Journal of Fluorine Chemistry 175 (2015) 84–109

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Review

# Fluorine-containing pyrazoles and their condensed derivatives: Synthesis and biological activity

Galina N. Lipunova [a], Emiliya V. Nosova [b,*], Valery N. Charushin [a,b], Oleg N. Chupakhin [a,b]

[a] I. Postovsky Institute of Organic Synthesis, Ural Division of the Russian Academy of Sciences, 22 S. Kovalevskoy Street, 620219 Ekaterinburg, Russia
[b] Department of Organic Chemistry, Chemical Technology Institute, Ural Federal University, 19 Mira Street, 620002 Ekaterinburg, Russia

ARTICLE INFO

*Article history:*
Received 22 January 2015
Received in revised form 23 March 2015
Accepted 27 March 2015
Available online 7 April 2015

*Keywords:*
Fluoropyrazoles
Substitution reactions
Heterocyclization
Biological tests
Antiviral activity

ABSTRACT

In the frames of this review article the recently obtained data on new synthetic approaches to fluorinated pyrazoles and their condensed analogs, as well as their biological activities have been analyzed.


**Contents**



## 1. Introduction

Pyrazole derivatives play an important role in medicinal chemistry. Indeed, antineoplastic, anti-inflammatory, antipsychotic, antimicrobial, antiviral, analgesic and antifungal agents bearing the pyrazole fragment have been widely used as therapeutical drugs. Also many pyrazoles are involved in vitally important processes, as receptors antagonists, inhibitors of various types of kinases, *etc.* For instance, phenylbutazone (Fig. 1) is used for treatment of rather complicated forms of arthritis, and metamizole is well known analgesic.

* Corresponding author. Tel.: +7 343 3754501; fax: +7 343 3740458.
*E-mail addresses:* lipunova@ios.uran.ru (G.N. Lipunova), emily74@rambler.ru (E.V. Nosova).

http://dx.doi.org/10.1016/j.jfluchem.2015.03.011
0022-1139/

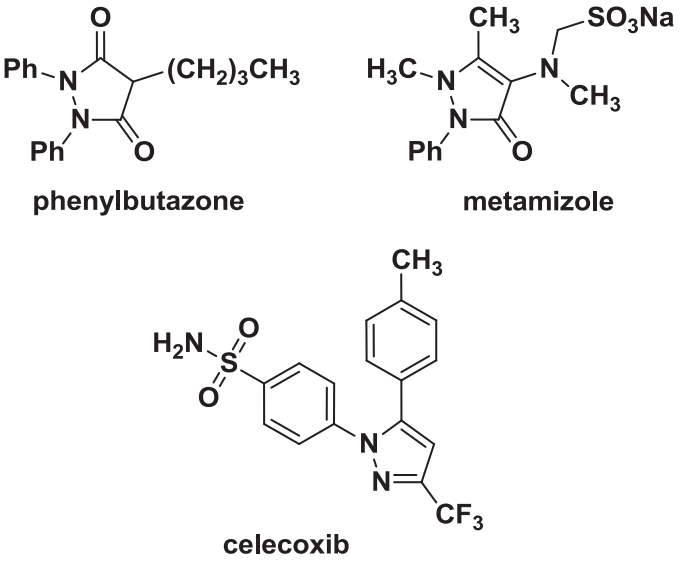
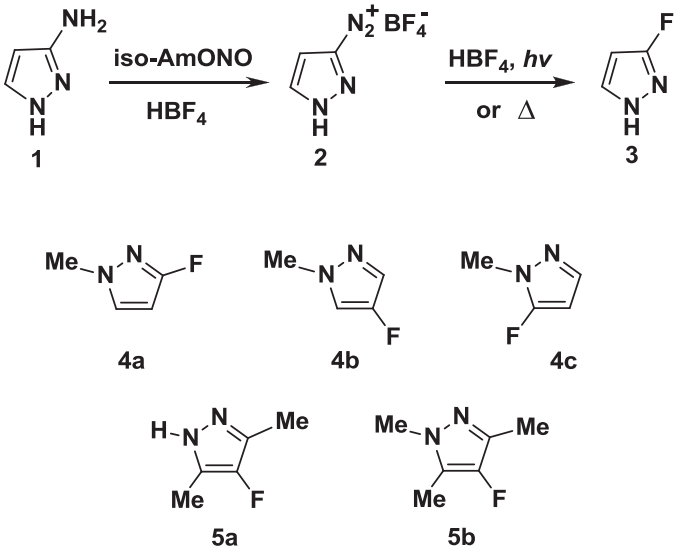



**Fig. 1.** Structures of phenylbutazone, metamizole and celecoxib.




**Scheme 1.**

It is known that incorporation of fluorine atoms into molecules of heterocyclic compounds leads to a significant increase in their biological activities [1–4]. Fluorinated pyrazoles proved to be important "building blocks" for the synthesis of drugs and agrochemicals [5]. Indeed, the well known anti-inflammatory drug **celecoxib** (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfamide) (Fig. 1) contains not only fluorine atoms, but also pyrazole ring [6]. Celecoxib – one of the mostly successful and well-sold drugs, acting as selective inhibitors of cyclooxygenase 2 (COX 2). It is considered to be a promising as anti-inflammatory and analgetic drug, since it avoids undesirable side effects, which are characteristic for other anti-inflammatory nonsteroid preparations [7].

Some data on the synthesis of fluorinated pyrazoles are available in a short review article dated from 1977, which is dedicated to fluorinated azoles [8]. In the recently published book [9] there is a special chapter, describing fluorinated pyrazoles and indazoles, in which a number of methods for the synthesis of fluoroalkylpyrazoles and indazoles, as well as synthetic approaches to 3(5)- and 4-fluoropyrazoles are shortly presented. However, a small attention has been paid to biological activity of pyrazole derivatives, while their condensed analogs have not been discussed.

In the current review article synthetic approaches to a variety of fluorinated pyrazoles and their condensed analogs have to be considered, including chemical transformations and hetero-cyclization reactions of the key intermediates. Also the data on biological activity of these compounds are supposed to be discussed.

## 2. Synthesis of fluoropyrazoles

Incorporation of fluorine atoms into the pyrazole ring (nucleophilic substitution of a functional group, or targeted fluorination), or all kind of cyclocondensation reactions based on fluorinated "building blocks" represent the main synthetic pathways to obtain fluorinated pyrazoles.

### 2.1. Nucleophilic substitution reactions

**The Balz–Schiemann reaction** (fluoro-dediazoniation) appears to represent the first synthetic approach to fluoropyrazoles. So, diazoniation of 3(5)-aminopyrazole (**1**) with isoamyl nitrite in tetrafluoroboric acid, followed by thermal decomposition of tetrafluoroborate **2** by action of NaF-KF at 190 °C has resulted in the formation of 3(5)-fluoropyrazole (**3**) in a very low yield (0.3%) [10]. Later on, irradiation of pyrazolyl diazonium salts in their solutions in $HBF_4$ enabled one to improve yields of fluoropyrazole (**3**), 1-methyl-3-fluoropyrazole (**4a**), 1-methyl-4-fluoropyrazole (**4b**), 3,5-dimethyl-4-fluoropyrazole (**5a**) and 1,3,5-trimethyl-4-fluoropyrazole (**5b**) up to 33–60% (Scheme 1) [11,12]. 1-Methyl-5-fluoropyrazole (**4c**) was obtained from 1-acetyl-3-fluoropyrazole and methyl fluorosulfonate, and also by direct methylation of **3** with dimethylsulfate [12]. It has been shown that $^{19}F$ chemical shifts of N-methyl fluoropyrazoles **4a–c** cover a huge range (*ca.* 50 ppm) and show a good correlation with chemical shifts of H(3), H(4) and H(5) protons of 1-methylpyrazole. Also, it is worth mentioning that an unexpectedly long-range coupling $^5J$ (F-$CH_3$) has been observed for pyrazole **4a** [12].

According to data of Table 1, chemical shifts of fluorine atoms in N-methylderivatives **4a–c** depend on position of fluorine atom in pyrazole ring, the signal of fluorine in **4a** appears to be shifted further downfield, whereas the signal of fluorine in **4b** is shifted further upfield [12].

Also the Balz–Schiemann reaction was used for the synthesis of difluoropyrazole derivatives **6–8** [13]. Compound **6a** was obtained from aminopyrazole **1** which was converted into 4-nitro derivative, and further into 3(5)-fluoro-4-nitropyrazole in 53% yield. The subsequent catalytic hydrogenation and the Schiemann reaction gave the compound **6a** (Scheme 2). Treatment of this pyrazole with diazomethane in the presence of $BF_3$ afforded the corresponding difluoro derivative **6b**. At the same time, methylation of **6a** with dimethyl sulfate at 40 °C led to 4,5-difluoro derivative **7b**. Synthesis of 3,5-difluoropyrazoles **8a–c** was based on using monofluoro derivative **3**.

Compounds **6–8** have been characterized by $^1H$ and $^{19}F$ NMR data. Discussing the features of $^{19}F$ NMR spectra and, in particular,

**Table 1**
Chemical shifts in $^{19}F$ NMR spectra of monofluoro 1-methylpyrazoles **4** ($CDCl_3$, $CF_3COOH$ as standard) [12].

| Comp. | $\delta_F$ | $J$ (Hz) |
|---|---|---|
| **4a** | $F_3 = 53.0$ | $J_{F\text{-}Me} = 1.1$, $J_{F3H5} = 2.5$, $J_{F3H4} = 6.0$ |
| **4b** | $F_4 = 99.0$ | $J_{F4H3} = 4.6$, $J_{F4H5} = 4.6$ |
| **4c** | $F_5 = 59.6$ | $J_{F\text{-}Me} = 1.2$, $J_{F5H3} = 2.3$, $J_{F5H4} = 6.0$ |