Organic LETTERS

Letter

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Unexpected Reactivity of Trifluoromethyl Diazomethane (CF_3CHN_2): Electrophilicity of the Terminal N-Atom

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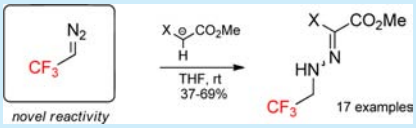
Supporting Information

ABSTRACT: After more than 70 years since its discovery, CF_3CHN_2 was found to possess a novel reactivity mode: *N*-terminal electrophile. With *C*-nucleophiles it gives hydrazones that are easily transformed into valuable CF_3-heterocycles.

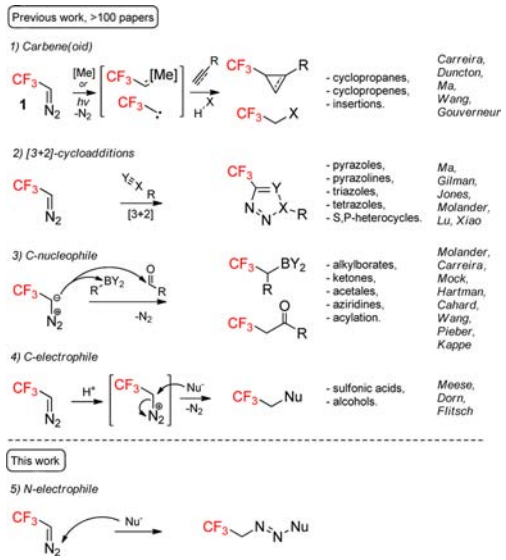


Derivatization of organic compounds by fluorine-containing units often beneficially affects their physicochemical and biological properties.[1,2] Consequently, ca. 20% of pharmaceuticals and agrochemicals contain at least one fluorine atom, the trifluoromethyl group being especially prevalent.[3] Therefore, innovative reactions toward CF_3-bearing building blocks from cheap and available starting materials are at the heart of modern commercial needs.[4]

In 1943, Gilman and Jones synthesized gaseous CF_3CHN_2 (**1**) from trifluoroethylamine hydrochloride and sodium nitrite.[5] Since then, reagent **1** has been blossoming in chemistry. Especially, it became popular after 2010, when conditions for the in situ generation of compound **1** in solution were developed.[6] More than 100 publications already appeared on reagent **1**, comprising roughly four reactivies: (1) CF_3CH:-carbene insertion and [2+1]-cycloaddition (Scheme 1).[7−9] For example, recently the metal-catalyzed *N*-trifluoroethylation of anilines was developed. (2) [3+2]-cycloaddition of CF_3CHN_2 with diverse polarized double/triple bonds to give five-membered heterocycles was also studied.[10] (3) *C*-Nucleophilic addition of CF_3CHN_2 to boronic acids, ketones, aldehydes, and ketals was elaborated recently;[11] moreover, the latter method was already applied *in flow*.[11h] (4) *C*-Electrophilic reaction of CF_3CHN_2 with alcohols and sulfonic acids.[12] In this letter, we report a novel unexpected reactivity of CF_3CHN_2 as a *N*-terminal electrophile.

In 1847, Japp and Klingemann discovered a reaction in which positively charged aryldiazonium salts acted as *N*-electrophiles. They reacted with *β*-ketoesters under basic conditions to form arylhydrazones.[13] On the contrary, aliphatic diazo compounds are less active and their *N*-electrophilicity is far less known. There are several examples of diazocarbonyl compounds, where the diazo group is stabilized by conjugation with the carbonyl group.[14] For example, the common chemical reagent, ethyl diazoacetate (N_2CHCO_2Et), was recently shown to react as an *N*-electrophile in the presence of DBU.[14i] In addition, cyclopropyl diazomethane is known to possess *N*-electrophilic properties; the reaction, however, proceeds via a cyclopropyl diazonium cation.[15]

Scheme 1. Known (eqs 1−4) and Novel (eq 5) Reactivity of 1



In 2014, an "unexpected aldol product" of CF_3CHN_2 under Japp−Klingemann conditions, with CuCl as a catalyst, was reported.[9b] We were inspired by these results, but also surprised because the original reaction required no metal catalysis. Therefore, a model experiment was devised: a dry solution of CF_3CHN_2 in dichloromethane was treated with a simple *C*-nucleophile, $NaCH(CN)CO_2Me$ (**2**). After 5 min, the color of the reaction mixture changed from yellow (diazo compound) to deep orange (conjugated anion). After 24 h at room temperature, the reaction was completed. Standard workup afforded the

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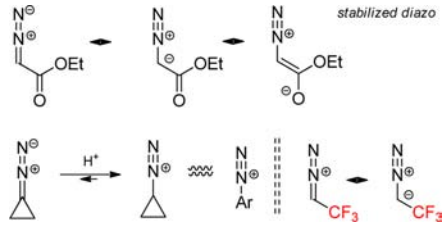
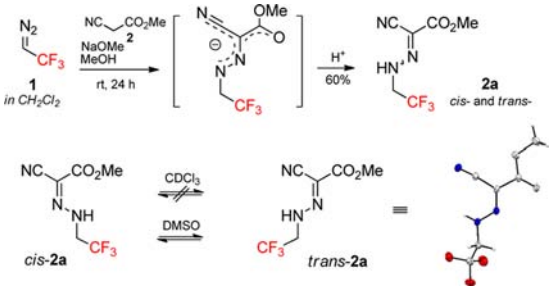


required hydrazone **2a** in 60% isolated yield as a mixture of *cis*- and *trans*-isomers (Scheme 2).[15] The reaction went smoothly,

Scheme 2. Synthesis of Hydrazone 2a; X-ray of Product *trans*-2a



but the product was extremely soluble in water, which prohibited its quantitative isolation. It is worth mentioning that the reaction required no catalyst or heating. We easily scaled this reaction up to prepare 1.5 g of **2a** in one run.

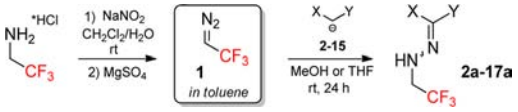
Interestingly, *cis*-**2a** and *trans*-**2a** were easily separated (see Supporting Information). The structure of *trans*-**2a** was confirmed by X-ray crystallographic analysis. The individual compounds were stable in both the solid phase and in $CDCl_3$, while in DMSO-d_6, they were quickly equilibrating to give a mixture of *cis*-**2a**/*trans*-**2a**.

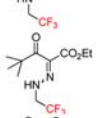
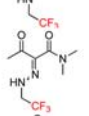
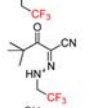
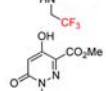
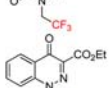
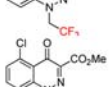
To study the scope of the reaction, we tested diverse methylenic-active substrates **3**–**8** (Table 1). The corresponding sodium salts were prepared *in situ* using either NaOMe/MeOH or NaH/THF. While substrates **3**–**6** afforded the expected hydrazones **3a**–**6a**, compounds with additional electrophilic groups (**7** and **8**) unexpectedly gave CF_3-heterocycles **7a** and **8a**. Inspired by this result, the scope of the cyclization was studied. Various substrates **9**–**17** were treated with **1** leading to the corresponding cinnolinones **9a**–**17a** in good yields (55–69%). The structures of **7a** and **17a** were confirmed by X-ray diffraction analysis.[22]

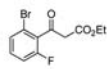
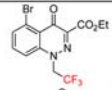
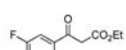
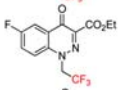
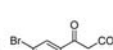
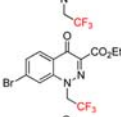
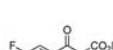
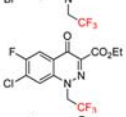
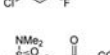
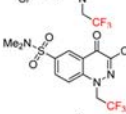
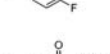
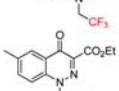
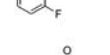
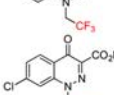
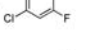
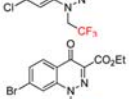
The reaction mechanism presumably proceeds as follows: the *C*-nucleophile attacks the *N*-terminal atom of CF_3CHN_2 to form the unstable intermediate **A**, which rapidly isomerizes into the stable conjugated anion **B** (Scheme 3).[16] Acidification gives the target hydrazones **2a**–**6a**. For substrates **7**–**17**, internal electrophilic groups react with the N-atom in **B** to form the corresponding heterocycles by amide synthesis (**7a**) or nucleophilic aromatic substitution of an activated F-atom (S_NAr, **8a**–**17a**).[16,17]

The developed protocol has a huge perspective for agrochemical and pharmaceutical research, because the chemistry of hydrazones is very broad,[18] offering a great number of

Table 1. Reaction Scope



	substrate	product	Yield (%)[a]
2		**2a**[a] 	60 *X-Ray*
3		**3a**[b] 	46
4		**4a**[b] 	61
5		**5a** 	56
6		**6a** 	37
7		**7a**[a] 	61 *X-Ray*
8		**8a**[b] 	66
9		**9a**[a] 	58

	substrate	product	Yield (%)[a]
10		**10a** 	65
11		**11a**[b] 	55
12		**12a**[b] 	62
13		**13a**[b] 	65
14		**14a**[b] 	69
15		**15a** 	64
16		**16a**[b] 	65
17		**17a**[b] 	65 *X-Ray*

[a]Method A: Substrate (1.0 equiv), NaOMe (1.1 equiv), MeOH + CF_3CHN_2 (3.0 equiv) in CH_2Cl_2, rt, 24 h. [b]Method B: Substrate (1.0 equiv), NaH (1.2 equiv), THF + CF_3CHN_2 (3.0 equiv) in toluene, rt, 24 h.

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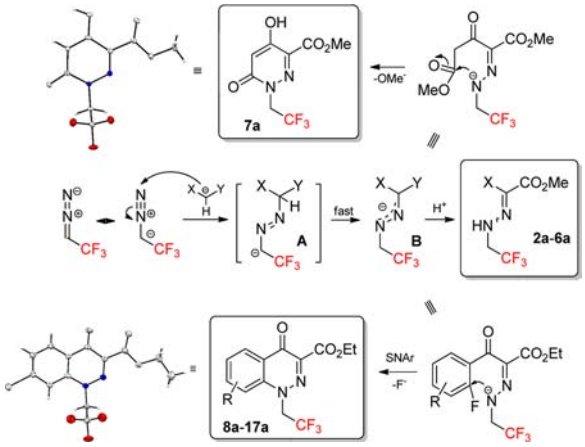
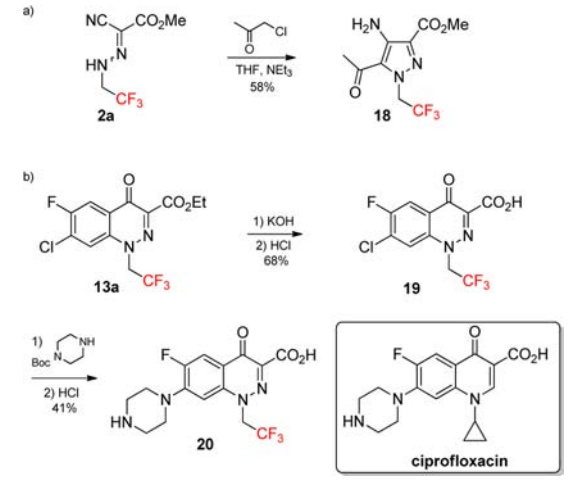
Scheme 3. Proposed Reaction Mechanism; X-ray of Products 7a, 17a



transformations for **2a**−**6a**, while the fluorinated pyrazines **7a** and cinnolinones **8a**−**17a** are already interesting building blocks by themselves. A one-step reaction of hydrazone **2a** with chloroacetone under basic conditions afforded the novel CF_3-pyrazole **18**, demonstrating the usefulness of the method (Scheme 4).[19,20] On the other hand, products **8a**−**17a** closely resemble the central core of antibiotic drug ciprofloxacin.[21] In fact, hydrolysis of **13a** into **19** followed by the reaction with *N*-Boc-piperazine and *N*-deprotection gave acid **20**.

Scheme 4. Practical Application of the Synthesized CF_3-Hydrazones: (a) Synthesis of CF_3-Pyrazole 18; (b) Synthesis of Cinnolilone 20, an Analogue of Antibacterial Drug Ciprofloxacin



In summary, this work describes three important findings:

(1) After more than 70 years, since its discovery in 1943 (and more than 100 manuscripts), a novel reactivity for CF_3CHN_2 has been found as an *N*-terminal electrophilic reagent.

(2) A novel approach toward CF_3-aliphatic hydrazones from cheap and available starting materials has been developed. The reaction is extremely practical: (a) it is a one-pot transformation; (b) requires no catalysts; (c) requires no heating; and (d) allows preparation of the target products in gram quantities.

(3) The obtained hydrazones can be easily transformed into novel CF_3-heterocyclic building blocks and bioactive compounds (analogues of *ciprofloxacin*), and potentially to other structures valuable for the agrochemistry and pharmaceutical industry.

We do believe that the discovered novel reactivity of CF_3CHN_2 as an *N*-electrophile will soon be used by the organic community, as the diversity of *C*-nucleophiles is very broad, and the CF_3CH_2N-motif is frequent in numerous drugs (Figure 1).

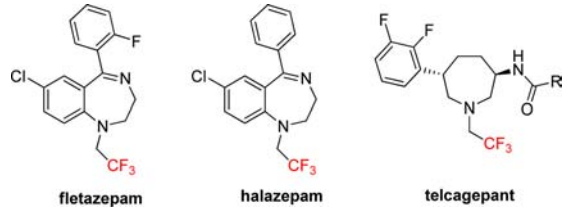


Figure 1. Drugs with CF_3CH_2N-motif.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01565.

Experimental procedures and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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