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Regioselective Cycloaddition of Trifluorodiazoethane with Electron-Deficient Allenic Esters and Ketones: Access to CF_3-Substituted Pyrazolines and Pyrazoles

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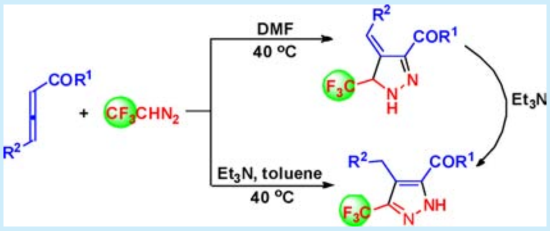
Supporting Information

ABSTRACT: A highly regioselective cycloaddition procedure of electron-deficient allenes with trifluorodiazoethane (CF_3CHN_2) is described. In absence of bases, the reaction proceeded smoothly to give 5-(trifluoromethyl)pyrazolines, whereas the utility of Et_3N led to the formation of 3-(trifluoromethyl)pyrazoles.



Trifluoromethyl-substituted pyrazolines and pyrazoles are privileged structural motifs found in many pharmaceuticals and bioactive compounds (Figure 1),[1] and thus, the development of new methodologies for constructing these compounds has been an active research area in organic synthesis and drug chemistry.[2] The cycloaddition of 2,2,2-trifluorodiazoethane (CF_3CHN_2) with alkenes and alkynes represents a convenient access to trifluoromethylated pyrazolines and pyrazoles (Scheme 1a). In this context, the earlier studies focused on the use of liquid CF_3CHN_2 purified at superlow temperature.[3] Unfortunately, these methods usually suffer from relatively harsh reaction conditions and limited dipolarophile scope. To overcome the problems, our group developed silver-mediated [3 + 2] cycloaddition of alkynes with the stock solution of CF_3CHN_2 in organic solvents,[4] whereas Mykhailiuk and co-workers reported the [3 + 2] cycloaddition of the in situ generated CF_3CHN_2 with electron-deficient alkenes and alkynes to give a series of trifluoromethyl-substituted pyrazolines and pyrazoles.[5] In comparison with the previous methods, these newly protocols employ milder conditions and afford the desired adducts with improved functional group tolerance. Despite this promising progress, it is still highly desirable to develop new cycloaddition reactions

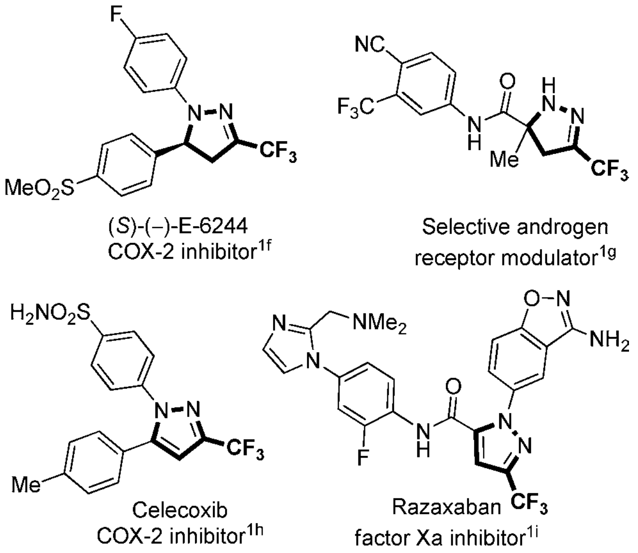
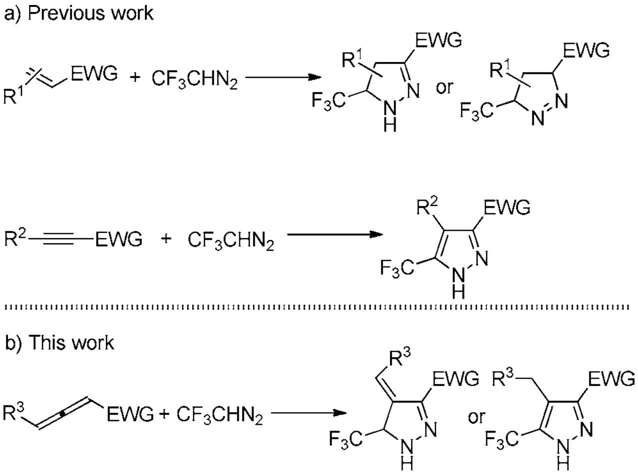


Figure 1. Bioactive molecules based on trifluoromethylated pyrazolines and pyrazoles.

Scheme 1. Cycloaddition Reactions of CF_3CHN_2 with Electron-Deficient Alkenes, Alkynes, and Allenes



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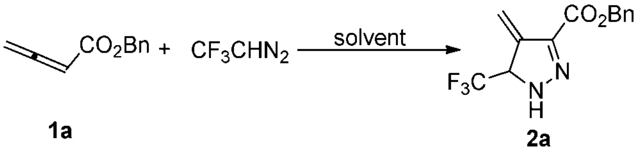
with CF_3CHN_2 and to broaden the diversity of trifluoromethylated pyrazoline and pyrazole species.

In recent years, allenes, in particular electron-deficient allenes, have emerged as attractive building blocks in organic synthesis,[6] and many cycloaddition reactions of electron-deficient allenes have been developed for the construction of carbo- and heterocyclic molecules.[7] However, the use of electron-deficient allenes as the dipolarophiles for the cycloaddition reaction of CF_3CHN_2 still remains elusive. Herein, we report our efforts in the development of this cycloaddition process (Scheme 1b). Such studies would be of benefit in expanding the diversity of pyrazoline and pyrazole derivatives in synthetic chemistry.

We began our investigations by evaluating the stock solution of CF_3CHN_2 in several solvents, and the results are shown in Table 1. To our surprise, at room temperature and without any additive, the cycloaddition of benzylbuta-2,3-dienoate **1a** with CF_3CHN_2 in *N,N*-dimethylformamide (DMF) proceeded to give 5-trifluoromethylpyrazoline **2a** as a single regioisomer in 50% yield (entry 1). Increasing the reaction temperature provided **2a** in higher yields (entries 2 and 3). Good yield of the cycloadduct **2a** was also obtained in tetrahydrofuran (THF) (entry 4). The utility of other solvents, such as toluene, dichloroethane (DCE), dichloromethane (DCM), and 1,2-dimethoxyethane (DME), led to a corresponding decrease in the yield for **2a** (entries 5−8). The cycloaddition reaction of **1a** with CF_3CHN_2 did not occur in acetonitrile (entry 9). Finally, the yield of the cycloadduct **2a** could be further improved to 88% in DMF with prolonged reaction time (entries 10 and 11).

Table 1. Screening Optimal Conditions[a]

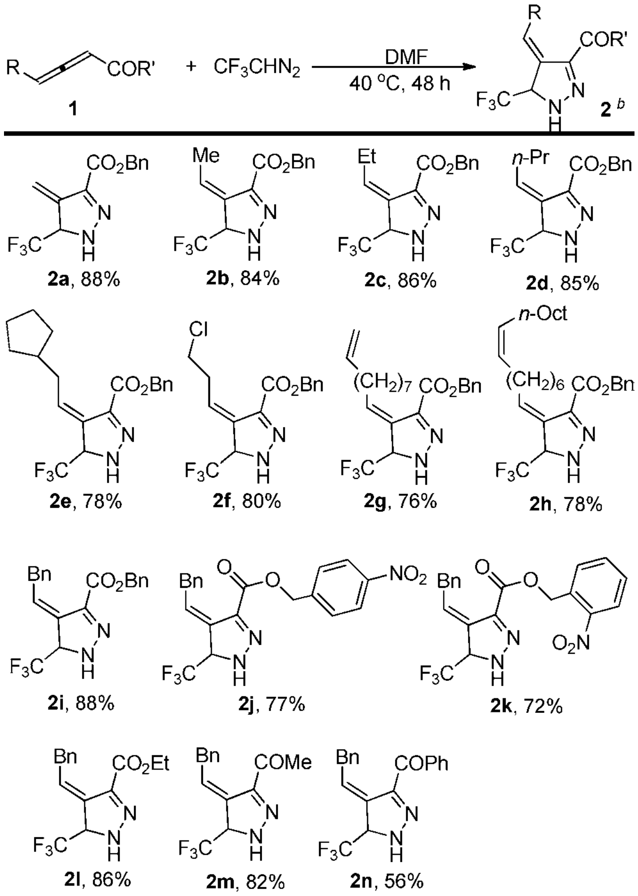


entry	CF_3CHN_2 in solvent (mol/L, equiv)	temp (°C)/time (h)	yield[b] (%)
1	DMF (0.15, 2.0)	25/30	50
2	DMF (0.15, 2.0)	40/30	83
3	DMF (0.15, 2.0)	60/30	82
4	THF (0.2, 2.0)	40/30	82
5	Toluene (0.15, 2.0)	40/30	68
6	DCE (0.3, 3.0)	40/30	45
7	DCM (0.2, 3.0)	40/30	10
8	DME (0.15, 3.0)	40/30	10
9	CH_3CN (0.2, 3.0)	40/30	0
10	DMF (0.15, 2.0)	40/48	88
11	DMF (0.15, 2.0)	40/60	85

[a] General reaction conditions: benzyl allenoate **1a** (0.2 mmol, 1.0 equiv) and CF_3CHN_2 in appropriate solvent were reacted in a sealed tube at constant temperature. [b] Isolated yield.

With these optimized conditions in hand, we set out to investigate the scope of this cycloaddition reaction (Scheme 2). A broad range of γ-alkyl-substituted allenoate esters have been successfully employed in our approach, and a series of 5-(trifluoromethyl)pyrazolines **2b−f** were obtained in 78−86% yields. Two γ-alkenyl-substituted allenoate esters were subjected to this cycloaddition reaction under the same conditions, and the corresponding products **2g** and **2h** were obtained in good yields without any detectable quantities of other cycloaddition or cyclopropanation byproducts despite the presence of olefin moieties in the reactants. Several allenoates with different ester substituents were also capable in this approach to give the cycloadducts **2i−l** in high yields. The exocyclic C=C double bond was determined to be *Z* geometry by a 2D-NOESY analysis of **2i** (see the Supporting Information). Furthermore, this can be rationalized by assuming that trifluorodiazoethane is approaching from the less hindered side of the substituted allene to generate (*Z*)-product (Figure 2). In addition, enhanced 1,3-allylic strain in the formed (*E*)-cycloadduct should favor formation of the (*Z*)-product. Subsequently, two allenic ketones could also be used as the dipolarophile partners, thus providing the cycloadducts **2m** and **2n** in the yield of 82% and 56%, respectively. Finally, we investigated the cycloaddition reaction of trifluorodiazoethane with γ-aryl-substituted allenoate esters, such as benzyl γ-phenylbuta-2,3-dienoate, benzyl γ-(2-thiophenyl)buta-2,3-dienoate, and ethyl γ-phenylbuta-2,3-dienoate. These substrates were found to be unsuitable for this transformation, and no desired cycloadducts were obtained even when the reaction temperature was increased to 80 °C.

Scheme 2. Cycloaddition of CF_3CHN_2 with Electron-Deficient Allenes 1 into 5-Trifluoromethylpyrazolines 2[a]



[a] General reaction conditions: allene **1** (0.2 mmol, 1.0 equiv) and CF_3CHN_2 (0.4 mmol, 2.0 equiv) in DMF were reacted in a sealed tube at 40 °C for 48 h. [b] Isolated yield.

It is noteworthy that, under the catalysis of triethylamine, 5-(trifluoromethyl)pyrazoline **2a** could be readily isomerized into the 3-(trifluoromethyl)pyrazole **3a** in essentially quantitative yield (Scheme 3). Furthermore, the structure of **3a** was

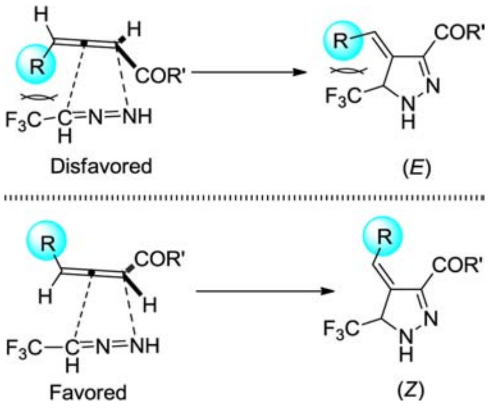
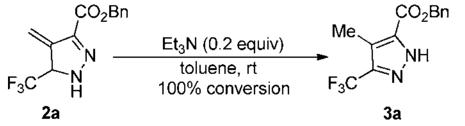


Figure 2. Steric interactions favoring formation of (*Z*)-cycloadducts.

Scheme 3. Isomerization of 2a into 3a

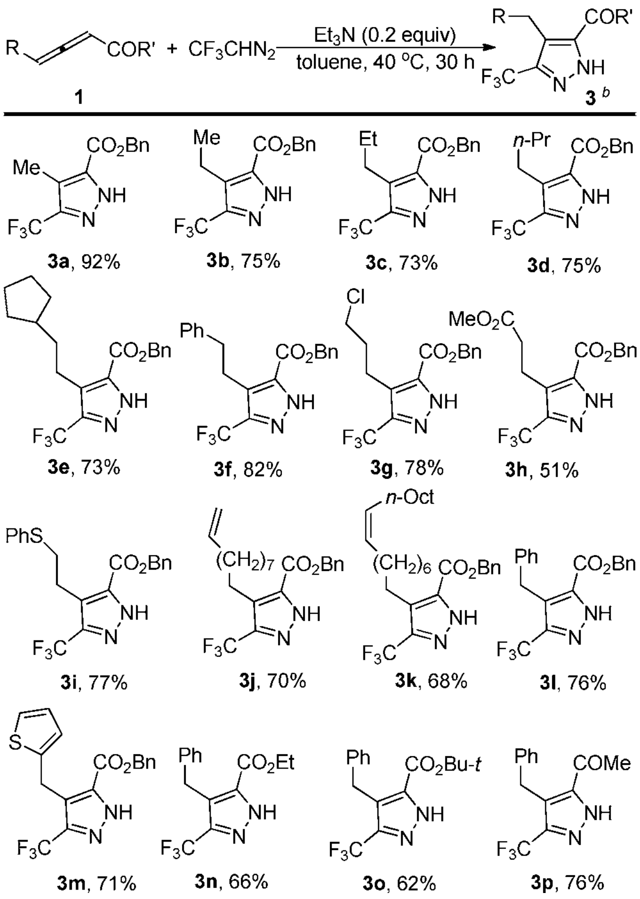


confirmed by means of X-ray crystallographic analysis (see the Supporting Information). These interesting findings prompted us to investigate further Et_3N-triggered one-pot cycloaddition of CF_3CHN_2 with electron-deficient allenic esters and ketones. Careful reaction optimization revealed that the cycloaddition is best conducted with 20 mol % of Et_3N in toluene at 40 °C (see the Supporting Information). Results of the cycloaddition of various electron-deficient allenes with CF_3CHN_2 are summarized in Scheme 4.

We found that the allene scope of the Et_3N-triggered cycloaddition with trifluorodiazoethane is fairly broad. A series of γ-alkyl-substituted allenoate esters delivered the cycloadducts **3a**−**f** in good to high yields. Moreover, γ-alkyl linkers carrying chloro, ester, and thioether substituents, as well as olefin moieties are compatible with this cycloaddition reaction, furnishing 5-(trifluoromethyl)pyrazoles **3g**−**k** in 51−78% yields. γ-Aryl- and heteroaryl-substituted allenoate esters also participated in this transformation, giving rise to the cycloadducts **3l** and **3m** in the yield of 76% and 71%, respectively. In addition, other electron-deficient allenic esters and ketones were employed as dipolarophile substrates, and the corresponding cycloadducts **3n**−**p** were obtained in good yields. It is well known that 3-alkynoates can be readily isomerized to allenoates upon treatment with organic bases.[8] Thus, the present protocol was further extended to a one-pot sequential isomerization/cycloaddition of 3-alkynoate **4** with trifluorodiazoethane in the presence of triethylamine, and the desired cycloadduct **3n** was produced in 84% yield (Scheme 5). In sharp contrast, in the absence of Et_3N the cycloaddition reaction of 3-alkynoate **4** with CF_3CHN_2 did not proceed smoothly, and only a trace of product **3n** was detected by ^{19}F NMR spectrometry.

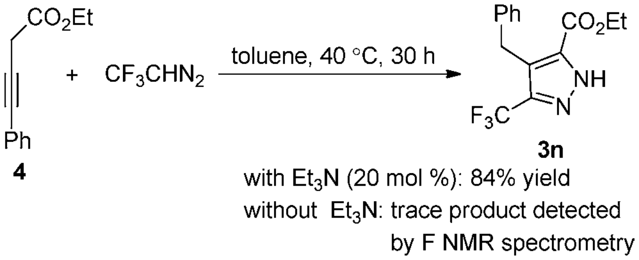
In summary, we have successfully developed a novel and efficient procedure for highly regioselective cycloaddition of electron-deficient allenic esters and ketones with trifluorodiazoethane. A variety of 5-(trifluoromethyl)pyrazolines and 3-(trifluoromethyl)pyrazoles can be accessed in good to high yields under the mild reaction conditions. Further application of this cycloaddition reaction and detailed mechanistic studies are underway in our laboratory.

Scheme 4. Et_3N-Triggered Cycloaddition of CF_3CHN_2 with Electron-Deficient Allenes 1[a]



[a]General reaction conditions: allene 1 (0.2 mmol, 1.0 equiv), CF_3CHN_2 (0.4 mmol, 2.0 equiv), and Et_3N (0.04 mmol, 0.2 equiv) in toluene reacted in sealed tube at 40 °C for 30 h. [b]Isolated yield.

Scheme 5. Et_3N-Catalyzed One-Pot Sequential Isomerization/Cycloaddition of 3-Alkynoate 4



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, spectral data of all the new compounds, and X-ray data for **3a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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