Difluoromethylation

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In Situ Generation of Difluoromethyl Diazomethane for [3+2] Cycloadditions with Alkynes**

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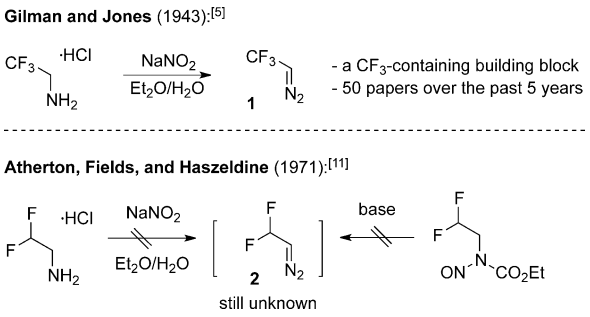
Dedicated to Professor Andrei Tolmachev on the occasion of his 58th birthday

Abstract: *A novel approach to agrochemically important difluoromethyl-substituted pyrazoles has been developed based on the elusive reagent CF_2HCHN_2, which was synthesized (generated in situ) for the first time and employed in [3+2] cycloaddition reactions with alkynes. The reaction is extremely practical as it is a one-pot process, does not require a catalyst or the isolation of the potentially toxic and explosive gaseous intermediate, and proceeds in a common solvent, namely chloroform, in air. The reaction is also scalable and allows for the preparation of the target pyrazoles on gram scale.*

The derivatization of organic compounds with fluorinated units often affects their physicochemical and biological properties.[1,2] Consequently, approximately 20% of all pharmaceuticals and agrochemicals contain at least one fluorine atom. The trifluoromethyl and difluoromethyl groups are particularly prevalent.[3] Chemists, however, mostly incorporate these units by direct fluoroalkylation reactions[4] and tend to underestimate the corresponding building blocks. Hence, novel reagents to synthesize trifluoromethyl- and difluoromethyl-substituted compounds are of value.

In 1943, Gilman and Jones synthesized CF_3CHN_2 (**1**) from trifluoroethylamine hydrochloride and sodium nitrite (Scheme 1).[5] At first, this potentially toxic and explosive gas did not find wide application in synthesis. The situation drastically changed in 2010, when Morandi and Carreira developed convenient conditions to generate **1** in situ in a solution[6a] and subsequently performed many catalytic transformations.[6] Since then, reagent **1** has been frequently used: Ma et al. have developed diverse [3+2] cycloadditions of **1**,[7] and Molander and co-workers synthesized unique trifluoromethylated boronic acid derivatives.[8] In total, more than 50 publications have appeared in this area over the past five years.[9,10]



Scheme 1. Known trifluoromethylation (**1**) and unknown difluoromethylation (**2**) reagents.

In 1971, Atherton, Fields, and Haszeldine reported unsuccessful attempts to prepare the closest homologue of **1**, CF_2HCHN_2 (**2**, Scheme 1).[11] Despite other efforts,[12] the conceptually attractive reagent **2** has remained unknown to date.

It is rather surprising that at a time when chemists can synthesize extremely complex compounds in more than 100 chemical steps,[13] a very small reagent with only two carbon atoms and true potential for the synthesis of pharmaceuticals is still unknown. In strict contrast to trifluoromethyl-containing reagent **1**, reagent **2** cannot be employed thus far.[14] The development of synthetic procedures that render this reagent accessible and fill this gap in modern chemistry[15] is therefore urgently required.

Herein, the generation of chemical reagent **2** and a representative first reaction, its [3+2] cycloaddition with alkynes, are described for the first time. This transformation represents a novel synthetic approach for the generation of difluoromethyl-substituted pyrazoles,[16] which are valuable building blocks for agrochemistry (Figure 1).[17]

First, it was attempted to generate reagent **2** under conditions that were elaborated for the preparation of **1** in aqueous media[6a,9f,12,18] (Scheme 2). In particular, difluoroethylamine hydrochloride and sodium nitrite were reacted in a suspension of water and dichloromethane at room temperature to afford a mixture of difluoroethanol and diazoacetaldehyde along with some unidentified products. Presumably, difluoroethanol was obtained by the reaction of common

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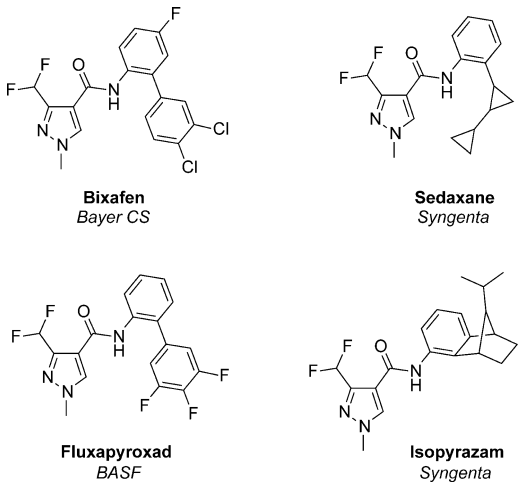
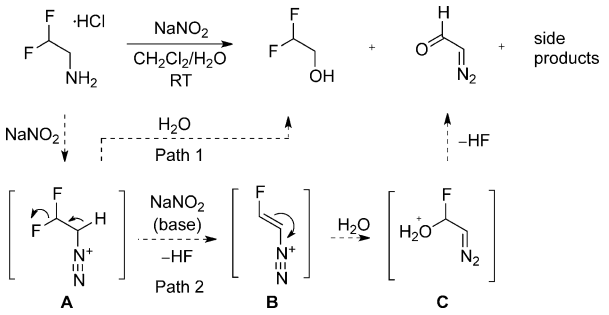


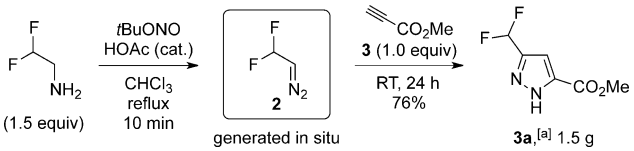
Figure 1. Marketed fungicides that contain difluoromethylated pyrazoles.



Scheme 2. Unsuccessful attempts to generate CF_2HCHN_2 (**2**).

intermediate **A** with water (Scheme 2, path 1) whereas diazoacetaldehyde was formed by the reaction of **A** with $NaNO_2$ (base), elimination of HF (intermediate **B**), and subsequent hydrolysis (intermediate **C**, path 2). Once the reaction mechanism had been understood, it became evident that the preparation of reagent **2** should be attempted under non-aqueous (to avoid path 1), non-basic (to avoid path 2) conditions.

In 1975, Takamura and Mizoguchi achieved the diazotization of α-amino acid derivatives in organic media using *tert*-butyl nitrite.[19] In contrast to sodium nitrite, *tert*-butyl nitrite is non-basic, and was therefore tested next for the synthesis of **2**. In fact, it was found that a colorless solution of difluoroethylamine, *tert*-butyl nitrite, and acetic acid (catalytic amounts) in chloroform became strongly yellow after heating at reflux for approximately ten to fifteen minutes, indicating the formation of CF_2HCHN_2 (**2**; Scheme 3). To trap the putative intermediate **2**, the heating was stopped after ten minutes, and alkyne **3** was added. After one day at room temperature, the crystalline pyrazole **3a** was obtained in 76% yield after purification by column chromatography. The structure of **3a** was confirmed by X-ray crystallography (Figure 2). Presumably, difluoromethylated pyrazole **3a** was formed by a [3+2] cycloaddition[20] of the in situ generated CF_2HCHN_2 and alkyne **3**. It is important to note that the developed one-pot reaction does not involve the isolation of



Scheme 3. In situ generation of CF_2HCHN_2 (**2**) in non-aqueous media and its first reaction. [a] Structure confirmed by X-ray crystallography.

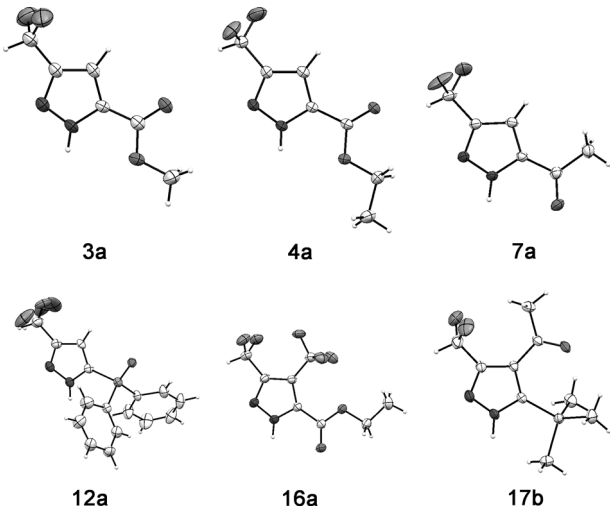
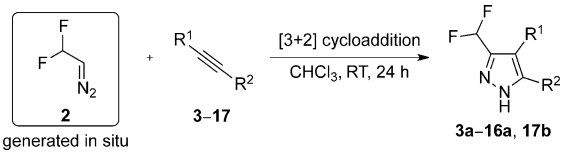


Figure 2. X-ray crystallographic analyses.[22]

the potentially toxic and explosive CF_2HCHN_2.[21] Moreover, an inert atmosphere is not required, and the convenient synthesis of gram quantities of product **3a** was achieved.

Next, to study the scope of the developed reaction, various electron-deficient mono- (**4**–**13**) and disubstituted alkynes (**14**–**17**) were tested (Table 1). Substrates with

Table 1: Reaction scope.



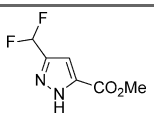
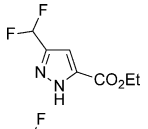
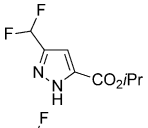
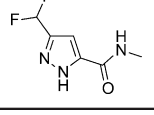
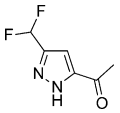
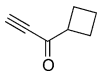
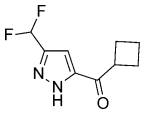
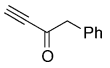
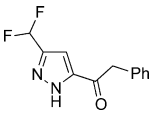
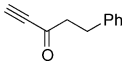
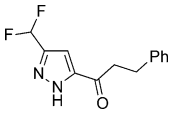
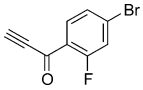
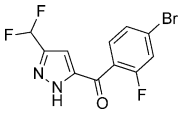
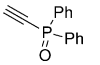
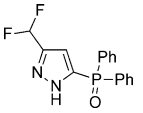
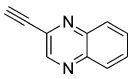
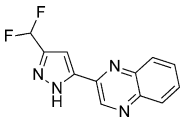
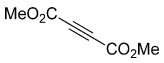
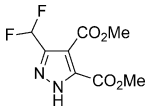
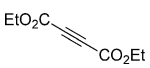
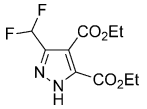
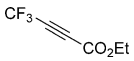
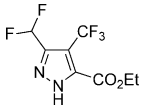
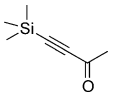
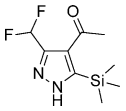
Alkyne		Product		Yield [%][a]
3		**3a**		76[b]
4		**4a**		74[b]
5		**5a**		82
6		**6a**		51[c]

Table 1: (Continued)

Alkyne		Product		Yield [%][a]
7		7a		81[b]
8		8a		83
9		9a		78
10		10a		71
11		11a		79
12		12a		54[b,c]
13		13a		29[c]
14		14a		69
15		15a		73
16		16a		59[b]
17		17b		41[b,c,d]

[a] Reagent **2** was generated from $CF_2HCH_2NH_2$ (2.0 equiv). [b] Structure confirmed by X-ray analysis. [c] $CF_2HCH_2NH_2$ (5.0 equiv), 72 h. [d] A mixture of the isomers **17a** and **17b** was formed (1:7), from which pure isomer **17b** was isolated by crystallization.

strongly electron-withdrawing groups, namely compounds **3**–**5**, **7**–**11**, and **14**–**16**, smoothly reacted to afford the corresponding pyrazoles in good yields. Alkynes **6**, **12**, **13**, and **17**, which feature weakly electron-withdrawing substituents, reacted slowly, and a larger excess of CF_2HCHN_2 was required to achieve acceptable yields. Unfortunately, less activated ($pCF_3C_6H_4C{\equiv}CH$) or unactivated alkynes (PhC≡CH) could not be transformed into the desired products. These results suggest that the reaction between CF_2HCHN_2 and alkynes is a type I [3+2] cycloaddition:[20] It is accelerated by electron-withdrawing groups on the alkyne and decelerated by electron-donating groups.

The reaction was found to be regioselective: With monosubstituted alkynes, the regioisomer with substituents at the 3- and 5-positions of the pyrazole core was formed (Figure 2). The only unexpected result was obtained with alkyne **17**; the electronically favorable isomer **17a** (with an electron-withdrawing substituent at the 5-position) was formed as the minor product while **17b** was generated as the major one. Presumably, steric effects (in **17a**, the bulky $SiMe_3$ group is located between two other substituents) overrule electronic effects in this case.

In summary, this work describes three important findings: 1) The reagent CF_2HCHN_2 was synthesized (generated in situ) for the first time. 2) The first reaction of CF_2HCHN_2, a [3+2] cycloaddition with alkynes, was investigated and found to be a type I cycloaddition. 3) A novel approach to agrochemically important difluoromethyl-substituted pyrazoles has been developed (Figure 1).[23] The reaction is extremely practical as it is a one-pot process, does not require a catalyst or the isolation of the potentially toxic and explosive gaseous intermediate, and proceeds in a common solvent, namely chloroform, in air. The reaction is also scalable and allows for the preparation of the target pyrazoles on gram scale.

I believe that with this practical procedure for the generation of CF_2HCHN_2 in hand, scientists will soon use CF_2HCHN_2 in other chemical reactions, for example, for the synthesis of difluoromethyl-substituted cyclopropanes, cyclopropynes, ketones, indoles, or boronic acids, and I hope that this reagent will become as useful in medicinal chemistry, agrochemistry, and organic synthesis as CF_3CHN_2 already is.

Keywords: alkynes · cycloaddition · difluoromethylation · fluorine · pyrazoles

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