Journal of Fluorine Chemistry 176 (2015) 78–81

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

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

An approach to (4-fluoroalkyl-1-alkyl-1*H*-pyrazol-3-yl)methylamines

Sergey P. Ivonin [a], Bohdan B. Kurpil' [a], Andrii V. Bezdudny [a], Dmitry M. Volochnyuk [a,b], Oleksandr O. Grygorenko [c,*]

[a] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska Street 5, Kyiv 02660, Ukraine
[b] Curpys Chemicals, Teremkivska Street 2-A, Office 1, Kyiv 03187, Ukraine
[c] Taras Shevchenko National University of Kyiv, Volodymyrska Street 64, Kyiv 01601, Ukraine

ARTICLE INFO

Article history:
Received 18 March 2015
Received in revised form 4 June 2015
Accepted 5 June 2015
Available online 10 June 2015

Keywords:
Organofluorine compounds
Pyrazoles
[4+1] Cyclization
Sulfur tetrafluoride
Diethylaminosulfur trifluoride (DAST)

ABSTRACT

An approach to the synthesis (4-di- and -trifluoroalkyl-1-alkyl-1*H*-pyrazol-3-yl)methylamines – promising building blocks for drug discovery and medicinal chemistry is described. The key step of the reaction sequence is fluorination of the corresponding non-symmetric trisubstituted pyrazole derivatives bearing phtalimide moiety with diethylaminosulfur trifluoride or sulfur tetrafluoride. The title compounds are obtained in 5–6 steps from the commonly available materials and 35–36% overall yields.

1. Introduction

Fluorinated pyrazoles represent an important chemotype which is widely used in drug discovery, agrochemistry, coordination chemistry and other areas [1]. These compounds are encountered among marketed drugs, drug candidates and agrochemicals, such as COX-2 selective nonsteroidal anti-inflammatory drugs celecoxib (**1**) and deracoxib (**2**), FXa inhibitor razaxaban (**3**) which reached phase II clinical trials, and fungicide penthiopyrad (**4**) (Fig. 1). Notably, all these examples are non-symmetric trisubstituted pyrazoles, which preparation is often a challenging task [2–4] since the classical [3 + 2] approach (that is, reaction of 1,3-dicarbonyl compounds or their synthetic equivalents with hydrazines) can lead to the mixtures of regioisomers. This is especially the case for *N*-alkylpyrazole derivatives. Recently, we have addressed this issue in a series of publications reporting regioselective synthesis of non-symmetric trisubstituted functionalized pyrazoles [5–8]. We relied on [4 + 1] approach to the construction of the heterocyclic ring, namely, reaction of *N*-alkylhydrazones with Vilsmeier–Haack reagent (Scheme 1). In particular, the phtalimide derivatives **5a,b** was prepared using this method in 92% yield (Scheme 2) [7].

In this work, we describe our efforts toward preparation of the previously unknown (4-fluoroalkyl-1-alkyl-1*H*-pyrazol-3-yl) methylamines **6** (Fig. 2) – promising building blocks for drug discovery and agrochemical programs. It should be noted that derivatives of only three of six possible isomeric fluoroalkyl-substituted pyrazolylmethylamines (**6**–**11**) were described prior this work, mostly in the patents [9–13]; some of these compounds

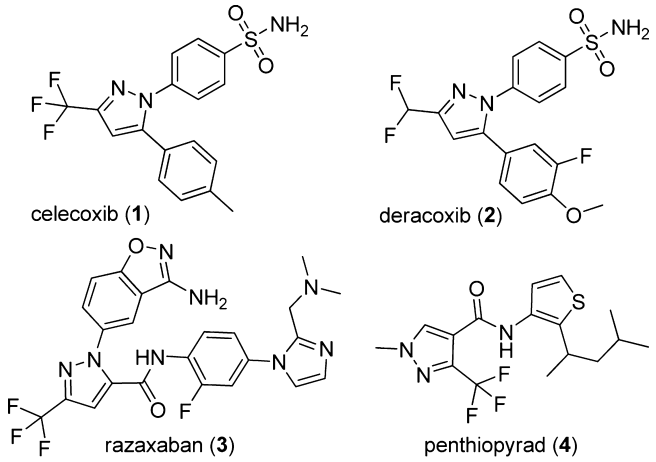
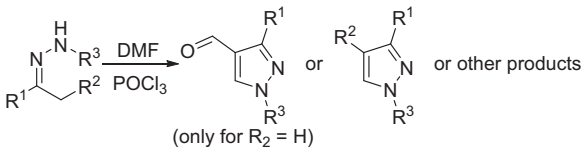


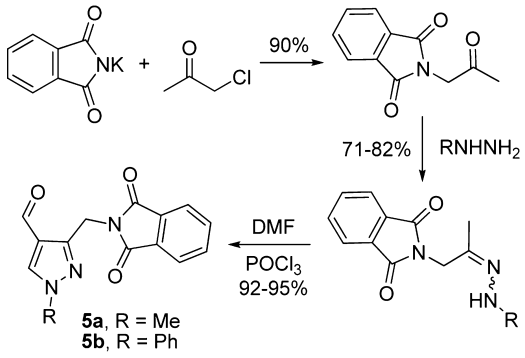
Fig. 1. Fluorinated pyrazoles among marketed drugs.

* Corresponding author. Tel.: +380 44 239 33 15; fax: +380 44 502 48 32.
E-mail address: gregor@univ.kiev.ua (O.O. Grygorenko).

http://dx.doi.org/10.1016/j.jfluchem.2015.06.003
0022-1139/



Scheme 1.

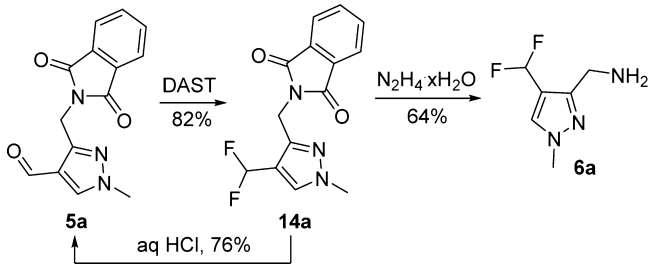


Scheme 2.

were found to be potent subtype 1 vanilloid receptor (VR1/TRPV1) ligands (*e.g.* **12**, K_i = 0.6 nM) [12] and positive AMPA receptor modulators with in vivo activity (**13**, EC_{50} = 0.79 μM) [13].

2. Results and discussion

In our approach to the synthesis of amines of the type **6**, we considered compounds **5** as the key intermediates. Reaction of aldehydes **5**, as well as the corresponding carboxylic acids or alcohols with sulfur-containing fluorinating reagents could be a method of choice to achieve this. It should be noted that such fluorinations in the presence of phtalimide moiety was described in the literature, however, it did not involve pyrazole derivatives [14–21]. It was found that fluorination of **5a** with diethylaminosulfur trifluoride (DAST) proceeded smoothly and led to formation of the corresponding difluoromethyl derivative **14a** in 82% yield (Scheme 3). Upon refluxing of **14a** with 15% aq HCl, the starting aldehyde **5a** was recovered, so that hydrolysis of the difluoromethyl moiety



Scheme 3.

occurred faster than removal of the phtalimide protective group. On the contrary, hydrazinolysis of **14a** resulted in deprotection of the amino function and gave the expected product **6a** (64% yield).

For the fluorination of the carboxylic acid **15**, obtained by oxidation of **5a** with potassium permanganate, sulfur tetrafluoride was used (Scheme 4) [22]. It should be noted that to the best of our knowledge, no examples of fluorination of the carboxylic acids with SF_4 in the presence of phtalimide moiety was reported previously. The reaction was performed at 85 °C for 16 h and led to the formation of the trifluoromethyl derivative **14b**. Acid-promoted deprotection of the hidden amino function in **14b** was accompanied by hydrolysis of the trifluoromethyl group and subsequent decarboxylation, giving the corresponding amine **16** (isolated as hydrochloride in 72% yield). Notably, the same product was obtained upon acidic hydrolysis of the starting carboxylic acid **15**, which can be used as a proof of the formation of a common intermediate **17** in both reactions. The target product **6b** (67%) was obtained by hydrazinolysis of **14b**.

In order to obtain the monofluoromethyl derivative **6c**, aldehyde **5a** was reduced catalytically to give alcohol **18** (84%), which in turn was fluorinated with DAST to yield **14c** (78%) (Scheme 5). Surprisingly, hydrazinolysis of **14c** in 2-propanol was accompanied by nucleophilic substitution of the fluorine atom with the molecule of solvent, leading to the formation of amine **19** (68%) instead of the expected product **6c**. For the characterization purposes, compound **19** was transformed into the *p*-nitrobenzoyl derivative **20** (63%). Other conditions were also tried for the cleavage of the phtalimide moiety in **14c**, namely: (a) dioxane, hydrazine hydrate, 50 °C, 12 h; (b) dioxane, anhydrous hydrazine, 50 °C, 12 h; (c) liquid HF, 20 °C, 4 d, followed by aq work-up. In all

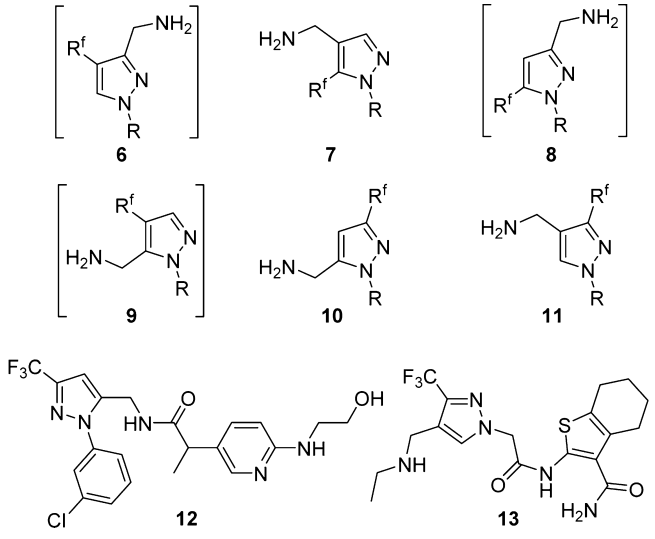
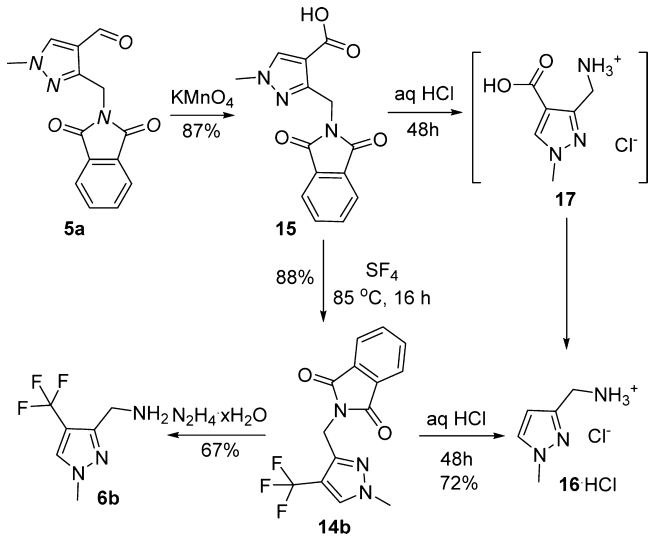


Fig. 2. Fluoroalkyl-substituted pyrazolylmethylamines **6**–**11** and their biologically active derivatives (previously unknown chemotypes are shown in square brackets).



Scheme 4.