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Ambident polyfluoroalkyl-substituted pyrazoles in the methylation reactions

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ABSTRACT

The reactivity of polyfluoroalkyl-containing pyrazoles has been estimated using the quantum chemical calculations. A good regioselectivity in the methylation of polyfluoroalkylpyrazoles was reached while varying the reaction conditions. Under basic conditions, methylation of such pyrazoles led to the preferred formation of 3-R^F-pyrazoles, whereas the use of dimethyl sulfate in the absence of a base resulted in the predominant formation of 5-R^F-pyrazoles. A proposed mechanism of methylation was discussed.

1. Introduction

Trifluoromethyl-containing pyrazoles are of significant practical interest because of the use of their derivatives as pharmaceutical agents and agrochemicals [1,2]. Among them there are one of the best selling drugs – Celebrex (celecoxib, anti-inflammatory drug, a selective inhibitor of COX-2), veterinary anti-arthritic Mavacoxib (trocoxil), as well as such drugs being under clinical studies as SC-560 (anticancer activity), AS-136A (antiviral action), and Razaxaban (anticoagulant activity) (Fig. 1) [3].

Fungicide Penthiopyrad [4], herbicide Fluazolate [5] and insecticide DP-23 have been used as agrochemicals (Fig. 2) [3].

The high importance of the pyrazole skeleton was shown in recent reviews [6–9]. The vast majority of bioactive pyrazoles represent *N*-substituted derivatives containing the methyl or aryl substituent at the nitrogen atom. The synthesis of such pyrazoles, including polyfluoroalkylated analogues, is based mainly on the cyclization of 1,3-bielectrophiles with substituted hydrazines, hydrazides, semicarbazide, etc. One of the most popular 1,3-bielectrophilic blocks are the polyfluoroalkyl-containing 1,3-dicarbonyl compounds and their derivatives. So, a large number of pyrazoles was produced by cyclization of various polyfluoroalkyl-1,3-diketones with substituted hydrazines (Scheme 1) [10–19]. However the formation of two regioisomers with trifluoromethyl group in the position C-3 (isomer I) or C-5 (isomer II) often takes place in these reactions. In the most cases, the 3-R^F-isomer is the major [10,12,15–20], and 5-R^F-pyrazole isomer is mostly isolated in a hydrated form [4,20–26].

A convenient method for the synthesis of N-substituted pyrazoles is the alkylation of pyrazole core. It should be noted that the alkylation is one of the basic methods for construction of the carbon skeleton of the molecule; this reaction is of great importance in organic synthesis, including preparation of medicinal agents. According to the recent estimates, the proportion of alkylation reactions in the design of new medicines is 17% [27].

Alkylation of polyfluoroalkylcontaining pyrazoles as ambident nucleophiles can proceed at two nonequivalent N^1 and N^2 reaction centers (conventional numeration) to form the corresponding 3-R^F- and 5-R^F-regioisomers (Scheme 2). The examples of nonselective alkylation of 5-methyl-3-polyfluoroalkylpyrazoles with various alkyl halides were described [28–31]. At the same time, benzylation of 4-substituted 5-methyl-3-trifluoromethylpyrazoles occurs regiospecifically to form 3-CF_3-isomer [32]. The data on methylation of 3-polyfluoroalkylpyrazoles are limited. It is known that the methylation of 5-methyl-3-trifluoromethylpyrazole and 4-bromo-3-trifluoromethylpyrazoles with methyl iodide leads to regiospecific formation of 3-CF_3-pyrazoles [33,34].

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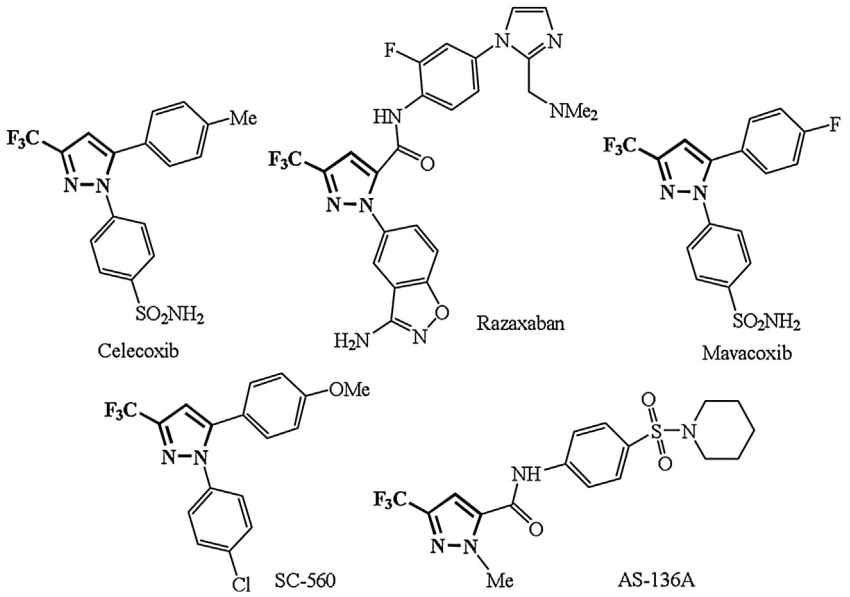


Fig. 1. Trifluoromethylpyrazole-based pharmaceutical agents.

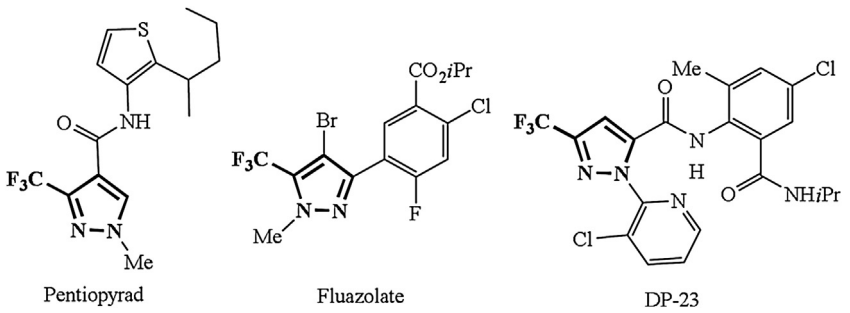
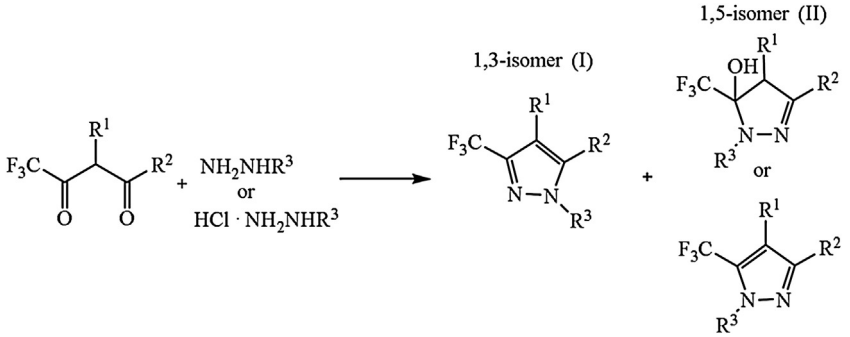
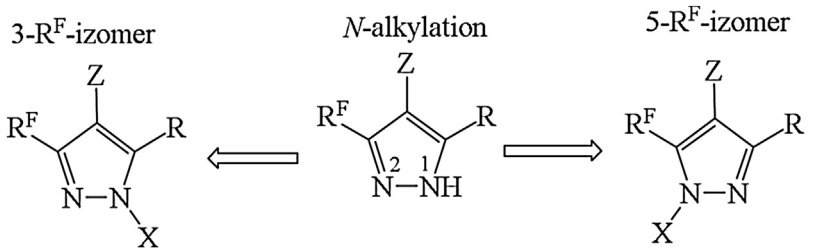


Fig. 2. Trifluoromethylpyrazole-based agrochemicals.



Scheme 1. Synthesis of N-substituted pyrazoles by cyclization of 1,3-diketones with hydrazines.



Scheme 2. Alkylation of polyfluoroalkylpyrazoles.