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Review

Synthesis of diversely fluorinated pyrazoles as novel active agrochemical ingredients

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ABSTRACT

Fluorine, the most electronegative element plays nowadays a key role in pharmaceutical, agrochemical and material sciences. It has been estimated that the number of fluorinated compounds currently under development represents some 30–50% of the total active ingredients in development. The search for new active substances with improved efficacy, lower mammalian toxicity, more favourable environmental profile and lower cost is a truly challenging task for R&D chemists within the crop protection companies. The present review will give an overview on the synthesis of pyrazoles bearing novel fluorinated substituents.

Contents

1. Introduction

As "a small atom with a big ego" [1], fluorine plays increasingly important roles in many fields such as agrochemical, medicinal and pharmaceutical research and material science [2,3].

The last 30 years were marked by an increased use of fluorinated compounds in agrochemical research as well as in pharmaceutical chemistry. The introduction of a single fluorine atom or a trifluoromethyl substituent have been widely studied, and the introduction of fluorinated alkyl groups into crop protection products is intensively performed.

SDHI fungicides (succinate dehydrogenase inhibitors) have been used in turf since the early 1990s. Also known as the carboxamide group of fungicides, most turfgrass managers will recognize the oldest member of this group, flutolanil (Prostar®). By 2003, BASF had registered the second active ingredient in this class of fungicides, boscalid (Emerald®). And in 2011, Dupont is

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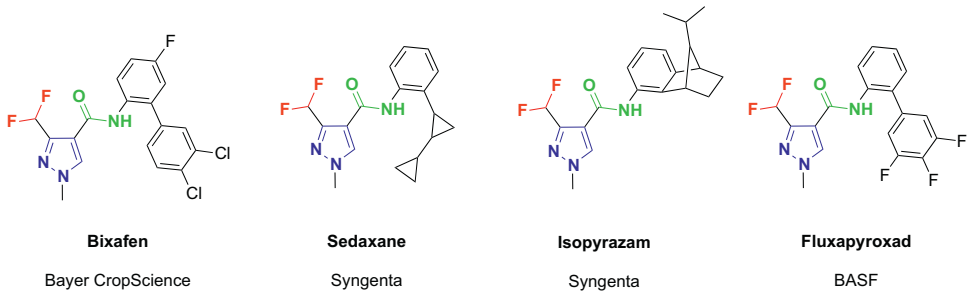

Fig. 1. Examples of fluorinated pyrazoles as SDHI.

scheduled to register the third fungicide in this class for use on turf, penthiopyrad (Velista®).

SDHI fungicides were discovered more than 40 years ago. Due to the limited disease and application spectrum of the "first generation" carboxamides, resistance under commercial conditions remained limited to a few diseases (basidiomycetes) and crops, e.g. *Puccinia horiana*, chrysanthemum rust, or *Ustilago nuda*, loose smut in barley. In addition to these "first generation" molecules, the group of SDH inhibitors was meanwhile increased, with new broad spectrum fungicides controlling a variety of diseases in various crops.

The name SDHI (succinate dehydrogenase inhibitors) comes from the fact that these fungicides interfere with the electron transport chain in fungi, producing in this way ATP as energy source. The SDHI/carboxamides interfere with succinate dehydrogenase and shut down the cell's energy production. When this happens, the fungus cannot grow, runs out of energy and dies.

At least four different compounds of this class recently reached the market (Fig. 1).

Ethyl difluoromethylpyrazole carboxylate is a main key intermediate for all the new active ingredients. A typical way to access to this compound comprises saponification towards pyrazolic acid, followed by chlorination with formation of the acid chloride and finally reaction with the appropriate amine to the carboxamide (Fig. 2).

In the present review article, we will give an overview on recent synthetic approaches towards difluoromethyl pyrazoles, mainly reported from 2000. However, we will not present the synthesis of CF_3-substituted pyrazoles, as Fustero has done this in an excellent review article [4].

2. Synthesis of pyrazoles bearing one fluorinated group

Several methods are described in the literature to prepare fluoroalkyl pyrazoles. Most of them consist in the use of fluorinated precursors and subsequent cyclisation. These fluorinated building blocks can be submitted to cyclocondensation with hydrazines to give the desired compounds (e.g., 1,3-diketones, α,β-unsaturated ketones, enaminones), or to 1,3-dipolar cycloadditions in the presence of diazomethane. Another way to obtain fluorinated pyrazoles is the construction of the fluoroalkyl group on the pyrazole ring [4].

It can also be noticed that the introduction of a single fluorine atom or a trifluoromethyl substituent has been widely studied, whereas the synthesis of difluoromethyl-substituted derivatives is scarcely described.

2.1. From 1,3-diketones

Among the existing methods for the synthesis of non-fluorinated pyrazoles, the use of 1,3-diketones is widespread. Numerous precursors are commercially available or can be readily prepared by a *pseudo*-Claisen condensation. The situation is different when fluorinated pyrazoles are considered. For example 1-difluoromethyl-4-aryl-1,3-diketones has proven to be very efficient [5] in the condensation with aryl hydrazines affording highly functionalised compounds in one step (Scheme 1). However, no regioselectivity issue has been discussed in these cases, despite the well known problems of regioselectivity in the reaction of substituted hydrazines with 1,3-diketones [6,7]. Moreover, the 1,3-diketones have to be prepared before which can reveal to be low-yielding in some cases.

Similarly, Norris et al. described the synthesis of 3-CHF_2-pyrazoles [8] from the reaction of 1,3-diketones and arylhydrazines (Scheme 2). When the reaction is carried out in isopropanol at 85 °C for 1–5 days under neutral conditions, depending on the nitrogen-substituent, either the formation of 3- and 5-difluoromethylpyrazoles (72% and 25% yield, respectively), or the formation of 3-difluoromethyl-5-hydroxypyrazoline (87% yield) along with 3-difluoromethylpyrazole (12%) has been observed.

The regioselectivity was improved when 10 mol% of concentrated sulfuric acid was added to the reaction mixture. In this case, no hydroxypyrazoles have been detected and the 3-CHF_2-pyrazoles were formed with perfect regioselectivity. Unfortunately, this work reports only on the use of aryl hydrazines and aryl-fluoroalkyl-1,3-diketones.

Gosselin et al., employing 50 mol% of 10 N HCl, have performed a similar study [9]. In this case the selectivity has been improved due to acid catalysis from 86:14 to 99.8:0.2. The yields are fair, between 60 and 98% depending on the 1,3-diketone and the hydrazine used (Scheme 3). Once again, the study only refers to aryl hydrazines, and aryl-fluoroalkyl 1,3-diketones.

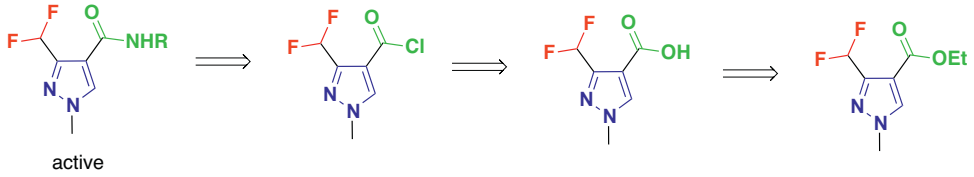

Fig. 2. Retrosynthetic analysis of the pyrazole key fragment.