Synthesis of 4,4-Difluoro-1H-pyrazole Derivatives

Jessica R. Breen* Graham Sandford†* Bhairavi Patel* Jonathan Fray*

Abstract Fluorination of 3,5-diarylpyrazole substrates by Selectfluor™ in acetonitrile gave 4,4-difluoro-1H-pyrazoles in addition to 4-fluoropyrazole derivatives. The structure of this new class of fluorinated heterocycle was established by X-ray crystallography.

Key words organofluorine, fluoroheterocycle, pyrazole, selective fluorination, fluoropyrazole

The importance of fluorine-containing aromatic and heterocyclic motifs to the pharmaceutical and agrochemical industries continues to grow1 because approximately 5–15% of the total number of drugs launched worldwide over the past 50 years bear fluorinated substituents.2 For example, many six-membered fluorinated heteroaromatic derivatives find applications in a wide variety of drugs and plant protection agents such as Xeloda (anticancer, Roche), Voriconazole (antifungal, Pfizer), Ancobon (antifungal, Valeant) and Diclosulam (herbicide, Dow Agroscience).2

Whilst there are many reported examples of the synthesis of commercially important fluorinated six-membered azaheterocyclic rings, processes for the preparation of related fluorinated five-membered ring systems are relatively rare.3 However, interest in fluoropyrazole derivatives has increased recently due to their potential use for treating diabetes,4 inflammatory disease,5 as gastric acid inhibitors6 and as acaricides.7 Consequently, protocols for the synthesis of a variety of selectively fluorinated pyrazoles have been reported using either fluorination or ‘fluorinated building block’ strategies. Fluorocyclocondensation reactions involving enamino ketones8 and fluorocyanoketones,9 gold-catalysed aminofluorination of alkynes10 and reaction of hydrazines with fluoro-β-dicarbonyl substrates11 offer efficient routes to various functional fluoropyrazole derivatives. Adaptation of established fluorination methodology such as halogen exchange12 or Balz–Schiemann processes13 has had limited success for the synthesis of fluoropyrazoles from appropriately functionalised pyrazole substrates due to low total yields over several synthetic steps. Potentially, the most efficient methods for the synthesis of fluoropyrazole systems are aromatic substitution processes using electrophilic fluorinating agents. A few examples of the preparation of various fluoroaminopyrazole systems from the reaction of aminopyrazole precursors with NFSI or Selectfluor™ have been recorded14 whilst several 4-fluoropyrazole derivatives have been prepared by reaction of Selectfluor™ with a range of N-arylpyrazole substrates.15

As part of a wider research programme concerning the synthesis of fluoroorganic systems using electrophilic fluorinating agents,16 we were interested in broadening the scope of ‘late-stage’ fluorination reactions of pyrazole derivatives for applications in the life-sciences industries. In this paper, we describe electrophilic fluorination reactions of various pyrazole derivatives with either Selectfluor™ or fluorine gas which led to the unexpected synthesis of novel 4,4-difluoro-1H-pyrazole systems.

Pyrazole substrates 1 were either obtained from commercial suppliers or synthesised by reaction of the appropriate diketone derivatives with hydrazine or phenyl hydrazine by heating to reflux in ethanol following literature procedures.17

We began our pyrazole fluorination studies by investigating reactions of representative pyrazole systems 1a-c with either Selectfluor™ or fluorine gas and the results are collated in Table 1. Reactions involving Selectfluor™ were carried out by heating the reaction mixture using microwave irradiation (conditions A). Fluorine gas, diluted to a 10% mixture in anhydrous nitrogen was passed at a controlled rate via a mass flow controller into a stirred solution of the substrate in acetonitrile using equipment discussed previously (conditions B).16 Monofluorinated pyrazoles 2a–c were formed in modest yields and could be purified by column chromatography on silica gel. In contrast, fluorination of 3,5-dimethyl-1H-pyrazole was inefficient because of extensive tar formation due to competing fluorination of the pendant methyl substituents and subsequent product contamination.
differences we studied reactions of diphenylpyrazole substrates and found that reaction of diphenylpyrazoles with two equivalents of Selectfluor™ or fluorine gas, reflecting the lower nucleophilicity of these substrates, and starting materials proved to be very difficult but could be achieved in several cases. Yields of the 4,4-difluoro-1H-pyrazole products 3a–h were improved upon reaction of the pyrazole substrates with two equivalents of Selectfluor™ (Table 2, conditions C).

Table 2 Synthesis of Fluoropyrazole and 1H-Difluoropyrazole Derivatives

<table>
<thead>
<tr>
<th>Pyrazole</th>
<th>Ar</th>
<th>Conditions</th>
<th>Fluoropyrazole 2, yield (%)</th>
<th>Difluoropyrazole 3, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1d</td>
<td>Ph</td>
<td>A</td>
<td>2d, 45</td>
<td>3a, 21</td>
</tr>
<tr>
<td>1e</td>
<td>4-ClC₆H₄</td>
<td>A</td>
<td>2e, 31c</td>
<td>3e, 22</td>
</tr>
<tr>
<td>1f</td>
<td>4-BrC₆H₄</td>
<td>A</td>
<td>2f, 37c</td>
<td>3f, 22</td>
</tr>
<tr>
<td>1g</td>
<td>4-F₃CC₆H₄</td>
<td>A</td>
<td>2g, 36c</td>
<td>3g, 31</td>
</tr>
<tr>
<td>1h</td>
<td>3-F₃CC₆H₄</td>
<td>A</td>
<td>2h, 41c</td>
<td>3h, 20</td>
</tr>
<tr>
<td>1i</td>
<td>4-MeOC₆H₄</td>
<td>A</td>
<td>2i, 45</td>
<td>3i, 27</td>
</tr>
<tr>
<td>1j</td>
<td>3-MeOC₆H₄</td>
<td>A</td>
<td>2j, 31</td>
<td>3j, 24</td>
</tr>
<tr>
<td>1k</td>
<td>2-MeOC₆H₄</td>
<td>A</td>
<td>2k, 42</td>
<td>3k, 23</td>
</tr>
</tbody>
</table>

In contrast, when 3,5-dialklypyrazoles 1d–k were reacted with fluorine gas, many fluorinated products were observed by ¹⁹F NMR analysis of the crude product mixture and no products could be isolated and purified. In these reactions, competing fluorination of the aromatic ring substituents occurs as determined by the observation of many signals in the aromatic region (δF = −140 to −160 ppm) of the ¹⁹F NMR spectra of the crude product mixture.

Difluorinated products 3a–h were characterized by distinctive singlet resonances at approximately δ = −115 ppm in their ¹⁹F NMR spectra and the structure of 3f was confirmed by X-ray crystallography (Figure 2). The difluoro-
nated pyrazole systems 3 are a novel class of fluorinated compounds although the corresponding dichlorinated systems have been reported and their use in Diels–Alder reactions has been explored.\(^\text{19}\)

Initial fluorination of pyrazole derivatives occurs selectively at the 4-position consistent with an electrophilic aromatic substitution process (Scheme 1) and further electrophilic fluorination reaction occurs at the same site to give a difluorinated salt 4 as an intermediate. Deprotonation on workup gives the observed 4,4-difluoro-1\(\text{H}\) pyrazole product 3.

![Scheme 1 Fluorination of pyrazole derivatives 2 and 3](image)

The outcome is consistent with the intermediate carbocation 4b being stabilized by the adjacent phenyl groups (R\(^1\) = aryl; Scheme 1) allowing difluorination to proceed as observed for 3,5-diarylpyrazole substrates.

For reaction with dibrominated system 1l, the hydroxypyrazoline 5 could be isolated albeit in low yield and, in some analogous reactions, \(^{19}\)F NMR analysis indicated the presence of hydroxylated systems consistent with 5 in crude product mixtures (Scheme 2). This minor product is formed by reaction of water with intermediate salt 4 in reaction workup, consistent with the mechanism shown in Scheme 1 and related reactions involving other halogenated 4\(\text{H}\)-pyrazoles.\(^\text{20}\) The hydroxypyrazoline product 5 could be identified by the presence of an AB system, with an appropriate \(J_{\text{AB}} = 128\) Hz coupling constant, in the \(^{19}\)F NMR spectrum.

![Figure 2 Molecular structure of 3f](image)

In conclusion, a method for the synthesis of unusual 4,4-difluoro-1\(\text{H}\)-pyrazole systems 3\(^\text{11}\) has been established using shelf-stable, readily handled Selectfluor\textsuperscript{TM} as the electrophilic fluorinating agent.

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**Supporting Information**
Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1378915.

**References and Notes**


(18) X-ray crystallographic data has been deposited at the Cambridge Crystallographic Data Centre as CCDC 1016969-1016970.


(21) **Typical Procedure (Conditions A):** 4-Fluoro-3,5-diphenyl-1H-pyrazole (2d) and 4,4-Difluoro-3,5-diphenyl-4H-pyrazole (3a): 3,5-Diphenyl-1H-pyrazole (0.30 g, 1.36 mmol) and Selectfluor™ (0.482 g, 1.36 mmol) were dissolved in MeCN (5 mL) and the mixture was heated by microwave irradiation for 15 min at 90 °C. The mixture was then extracted with CH₂Cl₂ (3 × 50 mL) and washed with NaHCO₃ (30 mL) and H₂O (30 mL). The combined extracts were dried (MgSO₄) and evaporated. Column chromatography on silica gel using hexane and EtOAc (1:1) as the eluent, gave 4-fluoro-3,5-diphenyl-1H-pyrazole (0.135 g, 45%) as pale yellow crystals; mp 185–188 °C. ^1H NMR (400 MHz, CDCl₃): δ = 7.41–7.47 (m, 2 H, 4-H), 7.48–7.51 (m, 4 H, 3-H), 7.77–7.80 (m, 4 H, 2-H), 10.3 (br s, 1 H, NH). ^13C NMR (126 MHz, CDCl₃): δ = 128.2 (Ar), 129.0 (Ar), 129.3 (Ar), 131.1 (C-3), 140.0 (C-4), 148.7 (Ar). ^19F NMR (376 MHz, CDCl₃): δ = –174.3 (s). MS: m/z (%; EI+) = 237.9 (100) [M]+, 107.8 (43), 76.9 (40). HRMS: m/z [M + H]+ calc for C₁₅H₁₂F₂N₂: 239.0983; found: 239.0972. 4,4-Difluoro-3,5-diphenyl-4H-pyrazole (3a): obtained as yellow crystals (0.122 g, 21%); mp 105–107 °C. ^1H NMR (400 MHz, CDCl₃): δ = 7.44–7.67 (m, 6 H, ArH), 8.06–8.15 (m, 4 H, ArH). ^13C NMR (126 MHz, CDCl₃): δ = 125.4 (t, 1 H, CF₂), 128.3 (Ar), 129.5 (Ar), 133.1 (Ar), 162.1 (t, 2 H, C-2). ^19F NMR (376 MHz, CDCl₃): δ = –116.3 (s). MS: m/z (%; EI+) = 256.1 (100) [M]+, 153.0 (45), 103.1 (99). HRMS: m/z [M + H]+ calc for C₁₅H₁₁F₂N₂: 257.0894; found: 257.0894.