



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

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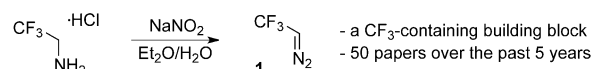
Dedicated to Professor Andrei Tolmachev on the occasion of his 58th birthday

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.

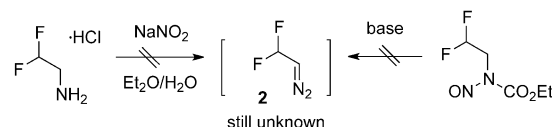
The derivatization of organic compounds with fluorinated units often affects their physicochemical and biological properties.^[1,2] Consequently, approximately 20% of all pharmaceuticals and agrochemicals contain at least one fluorine atom. The trifluoromethyl and difluoromethyl groups are particularly 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

Gilman and Jones (1943):^[5]



Atherton, Fields, and Haszeldine (1971):^[11]



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

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]

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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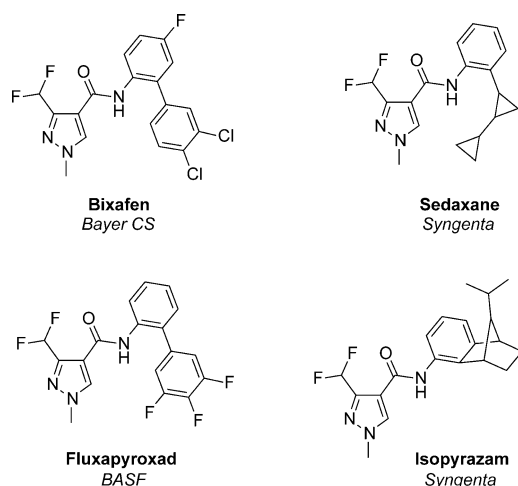
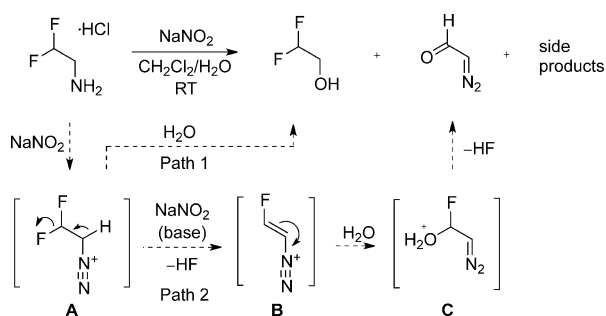


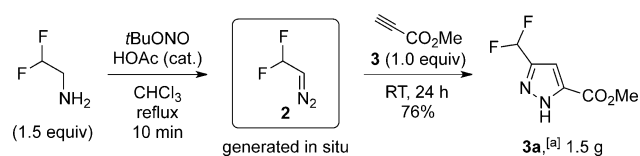
Figure 1. Marketed fungicides that contain difluoromethylated pyrazoles.



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.

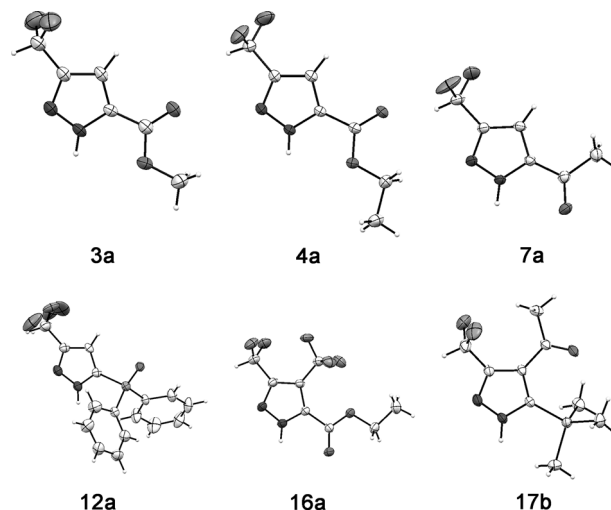


Figure 2. X-ray crystallographic analyses.^[22]

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		76 ^[b]	
4		74 ^[b]	
5		82	
6		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 CF₂HCH₂NH₂ (2.0 equiv). [b] Structure confirmed by X-ray analysis. [c] CF₂HCH₂NH₂ (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 CF₂HCH₂NH₂ was required to achieve acceptable yields. Unfortunately, less activated (*p*-CF₃C₆H₄C≡CH) or unactivated alkynes (PhC≡CH) could not be transformed into the desired products. These results suggest that the reaction between CF₂HCHN₂ 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 mono-substituted 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 SiMe₃ group is located between two other substituents) overrule electronic effects in this case.

In summary, this work describes three important findings: 1) The reagent CF₂HCHN₂ was synthesized (generated in situ) for the first time. 2) The first reaction of CF₂HCHN₂, 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 CF₂HCHN₂ in hand, scientists will soon use CF₂HCHN₂ 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 CF₃CHN₂ already is.

Keywords: alkynes · cycloaddition · difluoromethylation · fluorine · pyrazoles

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