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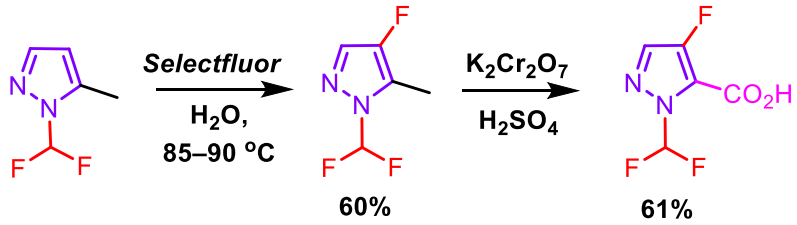
Pyrazole derivatives fluorinated both on the heterocycle and on the *N*-alkyl substituent

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We describe an efficient route to the first pyrazole derivatives that are fluorinated both on the heterocycle and on the *N*-alkyl substituent, namely 4-fluoro-1-(difluoromethyl)-5-methyl-1*H*-pyrazole and 4-fluoro-1-(difluoromethyl)-1*H*-pyrazole-5-carboxylic acid.



Keywords: 5-membered heterocycles; fluorinated pyrazoles; fluorinating reagents; fluorinated building blocks.

N-Fluoroalkylpyrazoles represent a rapidly expanding class of fluorinated heterocyclic compounds that merge the versatile reactivity of the pyrazole scaffold with the distinct electronic and steric effects conferred by fluoroalkyl substituents.[1–3] The strategic introduction of fluoroalkyl groups (e.g., $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2CF_3$) into heteroaromatic systems has emerged as a powerful approach in medicinal chemistry, agrochemistry, and materials science, since such modifications substantially influence key molecular properties.[4–7]

From a physicochemical perspective, fluoroalkyl moieties markedly alter the polarity, lipophilicity, and metabolic stability of organic molecules.[8] The high electronegativity of fluorine generates pronounced inductive effects, which polarize adjacent bonds and modulate the electron density within the pyrazole ring. Consequently, this impacts pKa values, hydrogen-bonding capacity, and dipole moments – parameters crucial for optimizing target affinity and pharmacokinetic profiles. Furthermore, the kinetic stability of the C–F bond often enhances

resistance to oxidative metabolism in vivo, thereby extending the biological half-life of candidate compounds.[9–11]

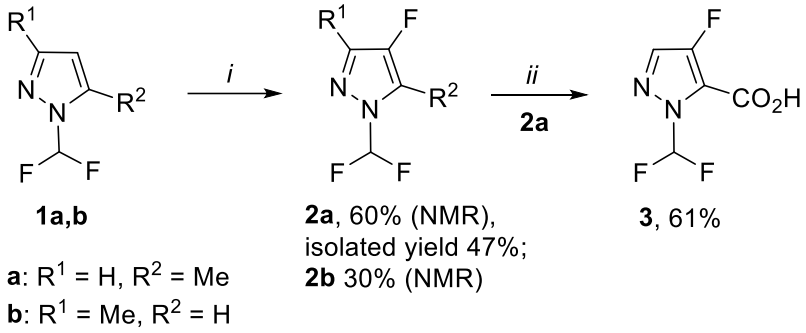
In drug discovery, *N*-fluoroalkylpyrazoles have attracted considerable attention owing to their capacity to improve membrane permeability while preserving aqueous solubility – a delicate balance vital for achieving oral bioavailability.[12,13] Several pharmaceutical agents incorporating fluoroalkylpyrazole motifs are currently under investigation or already in clinical use, underscoring the therapeutic potential of this scaffold.[5,6,14] Beyond biomedical applications, these compounds also hold promise for the development of functional materials, such as liquid crystals, dyes, organic radicals, and ligands for coordination chemistry, where precise control over electronic properties is essential.[15–17]

Despite their increasing significance, the synthesis of *N*-fluoroalkylpyrazoles remains challenging, and the preparation of basic fluorinated pyrazoles constitutes a particularly pressing issue. Given the considerable interest in fluorinated pyrazoles, including 1-fluoroalkylpyrazoles, we have focused on developing systematic approaches to synthesize representative series of compounds within this class.[18–20] In this work, we present a method for synthesizing the first pyrazole derivatives that feature both a fluorine atom within the heterocycle and an *N*-fluoroalkyl group.

We have previously described a one-pot synthesis of a mixture of isomers, namely 1-difluoromethyl-5-methylpyrazole (**1a**) and 1-difluoromethyl-3-methylpyrazole (**1b**).[18,20] Although the isomers have very similar boiling points (117.3 and 118.6 °C, respectively), they were successfully separated on a gram scale using an efficient distillation column. The purified isomers **1a** and **1b** were then used as starting materials for synthesizing a diverse range of 4-substituted *N*-difluoromethylated pyrazole derivatives, including 1-(difluoromethyl)-1*H*-pyrazole-5-carboxylic acid and 1-(difluoromethyl)-1*H*-pyrazole-3-carboxylic acid, as well as their corresponding methyl esters.

Attempts to fluorinate these esters using *Selectfluor* proved unsuccessful. In contrast, treatment of **1a** with *Selectfluor* in water at 90 °C afforded 4-fluoro-1-(difluoromethyl)-5-methyl-1*H*-pyrazole (**2a**) in up to 47% isolated yield (Scheme 1). According to NMR spectroscopy data, the isomeric 4-fluoro-1-(difluoromethyl)-3-methyl-1*H*-pyrazole (**2b**) was formed in approximately 30% yield. However, this product has not yet been isolated due to its low boiling point and high volatility.

Further oxidation of substituted 5-methyl-1*H*-pyrazole **2a** with potassium dichromate in sulfuric acid yielded 4-fluoro-1-(difluoromethyl)-1*H*-pyrazole-5-carboxylic acid (**3**) in 61% yield (Scheme 1).



Scheme 1 *Reagents and conditions: i, Selectfluor*, water, 85–90 °C, 3 h; ii. $K_2Cr_2O_7$, H_2SO_4, < 10 °C, 6 h.

In summary, we have developed the first pyrazole derivatives that are fluorinated both on the heterocycle and on the *N*-alkyl substituent, namely 4-fluoro-1-(difluoromethyl)-5-methyl-1*H*-pyrazole and 4-fluoro-1-(difluoromethyl)-1*H*-pyrazole-5-carboxylic acid. The synthesis of these compounds opens new avenues for preparing fluorinated pyrazole derivatives, which are of considerable interest for applications in medicinal chemistry, agrochemistry, and coordination chemistry.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.8202.

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