International Journal of Scientific Research in Engineering and Management (IJSREM)
Volume: 09 Issue: 05 | May – 2025 SJIF Rating: 8.586 ISSN: 2582-3930

Difluoromethylation of N-Pyrazole Using 1-Chloro-1, 1-Difluoromethane Under Mild Condition

Tushar D. Patil[1], Dr. N.P.Rathore[2]

ABSTRACT:

A simple and efficient protocol for the direct Difluoromethylation of pyrazoles has been developed. The reaction makes use of commercially available and easy handling ClCHF2 as difluoromethyl source, and provides a cost-efficient and environmentally benign access to some difluoromethylated biologically relevant molecules.

Keywords: Difluoromethylation Commercially feasible route, Spectral Analysis, Pyrazoles

INTRODUCTION

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 (CF2H) group has attracted much attention because this group can act as a lipophilic hydrogen-bond donor (CF2-H) and a weak hydrogen-bond acceptor (C-F). Moreover, the introduced CF2H group can appreciably affect the metabolic stability, lipophility, bioavailability, membrane permeability, and binding affinity of pharmaceutically relevant compounds.[2] Consequently, the CF2H moiety has been used as bioisostere in drug discovery (Fig. 1) 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] 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[6a,6b] and as important intermediates in drug discovery.[7]

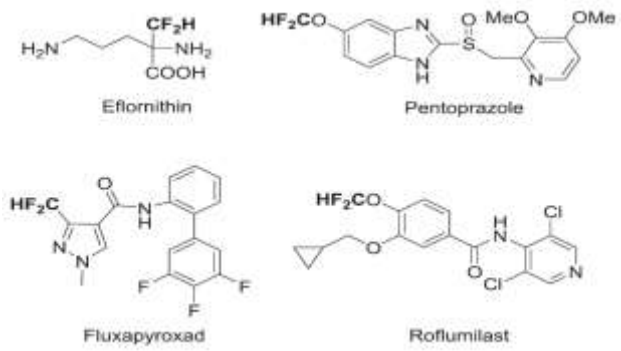


Fig. 1. Bioactive compounds containing the difluoromethyl group

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 Difuoromethane intermediate have been developed (Scheme 1)[9] Hu et al., in their recent works, used TMSCF2Br[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 TMSCF3 under neutral conditions.[9c] However, methods access to such structures were still limited.

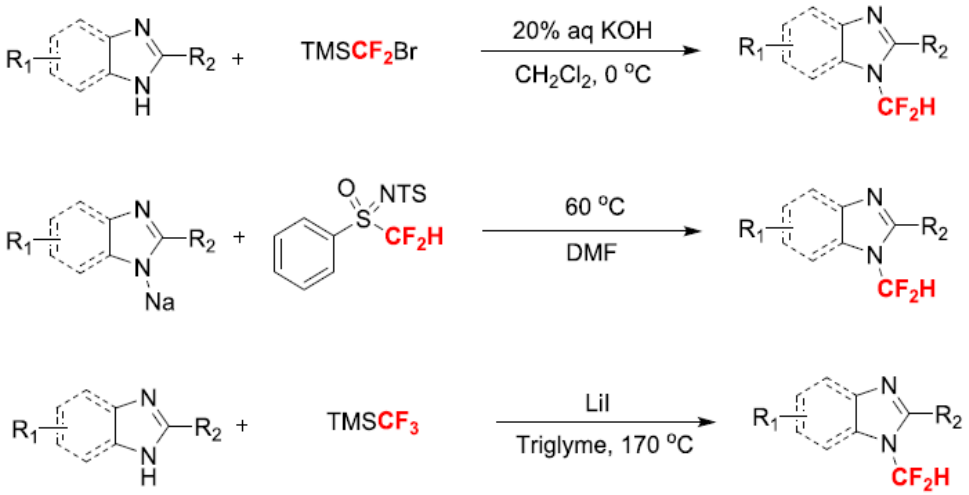


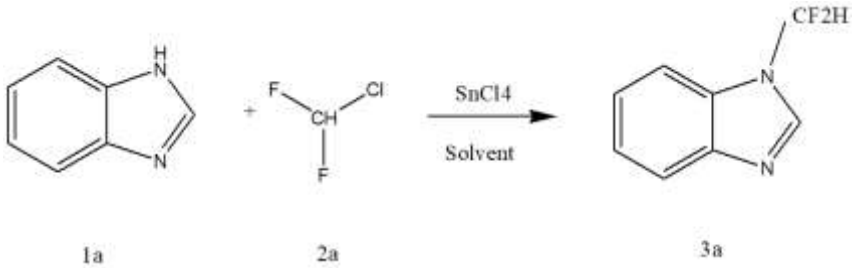
Fig.1. Difluoromethylation of some other heterocyclic molecules

Consequently, an alternative mild difluoromethylation procedure using commercial available reagents is still of higher desirable. In previous works, was proved to be an efficient

Difuoromethane 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 ClCHF2as Difuoromethane precursor (ScSheme 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 Difluorochloromethane in high efficiency, thus highlighting the atom economy of this protocol.

2. Synthesis of using SnCl4 to convert imidazol.to Difluoromethyl imidazol [3a]

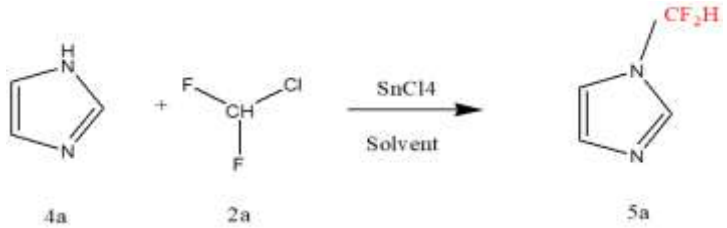


Catalyst (equiv)	Solvent	Temperature	Yield %	Reaction time(hrs)
0.5	EDC	75	88	1
0.5	EDC	80	95	1
0.5	EDC	85	96	1
0.5	EDC	60	85	3
0.5	EDC	65	86	2.5
0.5	EDC	55	89	4
0.2	EDC	55	81	8
0.5	EDC	50	85	5
0.5	DCM	30	80	12
0.5	DCM	25	75	15
0.5	DCM	20	87	15
0.5	DCM	15	81	16
0.5	DCM	10	78	18

* NMR yield determined by 19F NMR using fluorobenzene as an internal standard

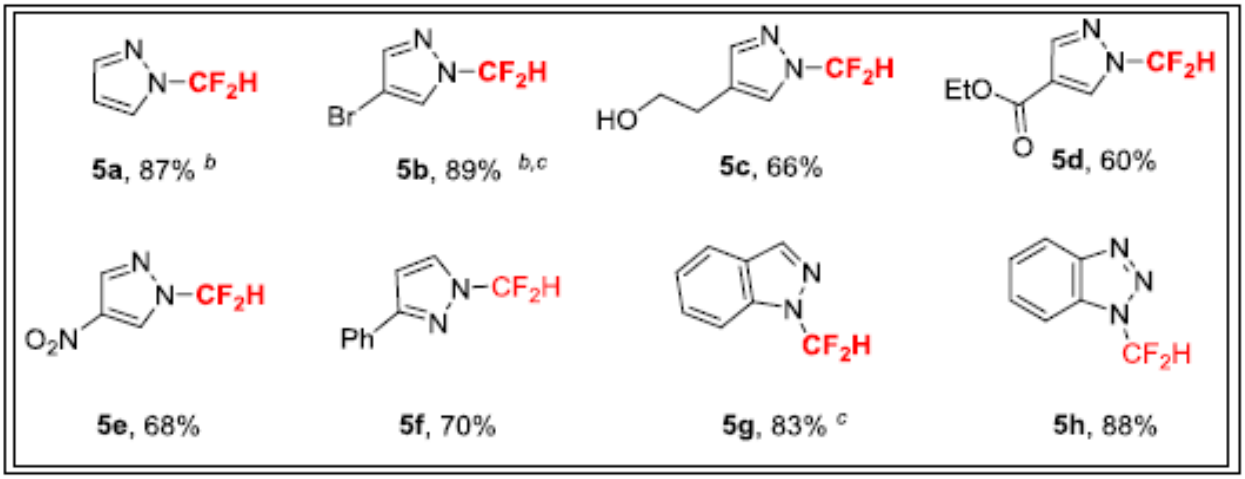
We began our investigating by treatment of Benzoimidazole 1a (1.0 equiv) with readily available Difuoromethane [2] (2.0 equiv) in the presence of SnCl4 (2.0 equiv) in MDC at room temperature. To our delight, 87% yield of desired difluoromethylated product 3a was detected after 15 h reaction (Table 1, entry 1). To improve the reaction efficiency further, different temperatures were tested. Only a trace yield of 3a was obtained when reaction taken lower temperature instead. However, reaction temperature 20 to 85°C can gave better results (Table 1, entries 3–5), and 78% yield was obtained when reaction monitor at 10 °C. The reaction efficiency was even increased when the loading of diethyl Difuoromethane [2] decreased to 1.0 equiv, and 78% yield of the desired product can be obtained (Table 1, entry 7). After a survey of the reaction medium utilized, The yield decreased to 75% when the reaction performed under the air atmosphere (Table 1, entry 14).

2. Synthesis of using SnCl4 to convert Pyrazoles.to Difluoromethyl pyrazole [5a]



4a 2a 5a

Catalyst (equiv)	Solvent	Temperature	Yield %	Reaction time(hrs)
0.5	EDC	75	87	1
0.5	EDC	80	89	1
0.5	EDC	85	88	1
0.5	EDC	60	83	3
0.5	EDC	65	70	1
0.5	EDC	55	60	4
0.2	EDC	55	68	8
0.5	EDC	50	77	5
0.5	DCM	30	80	8
0.5	DCM	25	71	10
0.5	DCM	20	55	10
0.5	DCM	15	49	10
0.5	DCM	10	43	12



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. On the basis of previous reports,11 together with the discovery of intermediate 6 which was demonstrated by NMR . A plausible reaction mechanism is proposed in Scheme 2. Directly attacks the difluorochloromethane (2) to generate difluorocarbene intermediate. Then, difluorocarbene react with imidazoles to afford the desired products. In conclusion, we have developed a simple and efficient method for N-Difluoromethylation of imidazoles and pyrazoles with a readily available, SnCl4 catalyst, and difluorochloromethane. The reaction underwent the formation of difluoromethane under very mild reaction conditions and very high atom economy is achieved in this process.

Acknowledgments

This work is not completed without the support and guidance of Dr. Neelu Jain and also thankfull to the Sri Satya Sai University of Technology and Medical Sciences, Sehore (M.P.).

References

1. Ojima I. Fluorine in Medicinal Chemistry and Chemical Biology. Wiley-Blackwell: Oxford, U.K; 2009; (b) Wang J, Sánchez-Roselló M, Aceña JL, et al. Chem Rev. 2014;114:2432; (c) Zhou Y, Wang J, Gu Z, et al. Chem Rev. 2016;116:422; (d) Preshlock S, Tredwell M, Gouverneur V. Chem Rev. 2016;116:719.

2. (a) Kirk KL. Org Process Res Dev. 2008; 12:305; (b) Prakash's GKS, Chacko S. Curr Opin Drug Discovery Dev. 2008;11:793.

3. (a) Meanwell NA. J Med Chem. 2011;54:2529–2591; (b) Feng Z, Min Q-Q, Fu X-P, An L, Zhang X. Nature Chem. 2017;9:918–923; (c) Ge S, Chaladaj W, Hartwig JF. J Am Chem Soc. 2014;136:4149–4152; (d) Feng Z, Min Q-Q, Zhang X. Org Lett. 2016;18:44–47; (e) Zafrani Y, Yeffet D, Sod-Moriah G, et al. J Med Chem. 2017;60:797–804; (f) Feng Z, Chen F, Zhang X. Org Lett. 2012;14:1938–1941; (g) Feng Z, Min Q-Q, Xiao Y-L, Zhang B, Zhang X. Angew Chem, Int Ed.

2014;53:1669–1673; (h) Lu C, Lu H, Wu J, et al. J Org Chem. 2018;83:1077–1083; (i) Fu X-P, Xiao Y-L, Zhang X. Chin J Chem. 2018;36:143–146; (j) Xu C, Guo W-H, He X, G Y-L, Zhang X-Y, Zhang X. Nat. Commun. 2018;9:1170; (k) Gu Y, Leng X, Shen Q. Nat Commun. 2014;5:5405; (l) Ran Y, Lin Q-Y, Xu X-H, Qing F-L. J Org Chem. 2016;81:7001–7007.

4. (a) For reviews see: Bando T, Sugiyama H. Acc Chem Res. 2006;39:935–944; (b) Breslow R. Acc Chem Res. 1991;24:317–324; (c) Townsend LB. Chem Rev. 1967;67:533–563; (d) Palui G, Aldeek F, Wang W, Mattoussi H. Chem Soc Rev. 2015;44:193–227.

5. Abate A, Petrozza A, Cavallo G, et al. Mater Chem A.. 2013;1:6572.

6. (a) Rivera G, Elizalde O, Roa G, Montiel I, Bernes SJ. Org Met Chem. 2012;699:82; (b) Liu T, Zhao X, Shen Q, Lu L. Tetrahedron. 2012;68:6535.

7. (a) Hodyna D, Kovalishyn V, Rogalsky S, Blagodatnyi V, Petko K, Metelytsia L. Chem Biol Drug Des. 2016;88:422–433; (b) Moore CL, Zivkovic A, Engels JW, Kuchta RD. Biochemistry. 2004;43:12367–12374.

8. Lyga JW, Patera RM. J Fluorine Chem. 1998;92:141–145.

9. (a) Li L, Wang F, Ni C, Hu J. Angew Chem, Int Ed. 2013;52:12390–12394; (b) Zhang W, Wang F, Hu J. Org Lett. 2009;11:2109–2112; (c) Prakash GKS, Krishnamoorthy S, Ganesh SK, Kulkarni A, Haiges R, Olah GA. Org Lett. 2014;16:54–57; (d) Mehta VP, Greaney MF. Org Lett. 2013;15:5036–5039; (e) Deng X-Y, L J-H, Zheng J, Xiao J-C. Chem Commun. 2015;51:8805–8808; (f) Wang F, Zhang L, Zheng J, Hu J. J Fluorine Chem. 2011;132:521–528; (g) Zheng J, Li Y, Zhang L, Hu J, Meuzelaarb GJ, Federselb H-J. Chem Commun. 2007;48:5149–5151.

10. (a) Yossi Z, Gali S-M, Yoffi S. Tetrahedron. 2009;65:5278–5283; (b) Huang Y, Wang A-J, Kong J, Lou Y-G, Li X-F, He C-Y. Synth Comm. 2018;48:91–96.

11. Zafrani Y, Amir D, Yehezkel L, et al. J Org Chem. 2016;81:9180–9187.

12. (a) He C-Y, Kong J, Li X, Li X, Yao Q, Yuan F