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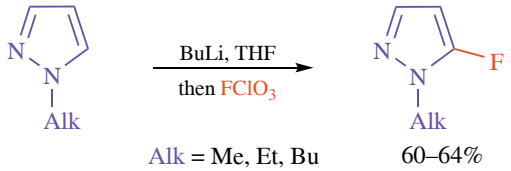
Practical one-pot synthesis of *N*-alkyl-5-fluoropyrazoles

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Three *N*-alkyl-5-fluoropyrazoles were prepared from the corresponding *N*-alkylpyrazoles (60–64% yields) by lithiation (BuLi) at the 5-position followed by treatment with perchloryl fluoride ($FClO_3$) in the same vessel. The obtained compounds can be regarded as versatile building blocks for the development of medicinal and agrochemical agents.



Keywords: 5-membered heterocycles, pyrazoles, fluoropyrazoles, perchloryl fluoride, organofluorine compounds.

Heterocycles are fundamental scaffolds in medicinal chemistry, forming the core of over 85% of drugs due to their structural versatility and ability to modulate key pharmacological properties such as solubility, binding affinity, and metabolic stability. The introduction of fluorine atoms into heterocyclic frameworks further enhances these attributes, improving bioavailability and metabolic resistance, and has become a key strategy in drug and agrochemical design.[1–4]

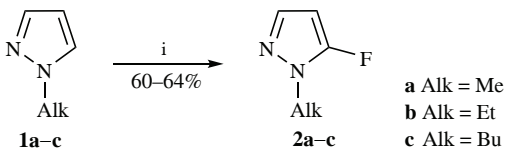
Among fluorinated heterocycles, fluoropyrazoles are of particular interest.[5–7] Their value is exemplified by the fungicide Penflufen, where incorporation of a 5-fluoropyrazole moiety significantly boosted potency and stability.[8,9] As a result, the 5-fluoropyrazole scaffold is now a prominent structural motif in both pharmaceutical and agrochemical research.[10–13] Beyond biological applications, fluoropyrazoles serve as ligands in coordination chemistry, enabling the design of metal complexes with improved thermal stability, luminescence properties, and unique magneto-structural features.[14–17] Several synthetic approaches to 5-fluoropyrazoles have been reported[18] including heterocycle assembly from fluorinated precursors,[19–23] nucleophilic substitution (*e.g.*, action of KF on 5-chloropyrazoles),[24,25] and electrophilic fluorination using reagents such as NFSI, Selectfluor, and XeF_2.[26–29] While these methods provide access to fluoropyrazole derivatives, there remains a need for efficient and selective routes to *N*-alkyl-5-fluoropyrazoles.

In this context, perchloryl fluoride ($FClO_3$) is a promising electrophilic fluorinating agent.[30–32] It acts as a two-centre electrophile capable of introducing fluorine at positions with mobile hydrogen atoms, typically in the presence of a base. Although its fluorination potential has been demonstrated for some heterocycles (*e.g.*, thiophenes), its application to pyrazoles remains underexplored. Herein, we present an efficient selective fluorination of *N*-alkylpyrazoles at the 5-position using $FClO_3$, offering a practical route to these valuable building blocks.

The initial protocol involved treatment of *N*-methylpyrazole **1a** with BuLi in THF at –78 °C, bubbling excess $FClO_3$ (1.25 : 1 molar ratio) through the reaction mixture, stirring for 3 h under cooling, and allowing the mixture to warm to room temperature. However, these attempts yielded the target product **2a** in low yields. Meantime, raising the reaction temperature to –20 °C significantly improved the yield, affording 5-fluoro-*N*-methylpyrazole **2a** in 64% yield (Scheme 1). We then extended this methodology to other *N*-alkylpyrazoles **1b**,**c**. LC-MS analysis confirmed approximately 80% content of the desired fluoropyrazoles **2a–c** in the reaction mixtures. After distillation, compounds **2a–c** were isolated in 60–64% yields. The process proved scalable: single batches produced 25–35 g of pyrazoles **2a–c**.

The structures of compounds **2a–c** were unequivocally confirmed by ^1H, ^{13}C, and ^{19}F NMR spectroscopy. Notably, for compounds **2a**,**b**, we successfully measured ^{15}N chemical shifts and ^{15}N–^{19}F coupling constants. Interestingly, the introduction of a fluorine atom at the 5-position of the pyrazole ring causes a significant upfield shift of the ^{15}N resonances compared to those of non-fluorinated analogues **1**. Specifically, for **2a**, the ^{15}N chemical shifts are –90.84 and –198.57 ppm; for **1a**, the corresponding shifts are –71.00 and –176.48 ppm. This upfield displacement reflects the electronic influence of the fluorine substituent on the pyrazole nitrogen environments. Additionally, we observed a $^3J_{N–F}$ coupling constant of 11.7 Hz, but only for the nitrogen atom at the 2-position. This selective coupling provides further evidence of the anisotropic electronic effects imposed by the fluorine substituent.

In summary, we elaborated a one-step synthesis of *N*-alkyl-5-fluoropyrazoles by direct lithiation/fluorination of pyrazoles with $FClO_3$. The procedure is scalable, and tens of grams of *N*-methyl-, *N*-ethyl-, and *N*-butyl-5-fluoropyrazoles were synthesized in one run. Given the high efficiency, simplicity, and low costs of our method, we believe that *N*-alkyl-5-fluoropyrazoles will soon find wide application in coordination chemistry, agrochemistry and medicinal chemistry as valuable building blocks.



Scheme 1 *Reagents and conditions*: i, BuLi (1.1 equiv.), THF, –20 °C, then $FClO_3$ (1.25 equiv.), 3 h.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.8110.

References

1 S. Fustero, A. Simón-Fuentes, O. Delgado and R. Román, in *Fluorine in Heterocyclic Chemistry*, ed. V. Nenajdenko, Springer, Heidelberg, 2014, vol. 1, pp. 279–321; https://doi.org/10.1007/978-3-319-04346-3_7.

2 L. V. Politanskaya, G. A. Selivanova, E. V. Panteleeva, E. V. Tretyakov, V. E. Platonov, P. V. Nikul'shin, A. S. Vinogradov, Ya. V. Zonov, V. M. Karpov, T. V. Mezhenkova, A. V. Vasilyev, A. B. Koldobskii, O. S. Shilova, S. M. Morozova, Ya. V. Burgart, E. V. Shchegolkov, V. I. Saloutin, V. B. Sokolov, A. Yu. Aksinenko, V. G. Nenajdenko, M. Yu. Moskalik, V. V. Astakhova, B. A. Shainyan, A. A. Tabolin, S. L. Ioffe, V. M. Muzalevskiy, E. S. Balenkova, A. V. Shastin, A. A. Tyutyunov, V. E. Boiko, S. M. Igumnov, A. D. Dilman, N. Yu. Adonin, V. V. Bardin, S. M. Masoud, D. V. Vorobyeva, S. N. Osipov, E. V. Nosova, G. N. Lipunova, V. N. Charushin, D. O. Prima, A. G. Makarov, A. V. Zibarev, B. A. Trofimov, L. N. Sobenina, K. V. Belyaeva, V. Ya. Sosnovskikh, D. L. Obydennov and S. A. Usachev, *Russ. Chem. Rev.*, 2019, **88**, 425; https://doi.org/10.1070/RCR4871.

3 M. A. Gromova, Yu. V. Kharitonov, L. V. Politanskaya, E. V. Tretyakov and E. E. Shults, *J. Fluorine Chem*., 2020, **236**, 109554; https://doi.org/10.1016/j.jfluchem.2020.109554.

4 L. Politanskaya, I. Bagryanskaya and E. Tretyakov, *J. Fluorine Chem*., 2018, **214**, 48; https://doi.org/10.1016/j.jfluchem.2018.06.011.

5 *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry and Application*, ed. V. A. Petrov, John Wiley & Sons, Inc., Hoboken, 2009; https://doi.org/10.1002/9780470528952.

6 P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, 2nd edn., Wiley, Weinheim, 2013; https://doi.org/10.1002/9783527651351.

7 B. Ugrak, T. Dutova, V. Rusak and E. Tretyakov, *J. Heterocycl. Chem*., 2026, **63**, 703; https://doi.org/10.1002/jhet.70167.

8 *The Pesticide Manual: A World Compendium*, 16th edn., ed. C. MacBean, British Crop Production Council, 2012; https://books.google.ru/books/about/The_Pesticide_Manual.html?hl=ru&id=EVuZMgEACAAJ&redir_esc=y.

9 H. Walter, in *Bioactive Carboxylic Compound Classes: Pharmaceuticals and Agrochemicals*, eds. C. Lamberth and J. Dinges, Wiley-VCH, Weinheim, 2016, pp. 405–425; https://doi.org/10.1002/9783527693931.ch31.

10 R. Dunkel, S. Gary, M. C. Grosjean-Cournoyer, P. Rinolfi and A. Tuch, *Patent WO2008015189 A2*, 2008; https://patentimages.storage.googleapis.com/b5/ee/e0/7407e4fe101ea0/WO2008015189A2.pdf.

11 H. L. Elbe, H. Rieck, R. Dunkel, Q. Zhu-Ohlbach, A. Mauler-Machnik, U. Wachendorff-Neumann and K. H. Kuck, *Patent WO2003010149 A1*, 2003; https://patentimages.storage.googleapis.com/28/a4/b2/28ff0f11801aa4/WO2003010149A1.pdf.

12 H. L. Elbe, H. Rieck, R. Dunkel, U. Wachendorff-Neumann, A. Mauler-Machnik, K. H. Kuck, M. Kugler and T. Jaetsch, *Patent WO2002008195 A1*, 2002; https://patentimages.storage.googleapis.com/0e/e8/4b/cbb52998edf509/WO2002008195A1.pdf.

13 H. L. Elbe, A. Mauler-Machnik, K. Stenzel, K. H. Kuck, M. Kugler and T. Jaetsch, *Patent DE19840322 A1*, 2000; https://patents.google.com/patent/DE19840322A1/en.

14 H. V. R. Dias, H. V. K. Diyabalanage, M. A. Rawashdeh-Omary, M. A. Franzman and M. A. Omary, *J. Am. Chem. Soc*., 2003, **125**, 12072; https://doi.org/10.1021/ja036736o.

15 A. Serykh, E. Tretyakov, P. Fedyushin, B. Ugrak, T. Dutova, A. Lalov, A. Korlyukov, A. Akyeva, M. Syroeshkin, A. Bogomyakov, G. Romanenko, N. Artiukhova, M. Egorov and V. Ovcharenko, *J. Mol. Struct*., 2022, **1269**, 133739; https://doi.org/10.1016/j.molstruc.2022.133739.

16 E. Kudryavtseva, A. Serykh, B. Ugrak, T. Dutova, D. Nasyrova, A. Korlyukov, M. Zykin, N. Efimov, A. Bogomyakov and E. Tretyakov, *Crystals*, 2023, **13**, 1528; https://doi.org/10.3390/cryst13101528.

17 E. Kudryavtseva, A. Serykh, B. Ugrak, T. Dutova, D. Nasyrova, D. Aleshin, N. Efimov, P. Dorovatovskii, A. Bogomyakov, S. Fokin, G. Romanenko, A. Sergeeva and E. Tretyakov, *Crystals*, 2023, **13**, 1655; https://doi.org/10.3390/cryst13121655.

18 F. Fabra, J. Vilarrasa and J. Coll, *J. Heterocycl. Chem*., 1978, **15**, 1447; https://doi.org/10.1002/jhet.5570150839.

19 Y. Ohtsuka, D. Uraguchi, K. Yamamoto, K. Tokuhisa and T. Yamakawa, *Tetrahedron*, 2012, **68**, 2636; https://doi.org/10.1016/j.tet.2012.01.075.

20 H. Liu, D. Audisio, L. Plougastel, E. Decuypere, D. A. Buisson, O. Koniev, S. Kolodych, A. Wagner, M. Elhabiri, A. Krzyczmonik, S. Forsback, O. Solin, V. Gouverneur and F. Taran, *Angew. Chem., Int. Ed*., 2016, **55**, 12073; https://doi.org/10.1002/anie.201606495.

21 J. Ichikawa, M. Kobayashi, Y. Noda, N. Yokota, K. Amano and T. Minami, *J. Org. Chem*., 1996, **61**, 2763; https://doi.org/10.1021/jo951814e.

22 J.-N. Volle and M. Schlosser, *Eur. J. Org. Chem*., 2000, 823; https://doi.org/10.1002/(SICI)1099-0690(200003)2000:5<823::AID-EJOC823>3.0.CO;2-M.

23 Y.-F. Wang, G. H. Lonca and S. Chiba, *Angew. Chem., Int. Ed*., 2014, **53**, 1067; https://doi.org/10.1002/anie.201307846.

24 A. Neeff and S. Pazenok, *Patent US2009/0306401 A1*, 2009; https://patentimages.storage.googleapis.com/3b/12/f2/ec6bbcf96de9d0/US20090306401A1.pdf.

25 S. Pazenok, N. Lui and S. Gary, *Patent US2011/288305 A1*, 2011; https://patentimages.storage.googleapis.com/41/6d/f7/2ab71d30ef57a1/US20110288305A1.pdf.

26 V. Levchenko, Y. V. Dmytriv, A. V. Tymtsunik, K. Liubchak, A. Rudnichenko, A. V. Melnyk, S. Y. Veselovych, Y. V. Borodulin, O. M. Otsalyuk, A. A. Tolmachev and P. K. Mykhailiuk, *J. Org. Chem*., 2018, **83**, 3265; https://doi.org/10.1021/acs.joc.8b00199.

27 X. Yuan, J.-F. Yao and Z.-Y. Tang, *Org. Lett*., 2017, **19**, 1410; https://doi.org/10.1021/acs.orglett.7b00335.

28 F. Giornal, S. Pazenok, L. Rodefeld, N. Lui, J-P. Vors and F. R. Leroux, *J. Fluorine Chem*., 2013, **152**, 2; https://doi.org/10.1016/j.jfluchem.2012.11.008.

29 J. C. Sloop, C. Holder and M. Henary, *Eur. J. Org. Chem*., 2015, 3405; https://doi.org/10.1002/ejoc.201500258.

30 A. Engelbrecht and A. Atzwanger, *Monatsh. Chem.*, 1952, **83**, 1087; https://doi.org/10.1007/BF00899646.

31 V. M. Khutoretskii, L. V. Okhlobystina and A. A. Fainzil'berg, *Russ. Chem. Rev.*, 1967, **36**, 145; https://doi.org/10.1070/RC1967v036n03ABEH001593.

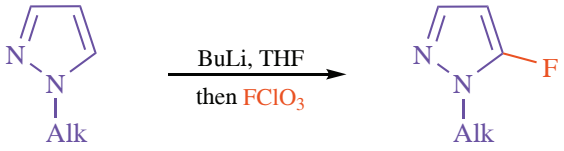
32 G. Barth-Wehrenalp, *J. Inorg. Nucl. Chem*., 1956, **2**, 266; https://doi.org/10.1016/0022-1902(56)80056-0.

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Contents entry

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Alk = Me, Et, Bu

60–64%

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