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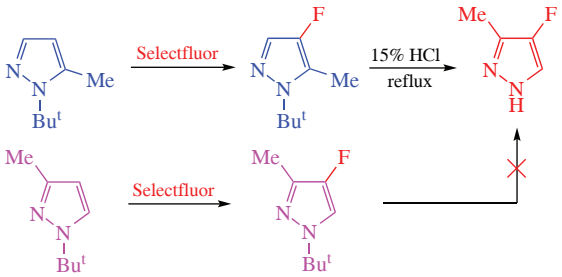
Practical synthesis of 4-fluoro-3-methylpyrazole

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The electrophilic fluorination of 1-*tert*-butyl-3-methyl- and 1-*tert*-butyl-5-methylpyrazoles with Selectfluor affords the corresponding 4-fluoropyrazoles, in distinction to *N*-unsubstituted 3-methylpyrazole. 1-*tert*-Butyl-4-fluoro-5-methylpyrazole readily undergoes HCl-assitied *N*-de-*tert*-butylation yielding 4-fluoro-3-methylpyrazole whereas the isomer with 3-positioned methyl group tolerates the deprotection. The procedure is practical (aqueous medium), scalable, and employs commercial reagents.



Keywords: 5-membered heterocycles, pyrazoles, fluoropyrazoles, fluorinating reagents, Selectfluor, organofluorine compounds.

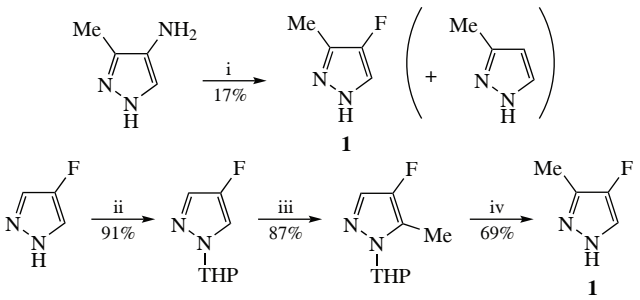
Heterocycles are fundamental scaffolds in drug design, they are present in ~85% of bioactive compounds,[1,2] and the introduction of fluorine into the heterocyclic nuclear has become a key strategy in medicinal chemistry. Today, ~20% of marketed pharmaceuticals and ~50% of agrochemicals are fluorinated, with over 30% of blockbuster drugs containing fluorine.[3,4] The C–F bond imparts valuable properties such as high bond strength, minimal steric hindrance, enhanced metabolic stability, improved bioavailability, and modulated physicochemical traits[5–7] making fluorinated heterocycles versatile platforms, as demonstrated by numerous FDA-approved drugs.[8,9]

Despite growing interest, incorporating fluorinated moieties remains challenging.[10–14] Among the most promising strategies are the following: late-stage fluorination,[15–17] difluorocarbene-based approaches,[18–20] catalyzed and photocatalyzed reactions,[21–23] and microwave-assisted synthesis.[24,25] A special case involves polyfluorinated heterocycles, where the cumulative effect of multiple fluorine atoms facilitates nucleophilic substitution reactions, leading to less fluorinated derivatives.[26–28] While late-stage fluorination and other advanced methods are promising, the use of fluorinated building blocks from the outset is still the prevailing strategy, underscoring the need for efficient routes to basic fluorinated heterocycles.[29]

Fluorinated pyrazoles represent a rapidly expanding research area since over 50% of related publications have appeared in the last five years spanning drug discovery, agrochemistry, and coordination chemistry (>60 000 results in SciFinder/Reaxys).[30–32] Significant efforts have also been focused on synthesizing low molecular weight fluorine-containing pyrazoles,[33–35] *e.g.*, 4-fluoropyrazole[36,37] and 5-fluoropyrazole.[38–40] However, the literature lacks efficient methods for preparing 3-methyl-4-fluoro- and 3-methyl-5-fluoropyrazole derivatives attractive due to the synthetic versatility of the methyl group. Herein, we present a convenient and scalable procedure for preparing 3-methyl-4-fluoropyrazole **1**.

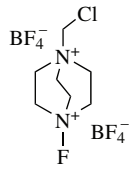
Data on the synthesis and properties of 3-methyl-4-fluoropyrazole **1** remain scarce. In a patent by Arndt *et al.*,[41] compound **1** was prepared *via* a diazotization–fluorination sequence: 4-amino-3-methylpyrazole was treated with aqueous $NaNO_2$ and HBF_4, followed by UV irradiation (Scheme 1, step i). This reaction yielded a 4 : 1 mixture of 3-methyl-4-fluoropyrazole **1** and 3-methylpyrazole, from which the target product was isolated in 17% yield. Notably, compound **1** demonstrated efficacy as a prolonged nitrification inhibitor in naturally alkaline soils. An alternative route to fluoropyrazole **1** with improved efficiency (55% overall yield) involved THP protection of the NH moiety in 4-fluoropyrazole, lithiation, alkylation, and deprotection (see Scheme 1, steps ii–iv). The resulting compound has found application in the synthesis of heterocyclic molecules, particularly in the development of novel pharmaceutical compositions.[42,43]

To establish a simpler and more efficient method for the preparation of 3-methyl-4-fluoropyrazole **1**, we first explored direct fluorination of 3-methylpyrazole. However, reactions with common electrophilic fluorinating agents (*e.g.*, Selectfluor) yielded complex mixtures in which the target compound **1** was undetectable. So, we then turned to a protective-group strategy. A mixture of isomeric 1-*tert*-butyl-3-methylpyrazole **2a** and 1-*tert*-butyl-5-methylpyrazole **2b** was prepared by reacting 4,4-diethoxybutan-2-one with *tert*-butyl hydrazine (Scheme 2). The isomers were separated employing high-efficiency vacuum distillation. Notably, both **2a** and **2b** underwent electrophilic



Scheme 1 *Reagents and conditions*: i, $NaNO_2$, HBF_4, then UV-irradiation, water; ii, dihydropyran, CF_3CO_2H; iii, BuLi, THF, then MeI; iv, HCl, MeOH.

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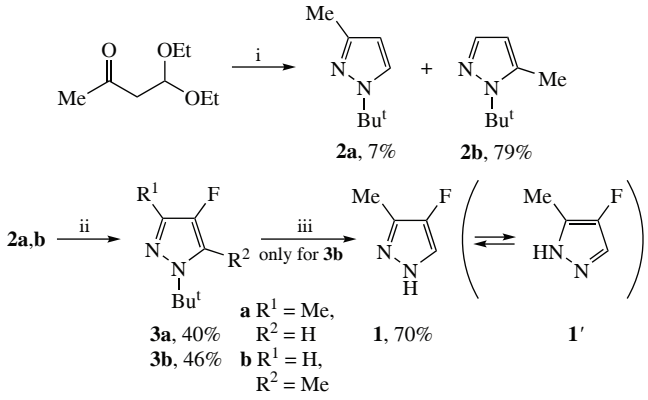
Selectfluor

fluorination with Selectfluor to afford 1-*tert*-butyl-4-fluoro-3-methylpyrazole **3a** and 1-*tert*-butyl-4-fluoro-5-methylpyrazole **3b**, respectively, with isolated yields of 40–46%.

A key finding from the hydrolysis studies was that only isomer **3b** underwent acid-catalyzed cleavage of the Bu^t–N bond to yield 4-fluoro-3-methylpyrazole **1** (formally, tautomer **1′** should initially be formed from **2b**, see Scheme 2). This selective transformation prompted us to optimize the conditions for initial condensation of 4,4-diethoxybutan-2-one with *tert*-butylhydrazine to maximize the ratio of isomer **2b** to **2a**. Systematic variation of reaction parameters including temperature, HCl concentration, and solvent composition (EtOH or water) enabled us to achieve a reproducible **2b** : **2a** ratio of 9 : 1, with an overall isolated yield of 95% for the isomeric mixture. The high proportion of the desired isomer **2b** makes the entire synthetic sequence from 4,4-diethoxy-2-butanone to product **1** operationally efficient and economically viable. Notably, the optimized protocol offers two additional advantages: all reactions are carried out in aqueous media, and the method relies solely on commercially available reagents, which enhances its suitability for large-scale applications.

The observed selectivity in the *N*-de-*tert*-butylation of isomers **3a**,**b** can be rationalized by a mechanism involving protonation of the pyridine-type nitrogen (N^2) of the pyrazole ring by a strong acid, which generates a highly polarized pyrazolium ion. The resulting positive charge on the ring induces steric and electronic effects that promote rupture of the N–Bu^t bond. Crucially, in isomer **3b** (*vs*. **3a**), the methyl group at the 5-position further increases steric hindrance, thereby favoring the N–C bond cleavage.

The structure of compounds **1**, **3a**, and **3b** were unequivocally confirmed by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy. Notably, for compound **3b**, we successfully acquired ^{15}N NMR data, including both chemical shifts and ^{15}N–^{19}F coupling constants. The observed ^{15}N chemical shifts, namely, –85.10 ppm (N^1) and –158.62 ppm (N^2), reflect the electronic influence of the fluorine substituent on the nitrogen environments within the pyrazole ring. The measured $^3J_{N–F}$ coupling constants further support this interpretation: 8.5 Hz for N^2, 2.2 Hz for N^1. These values are consistent with anisotropic electronic effects imposed by the fluorine substituent, which differentially perturbs the nitrogen atoms depending on their spatial and electronic relationship to the C–F bond.



Scheme 2 *Reagents and conditions*: i, H_2NNHBu^t, HCl, H_2O, 60 °C, 3 h; ii, Selectfluor, H_2O, 25–30 °C, 3 h; iii, 15% HCl, Δ, 20 h.

In summary, we have demonstrated that *N-tert*-butyl-substituted methylpyrazoles **2a**,**b** undergo electrophilic fluorination (in contrast to 3-methyl substituted *N*H-pyrazole) to yield the corresponding 1-*tert*-butyl-4-fluoro-3-methylpyrazole **3a** and 1-*tert*-butyl-4-fluoro-5-methylpyrazole **3b**. Only isomer **3b** undergoes HCl-assisted removal of the *N*-*tert*-butyl group to afford 4-fluoro-3-methylpyrazole **1**. The newly developed synthetic method for **1** offers several key advantages: practical convenience, scalability, use of readily available reagents, execution entirely in aqueous media. We anticipate that this approach will be of significant interest to the research community. Notably, compound **1** can serve as a pivotal precursor to a diverse family of functionalized 4-fluoropyrazoles, which are in high demand for applications in medicinal chemistry.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.8111.

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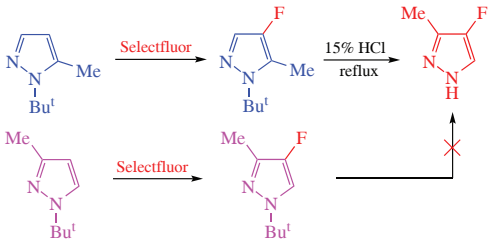
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