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Unexpected trifluoromethylated pyrazoles from ethyl 2-diazo-4,4,4-trifluoroacetoacetate and 1-diethylamino-prop-1-yne

Michel Guillaume[a]*, Zdenek Janousek[a], Heinz G. Viehe[a], Chantal Wynants[a], Jean-Paul Declercq[b], Bernard Tinant[b]

[a]*Laboratoire de Chimie Organique, Université Catholique de Louvain, Place L. Pasteur, B-1348 Louvain-La-Neuve, Belgium*
[b]*Laboratoire de Cristallographie, Université Catholque de Louvain, Place L. Pasteur, B-1348 Louvain-La-Neuve, Belgium*

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Abstract

Ethyl 2-diazo-4,4,4-trifluoroacetoacetate reacts with *N,N*-diethylamino-prop-1-yne via an unusual pathway: the ynamine first reacts with the carbonyl adjacent to CF_3, leading to a non-isolated vinyldiazomethane, which undergoes intramolecular cyclisation and then a [1,5]-shift to afford a pyrazole.

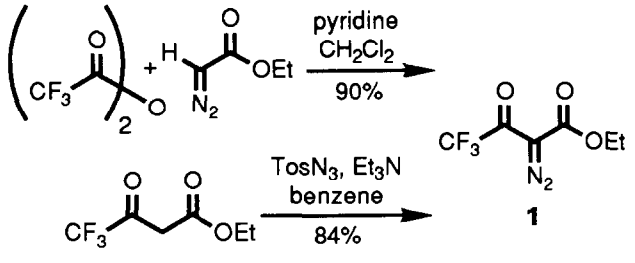
Keywords: Trifluoromethylated pyrazoles; Intramolecular cyclisation; Ynamine reaction; NMR spectroscopy; IR spectroscopy

1. Introduction

2-Diazo-1,3-dicarbonyl compounds are readily prepared from the corresponding 1,3-dicarbonyls by a diazo transfer reaction [1,2]. This method is applicable to ethyl 4,4,4-trifluoroacetoacetate, but the facile synthesis of ethyl 2-diazo-4,4,4-trifluoroacetoacetate (**1**) described by Weygand and Bestmann [3] involves the acylation of ethyl diazoacetate by trifluoroacetic anhydride in the presence of pyridine (Scheme 1).

2. Results and discussion

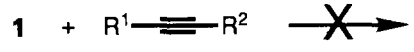
The diazo group of β-dicarbonyl compounds is known to act as a potential 1,3-dipole [4], but diazo compound **1** is not reactive towards electron-poor or non-activated acetylenes (Scheme 2). In contrast, with electron-rich 1-diethylamino-prop-1-yne (**2**), the reaction takes place exothermically, but the reaction product is not the expected 3*H*-pyrazole **3**, as suggested by non-trifluoromethylated examples from the literature [5]. The only isolated product was the pyrazole **4a** (Scheme 3).



Scheme 1.

The reaction is assumed to proceed via the diazoglutaconic amide ester **6** which arises via a [2+2] cycloaddition reaction of the ynamine on the activated carbonyl bond and subsequent ring-opening of the oxetene **5** [6] (Scheme 4).

In the next step, the vinyldiazomethane **6** undergoes intramolecular cyclisation to afford the 3-diethylcarbamoyl 3*H*-pyrazole **7**. This unstable intermediate undergoes a Van Alphen–Hüttel rearrangement [7,8], an allowed [1,5]-carbamoyl shift, leading to the stable pyrazole **4a**.



R^1	R^2
-H	-COOMe
-COOMe	-COOMe
-H	-Ph
-Ph	Ph

Scheme 2.

*Corresponding author.

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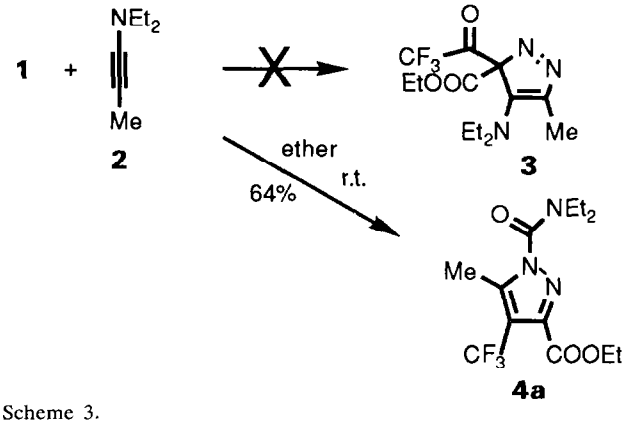
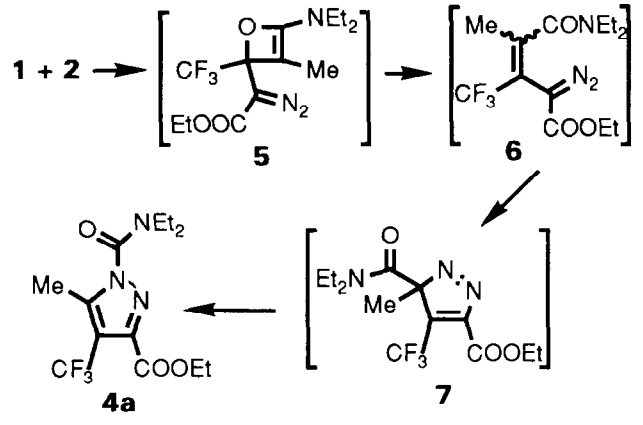
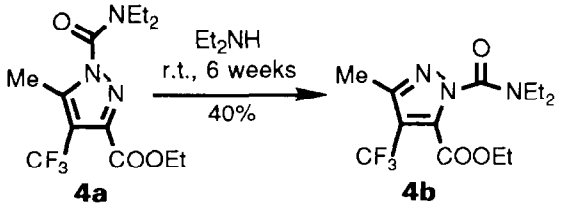


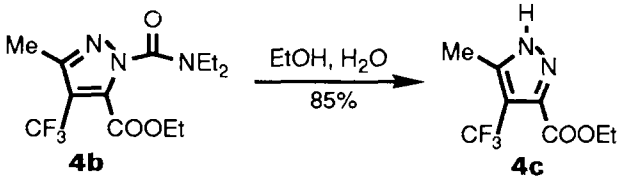
Scheme 3.



Scheme 4.



Scheme 5.



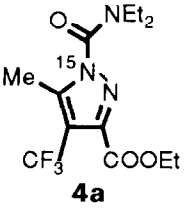
Scheme 6.

When the yellowish oil **4a** was left in diethylamine, colorless crystals of **4b** were formed, resulting from another [1,5]-sigmatropic shift (Scheme 5).

Compound **4b** is very sensitive to moisture and undergoes hydrolysis, leading to the derivative **4c**, the 4-trifluoromethyl pyrazole (Scheme 6).

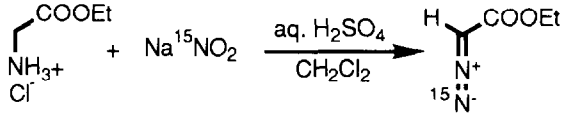
The isomeric pyrazoles **4a** and **4b** have similar NMR spectra. Nevertheless, they can be distinguished unambiguously by means of ^{13}C–^{15}N coupling, since ethyl diazoacetate with ^{15}N terminal nitrogen can be obtained by treatment of glycine ethyl ester with $Na^{15}NO_2$ in an acidic medium (Scheme 7).

Ethyl diazoacetate (^{15}N) is transformed to the corresponding ^{15}N ethyl 2-diazo-4,4,4-trifluoroacetoacetate, as shown in Scheme 1. By reaction with the ynamine, as shown in Scheme 3, the ^{15}N-enriched pyrazole **4a** is obtained.



The ^{13}C-decoupled spectrum shows the amide carbonyl as a doublet ($^1J_{C-N}$ coupling of 20.1 Hz), a characteristic of that isomer. Recently, we were able to crystallise **4a** after thorough purification and prolonged cooling below 20 °C. X-Ray analysis has confirmed the conclusion drawn from NMR analysis (see Fig. 1).

In conclusion, the ynamine reaction has shown that with the trifluoroacetoacetate sequential attack first occurs on the CF_3-activated carbonyl. This principle permits other synthetic applications [9] which we will describe later.



Scheme 7.

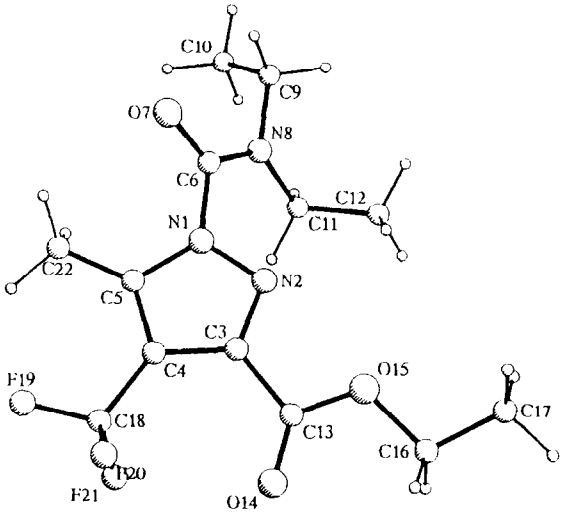


Fig. 1. The crystal structure of pyrazole **4a**.

3. Experimental details

NMR spectra were recorded on a Bruker AM 500 spectrometer, working at 500.13 MHz (^{1}H) and 125.76 MHz (^{13}C). TMS was used as internal reference. IR spectra were recorded on a Nicolet 205 spectrophotometer. Mass spectra were recorded on a Finnigan MAT (TSQ 70) with EI ionisation. Microanalyses were performed at University College, London.

Ethyl diazoacetate was purchased from Aldrich and used without further purification. Trifluoroacetic anhydride and ethyl trifluoroacetoacetate were used as received from Rhône-Poulenc. Tosyl azide synthesis was as described by Curphey [10]. Ynamine **2** was obtained by the method of Brandsma [11]. Sodium nitrite (99 atom.%^{15}N) was purchased from Isotec Inc. and ethyl diazoacetate was synthesised as described previously [12].

The X-ray analysis of compound **4a** was undertaken using a Huber four circle diffractometer with Cu Kα radiation ($\lambda = 1.5418$ Å) over the range $3° \leqslant 2\theta \leqslant 135°$ employing a parallelipiped crystal of crystal dimensions $0.40 \times 0.28 \times 0.25$ mm. The lattice parameters were refined using 15 reflections in the range $25° < 2\theta < 25°$.

Compound **4a**: M = 321.30, monoclinic, space group $P2_1/n$; $a = 4.983(1)$, $b = 18.340(13)$, $c = 17.452(12)$ Å, $\beta = 95.61(3)°$; $V = 1587(2)$ Å^3, $Z = 4$, $D_c = 1.35$ g cm^{-3}, $m = 10.6$ cm^{-1}, $F(000) = 672$.

The number of measured reflections was 2838 of which 1590 with $I > 2.5\sigma(I)$ were considered observed. The structure was solved using the SHELXS86 program with SHELX76 being employed for refinement using F values. All H atoms were in computed positions. Weighting $w = 1/(\sigma^2 + 0.00106F^2)$. Final R indices were: $R = 0.059$, with $Rw = 0.065$ and $S = 1.72$ for 1590 observed reflections.

Complete X-ray data have been deposited at the Cambridge Crystallographic Data Centre, Cambridge, UK.

3.1. Preparation of ethyl 2-diazo-3-oxo-4,4,4-trifluorobutyrate(1)

3.1.1. Method A

To a solution of ethyl trifluoroacetoacetate (1.84 g, 10 mmol) and tosyl azide (1.97 g, 10 mmol) in benzene (15 ml) was added triethylamine (1.01 g, 10 mmol) at 0 °C. The mixture was then allowed to warm at room temperature and stirred for 12 h. Pentane (25 ml) was added to complete precipitation of the tosyl amide and the mixture was filtered and evaporated. Flash chromatography on silica gel afforded **1** as a pale yellow oil; yield, 1.77 g (84%).

3.1.2. Method B

To a solution of ethyl diazoacetate (11.4 g, 100.0 mmol) and pyridine (8.69 g, 1.1 equiv.) in CH_2Cl_2 (100 ml) was added dropwise at 0 °C a solution of trifluoroacetic anhydride (23.1 g, 1.1 equiv.) in CH_2Cl_2 (25 ml). The mixture was then poured into water and neutralised with $NaHCO_3$. The water layer was removed and an oxalic acid solution (1 g in 25 ml water) added in order to remove pyridine. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×20 ml). The combined organic fractions were dried and evaporated. Distillation under reduced pressure (75 °C/10 mmHg) afforded **1** as a pale yellow oil; yield 18.9 g (90%). Analysis: $C_6H_5F_3N_2O_3$ (210.11) requires: C, 34.3; H, 2.4; N, 13.3%. Found: C, 34.4; H, 2.0; N, 13.2%.

Table 1
NMR and IR spectroscopic data for prepared compounds

Compound	^{1}H NMR δ (ppm), J (Hz)	^{13}C NMR δ (ppm)	^{19}F $-\delta$ (ppm)	IR (cm^{-1})
1	1.29 (t, J=7.1); 4.30 (q, J=7.2)	14.1; 62.8; 75.8; 116.1; 158.8; 172.7	74.3	3000–2800; 2169; 1746; 1713; 1675; 1468; 1450; 1398; 1380; 1309; 1211; 1174; 1018
4a	1.15 (t, J=6.9); 1.25 (t, J=7.0); 1.33 (t, J=7.1); 2.46 (q, ^4J_F=1.8); 3.18 (q, J=7.0); 3.48 (q, J=7.1); 4.36 (q, J=7.2)	10.9; 12.3; 13.9; 13.9; 42.5; 43.9; 61.7; 111.9; 122.0; 141.2; 142.8; 150.1; 160.3	55.8	3000–2800; 1739; 1716; 1463; 1439; 1384; 1368; 1346; 1324; 1245
4b	1.12 (t, J=6.9); 1.20 (t, J=7.1); 2.30 (t, ^4J_F=1.5); 3.02 (q, J=7.1); 4.22 (q, J=7.2)	10.4; 12.8; 13.5; 42.1; 61.2; 110.1; 122.6; 140.8; 142.8; 160.7; 164.9	54.7	300–2800; 1728; 1589; 1524; 1455; 1325; 1249; 1138; 1037
4c	1.36 (t, J=7.2); 2.48 (q, ^4J_F=1.9); 4.39 (q, J=7.1); 10.32 (broad)	10.8; 13.7; 61.2; 110.0; 122.7; 140.4; 142.4; 161.0	55.1	3229; 3000–2800; 1712; 1514; 1474; 1456; 1274; 1259; 1179; 1143; 1064

3.2. Preparation of 3-carboethoxy-1-(N,N-diethylcarbamoyl)-5-methyl-4-trifluoromethyl pyrazole (4a)

To a solution of **1** (2.1 g, 10.0 mmol) in ether (15 ml) was added dropwise a solution of **2** (1.33 g, 1.2 equiv.) in the same solvent (10 ml). Flash chromatography on silica, using ether/petroleum ether 1:1, afforded **4a** as a pale yellow oil; yield, 2.05 g (64%). Analysis: $C_{13}H_{18}F_3N_3O_3$ (321.30) requires: C, 48.6; H, 5.6; N, 13.1%. Found: C, 48.5; H, 5.6; N, 12.7%.

3.3. Preparation of 5-carboethoxy-1-(N,N-diethylcarbamoyl)-3-methyl-4-trifluoromethyl pyrazole (4b)

Compound **4a** (2.0 g, 6.23 mmol) was dissolved in diethylamine (10 ml). After 6 weeks, the crystals were filtered and washed with 10 ml of solvent. Compound **4b** appeared as white needles, m.p. 70 °C; yield, 800 mg (40%). $C_{13}H_{18}F_3N_3O_3$ (321.30) was too unstable to allow elemental analysis.

3.4. Preparation of 3-carboethoxy-5-methyl-4-trifluoromethyl pyrazole (4c)

Compound **4b** (800 mg, 2.5 mmol) was dissolved in 10 ml of EtOH. After refluxing for 5 min and cooling, ice-cold water (25 ml) was added. The white precipitate was filtered and dried under high vacuum; m.p. 131 °C; yield, 470 mg (85%). Analysis: $C_8H_9F_3N_2O_2$ (222.17) requires: C, 43.2; H, 4.1; N, 12.6%. Found: C, 42.9; H, 4.1; N, 12.5%.

The NMR and IR spectral data for these compounds are listed in Table 1.

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