, methods access to such structures were still limited. Consequently, an alternative mild difluoromethylation procedure using commercial available reagents is still of higher desirable.

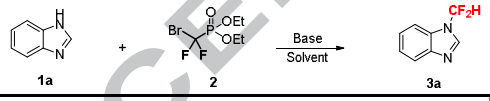
In previous works, $BrCF_2PO(OEt)_2$ was proved to be an efficient difluorocarbene precursor for difluoromethylation of phenols, thiophenols [10] and tertiary amines [11]. Inspired by those works, we envisioned the N-difluoromethylation of imidazoles and pyrazoles via this strategy would also be feasible. As part of our ongoing study on natural compounds fluoroalkylated modification,[12] herein, we report a general method for the N-difluoromethylation of imidazoles and pyrazoles utilizing readily available and bench stable $BrCF_2PO(OEt)_2$ as difluorocarbene precursor (Scheme 1). The notable features of this protocol include their mild reaction conditions, broad substrate scope and synthetic simplicity. Furthermore, the reaction conducted with 1:1 ratio of imidazoles/pyrazoles and diethyl bromodifluoromethylphosphonate in high efficiency, thus highlighting the atom economy of this protocol.



Scheme 1. N-Difluoromethylation of Benzoimidazoles and Imidazoles

We began our investigating by treatment of benzoimidazole **1a** (1.0 equiv) with readily available diethyl bromodifluoromethylphosphonate **2** (2.0 equiv) in the presence of Cs_2CO_3 (2.0 equiv) in MeCN at room temperature. To our delight, 26% yield of desired difluoromethylated product **3a** was detected after 12 h reaction. To improve the reaction efficiency further, different bases were tested. Only a trace yield of **3a** was obtained when Na_2CO_3 was used instead. However, K_3PO_4, K_2CO_3, and KOAc can gave better results (entries 3-5), and 73% yield was obtained when KF was used. The reaction efficiency was even increased when the loading of diethyl bromodifluoromethylphosphonate **2** decreased to 1.0 equiv, and 79% yield of the desired product can be obtained (entry 7). After a survey of the reaction medium utilized, DCE and DMSO were not suitable for this transformation and only trace yield of the desired product was detected. DMF and THF were less effective compared to MeCN. (entries 8, 10). The yield decreased to 48% when 1.0 equiv of KF was used (entry 11), and no desired product was detected in the absence of KF. The yield decreased to 64% when the reaction performed under the air atmosphere.

Table 1. Optimization of N-Difluoromethylation of Benzoimidazole **1a** with diethyl (bromodifluoromethyl)phosphonate **2.** [a]



Entry	Base (equiv)	Solvent	Yield (%) [b]
1	Cs_2CO_3 (2.0)	MeCN	26
2	Na_2CO_3 (2.0)	MeCN	Trace
3	K_2CO_3 (2.0)	MeCN	47
4	K_3PO_4 (2.0)	MeCN	64
5	KOAc (2.0)	MeCN	55
6	KF (2.0)	MeCN	73
7 [c]	KF (2.0)	MeCN	79 (77)
8 [c]	KF (2.0)	THF	65
9 [c]	KF (2.0)	DCE	Nr
10 [c]	KF (2.0)	DMF	68
11 [c]	KF (2.0)	DMSO	9
12 [c]	KF (1.0)	MeCN	48
13 [c]	-----	MeCN	Nr
14 [c,d]	KF (2.0)	MeCN	64

[a] Reaction conditions (unless otherwise specified): **1a** (0.4 mmol, 1 equiv), **2** (2.0 equiv), anhydrous solvent (3 mL) at r.t under Ar for 12 h.

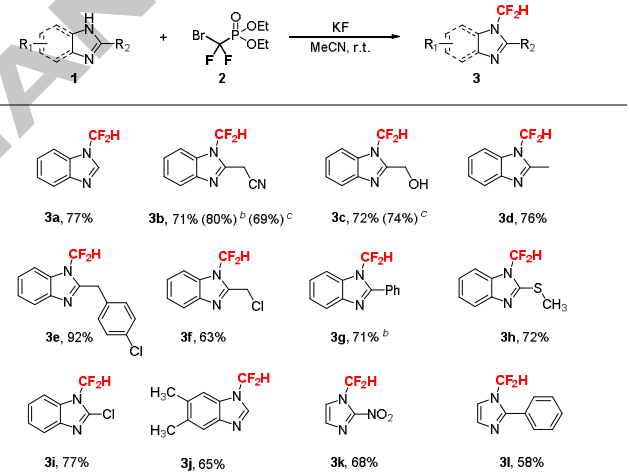
[b] NMR yield determined by ^{19}F NMR using fluorobenzene as an internal standard (isolated yield in parentheses).

[c] **1a** (0.4 mmol, 1 equiv), **2** (1.0 equiv), solvent (3 mL) at r.t for 12 h.

[d] The reaction was carried out under the air atmosphere.

We then investigated the generality and scope of the reaction under the optimal reaction conditions. Various benzimidazoles and imidazoles were subjected to our difluoromethylation protocol to obtain their N-difluoromethylated analogues and representative results are illustrated in Table 2. Substrates bearing cyano (**3b**), hydroxyl (**3c**), methyl (**3d**), halogen (**3e**, **3f**, **3i**), phenyl (**3g**), methylthio- (**3h**), nitro (**3k**) were all tolerated and afforded the corresponding products in good to excellent yields. Moreover, when the reaction performed on a gram scale (**3b**, **c**), comparable yields can still be obtained, which demonstrate the synthetic utility of the protocol.

Table 2. N-difluoromethylation of Benzimidazoles and Imidazoles.[a]



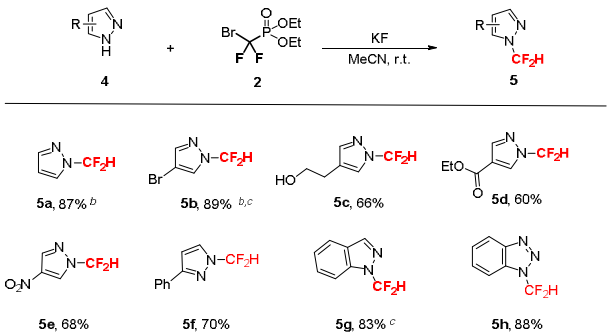
[a] Reaction conditions (unless otherwise specified): **1** (0.4 mmol, 1.0 equiv), **2** (1.0 equiv), KF (2.0 equiv), anhydrous MeCN (3 mL), room temperature, under Ar for 12 h.

[b] **1** (0.4 mmol, 1.0 equiv), KF (2.0 equiv), and **2** (2.0 equiv) were used.

[c] **1** (13 mmol, 1.0 equiv), KF (2.0 equiv), **2** (1.0 equiv) and 15 mL MeCN were used.

As pyrazoles are also very important N-containing heterocyclic found in numerous bioactive molecules, methods for introducing a difluoromethylene group to these structures are still limited. [9e] Therefore, the reaction of **2** with pyrazoles was also examined (**Table 3**). 1H-pyrazole and 4-bromo-1H-pyrazole give the product in excellent yield. 60%-70% yield were obtained when the substrate bearing hydroxyl (**5c**), ester (**5d**), nitro (**5e**) and phenyl (**5f**). Indazole (**5g**) and benzotriazole (**5h**) were also suitable substrates and good yield can still be obtained.

Table 3. N-Difluoromethylation of Pyrazoles.[a]

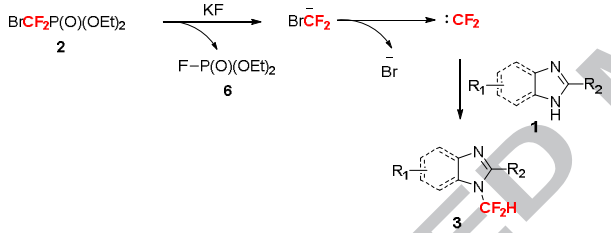


[a] Reaction conditions (unless otherwise specified): **4** (0.4 mmol, 1.0 equiv), **2** (1.0 equiv), KF (2.0 equiv), anhydrous MeCN (3 mL), room temperature, under Ar for 12 h.

[b] F-NMR yield

[c] **4** (0.4 mmol, 1.0 equiv), KF (2.0 equiv), and **2** (2.0 equiv) were used.

On the basis of previous reports, [11] together with the discovery of intermediate **6** which was demonstrated by NMR (see supporting information). a plausible reaction mechanism is proposed in Scheme 2. KF directly attacks the diethyl bromodifluoromethylphosphonate (**2**) to generate difluorocarbene intermediate. Then, difluorocarbene react with imidazoles to afford the desired products.



Scheme 2. Proposed Reaction Mechanism for the Reaction of Imidazoles with Bromodifluoromethylphosphonate **2.**

In conclusion, we have developed a simple and efficient method for N-Difluoromethylation of imidazoles and pyrazoles with a readily available, non-ozone-depleting liquid reagent, diethyl bromodifluoromethylphosphonate. The reaction underwent the formation of difluorocarbene under very mild reaction conditions and very high atom economy is achieved in this process.

Acknowledgments

This work was financially supported by the Young Elite Scientists Sponsorship Program by Cast of the China Association for Science and Technology (No. 2015-41), the National Natural Science Foundation of China (No. 81760624, 21702241), Key Programs of Guizhou Province (2018-1427).

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Supplementary Material

Detailed experimental procedures, and characterization data for

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Highlights
Readily available starting materials
Broad functional groups tolerance
Operationally simple and proceeds under mild reaction conditions.