Trifluoroacetaldehyde *N*-tosylhydrazone in [3+2] cycloaddition reaction for the synthesis of 5-(trifluoromethyl)pyrazolines

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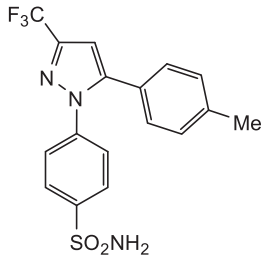
Trifluoroacetaldehyde *N*-tosylhydrazone used as a precursor for the *in situ* generation of CF_3CHN_2 by treatment with weak bases in safe concentration underwent [3+2] cycloaddition to electron deficient alkenes in the presence of *N,N*-diisopropylethylamine to give 5-(trifluoromethyl)pyrazolines in high yields. The reaction proceeded under mild conditions, tolerated a wide range of the substituents, and gave products promising for the drug design. The elaborated procedure avoided such drawbacks associated with the use of CF_3CHN_2 as volatility, toxicity, and explosion hazard.

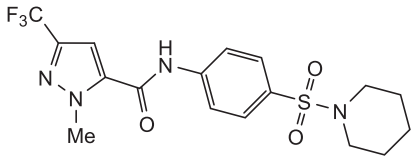
Key words: organofluorine chemistry, diazo compounds, [3+2] cycloaddition, pyrazolines, trifluoroacetaldehyde *N*-tosylhydrazone.

5-Trifluoromethylpyrazoles are valuable intermediates in the synthesis of new medications, agrochemicals, and biologically active compounds. The structures of pharmaceuticals bearing in their structures the substituted pyrazole ring with the 5-positioned CF_3 group are shown below. Therefore, the construction of the 5-trifluoromethylpyrazole scaffold become a subject of intensive studies in the field of synthetic and medicinal chemistry.[1] 5-Trifluoromethylpyrazoles are mainly synthesized by cyclocondensation of hydrazine with the appropriate 1,3-dicarbonyl compounds.[2—6] However, this method has some shortcomings, namely, formation of mixtures of regioisomers relative to positions 3 and 5 of pyrazole and laborious synthesis of the starting dicarbonyl compounds.

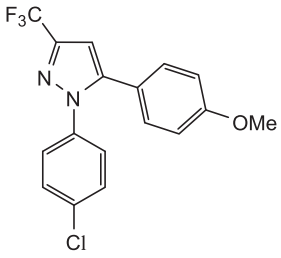
Recently, 2,2,2-trifluorodiazoethane become a widely used synthon for the construction of the



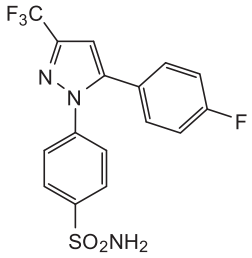
Celecoxib (arthritis)



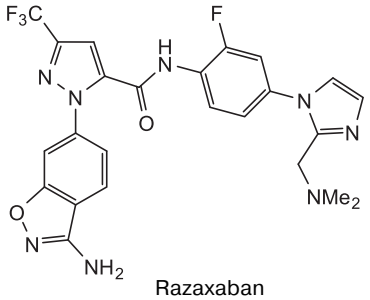
AS-136A
(antiviral agent, measles)



CS-560
(anticancer agent)



Mavacoxib
(COX-2 inhibitor)



Razaxaban
(anticoagulant)

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* Vol. 73, No. 4, pp. 1011—1017, April, 2024.

fluorine-containing building blocks.[7—24] Application of 2,2,2-trifluorodiazoethane as a 1,3-dipole in [3+2] cycloaddition to alkynes and alkenes allowed synthesis of trifluoromethyl-substituted pyrazoles and pyrazolines bearing different functional groups. However, this approach is not sufficiently developed for the preparative application. In 1979, Fields and Tomlinson[15] described the reaction of terminal alkynes with 2,2,2-trifluorodiazoethane carried out in a sealed tube. Unfortunately, the harsh reaction conditions and long reaction time (more than two weeks) make this process impractical. Therefore, this fact prompted some modifications of this method.

Thus, addition of Ag_2O (2 equiv.) and NaOAc (2 equiv.) to the reaction mixture provided high yields of the pyrazole derivatives at 45 °C within 5 h.[12] The use of nitroalkenes as dipolarophiles in the [3+2] cycloaddition reaction with 2,2,2-trifluorodiazoethane gave CF_3-substituted pyrazoles under mild reaction conditions because elimination of the nitro group resulted in the aromatization of the ring.[14] Another improvement of this method was the use of a continuous flow assembly.[13]

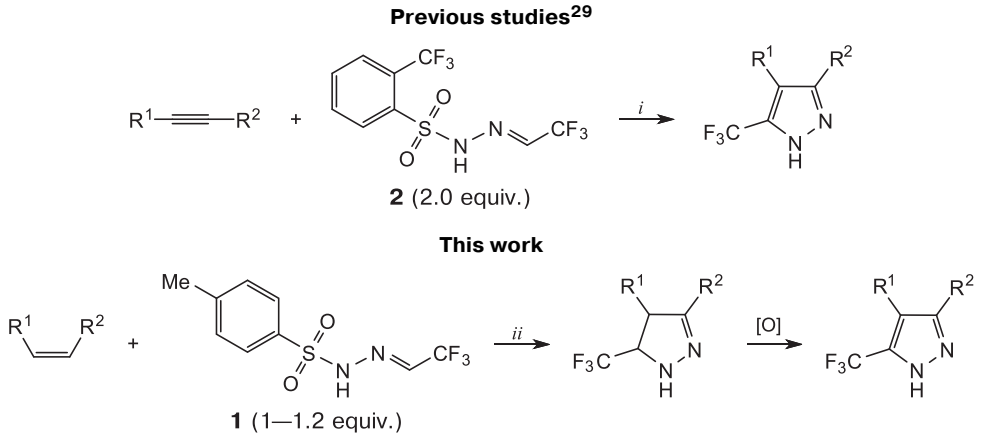
On the other hand, application of 2,2,2-trifluorodiazoethane as a 1,3-dipole suffers from several drawbacks, *e.g.*, volatility, low storage stability, toxicity, and explosion hazard. Synthesis of 2,2,2-trifluorodiazoethane is relatively complicated. This compound is mainly synthesized by the treatment of trifluoroethylamine hydrochloride ($CF_3CH_2NH_2 \cdot HCl$) with sodium nitrite ($NaNO_2$).[12,21,23] The use of 2,2,2-trifluorodiazoethane usually requires a large excess of the reagent, which makes synthesis quite expensive.

To overcome the abovementioned drawbacks, in the present work we applied trifluoroacetaldehyde *N*-tosylhydrazone (**1**) instead of 2,2,2-trifluorodiazoethane. *N*-Tosylhydrazones are well studied in organic synthesis as the precursors of the diazo compounds.[25—27] Earlier, we described the use of *N*-tosylhydrazone **1** as a precursor of CF_3CHN_2 in the Cu-catalyzed trifluoroethylation reaction of dialkyl phosphites, carboxylic acids, and thiols and demonstrated a wide synthetic potential of *N*-tosylhydrazone **1** in the synthesis of trifluoroethyl-containing compounds.[28]

The attempts to use trifluoroacetaldehyde *N*-arylsulfonyl hydrazones are known. In 2020, Bi and coworkers[29] described [3+2] cycloaddition of arylacetylenes to trifluoroacetaldehyde 2-(trifluoromethyl)phenylsulfonyl hydrazones **2** to synthesize a series of 5-aryl-3-trifluoromethylpyrazoles (Scheme 1). The suggested method is differed by that our goal was the synthesis of pyrazolines, which can be further oxidized to pyrazoles (see Scheme 1). The advantages of our approach are (i) the use of more readily available and cheap hydrazone, (ii) room temperature reaction protocol, and (iii) the use of ~1—1.2 equivalents of hydrazone instead of 2 equivalents.

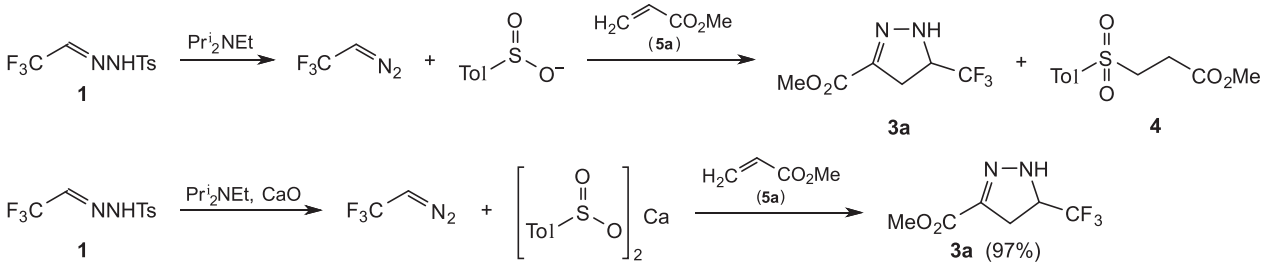
The reaction of trifluoroacetaldehyde *N*-tosylhydrazone (**1**) with methyl acrylate (1.5 equiv.) in the presence of the base that enabled decomposition of tosylhydrazone to trifluorodiazoethane and *p*-toluenesulfinate was used as a model reaction. The reaction course was monitored by ^{19}F NMR spectroscopy. The reaction was carried out in ethyl acetate in the presence of different bases for 24 h. The screen-

Scheme 1



Reagents and conditions: *i*. KOH (4.0 equiv.), dioxane, 10 h, 100 °C; *ii*. Pr^i_2NEt (0.5 equiv.), CaO (2.0 equiv.), EtOAc, 16 h, 20 °C.

Scheme 2

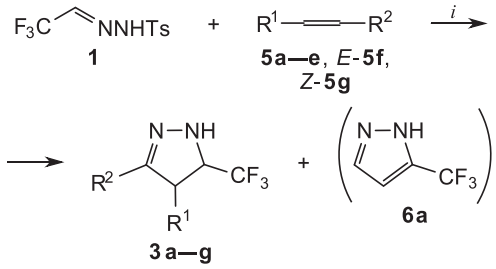


ing of the bases revealed that pyridine and triethylamine are too weak to enable the reaction. In the presence of some bases, *viz.*, $KOBu^t$, NaOEt, and NaOH, resinification of the reaction mixture took place. Other bases, *viz.*, K_2CO_3, Na_3PO_4, and DBU, gave product **3a** in moderate yields. It was found that Pr^i_2NEt (2 equiv.) is the base of choice for this reaction. Under these conditions, pyrazoline **3a** was obtained in almost quantitative yield. However, we encountered a great problem with isolation of the reaction product since methyl 3-(*p*-tolylsulfonyl)propionate (**4**) was formed along with the target product **3a**. Compound **4** is resulted from the Michael addition of *p*-toluenesulfinate generated upon decomposition of tosylhydrazone **1**. It should be noted that products **3a** and **4** cannot be separated by chromatography. Even when the starting compounds were used in an equimolar amounts, an inseparable mixture of both product (**3a** : **4** = 2 : 1) was obtained. To avoid the formation of compound **4**, we added 2 equiv. of CaO to the reaction mixture. In this case, *p*-toluenesulfinate is transformed to the calcium salt and precipitated, and pyrazoline **3a** become the only reaction product (Scheme 2). Under these conditions, we obtained compound **3a** in 97% yield. In the presence of calcium oxide, Pr^i_2NEt can be used in the catalytic amounts; it is advisable to use 0.5 equiv. of the base to complete reaction faster.

After optimization of the reaction conditions, we studied the scope of alkenes capable of undergoing [3+2] cycloaddition with tosylhydrazone **1** (Scheme 3, Table 1). At first, we examined the monosubstituted alkenes.

The obtained results indicated that hydrazone **1** reacted with electron-deficient alkenes **5a—g** to give high yields of the corresponding products (see Table 1, entries *1—5*). However, reaction of compound **1** with electron-rich and electron-neutral monosubstituted olefins (styrene, vinyl ethyl ether) failed to

Scheme 3



3, 5: R^1 = H, R^2 = CO_2Me (**a**), CO_2Et (**b**), CN (**c**), C(O)Me (**d**), SO_2Ph (**e**); $R^1 = R^2 = CO_2Me$ (**f**), $R^1 = R^2 = CO_2Et$ (**g**)

Reagents and conditions: *i*. Pr^i_2NEt (0.5 equiv.), CaO (2.0 equiv.), EtOAc, 16 h, 20 °C.

procced. When the reaction was carried out with 2 equiv. of Pr^i_2NEt in the absence of CaO, the reaction of compound **1** with phenyl vinyl sulfone (**5e**) gave 3-(trifluoromethyl)pyrazole (**6a**) as a main

Table 1. [3+2] Cycloaddition of hydrazone **1** to different alkenes[a]

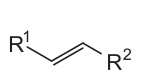
Entry	Alkene	Product (yield (%))
1	**5a**	**3a** (97)
2	**5b**	**3b** (99)
3	**5c**	**3c** (95)
4	**5d**	**3d** (68)
5	**5e**	**3e** (50)
6[b]	**5e**	**3e** (25) + **6a** (40)
7	*E*-**5f**	**3f** (99)
8	*Z*-**5g**	**3g** (99)

[a] Reaction conditions: hydrazone **1** (0.5 mmol (for **3a—d**) or 0.6 mmol (for **3e—f**)), alkene **5** (0.8 mmol (for **3a—d**) or 0.5 mmol (for **3e—f**)), Pr^i_2NEt (0.25 mmol), CaO (1 mmol), EtOAc (3 mL), 16 h, 20 °C.

[b] Reaction conditions: hydrazone **1** (0.6 mmol), alkene **5e** (0.5 mmol), Pr^i_2NEt (1 mmol), EtOAc (3 mL), 16 h, 20 °C.

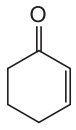
product. Apparently, product **6a** is a result of elimination of phenylsulfinate from compound **3e** in the presence of the base (entry *6*).

Next, we studied [3+2] cycloaddition reactions involving 1,2-disubstituted alkenes bearing at least one electron-withdrawing group. In this case, the reaction also proceeded with some selectivity. Alkenes *E*-**5f** and *Z*-**5g** bearing two electron-withdrawing substituents reacted under mild conditions to give trisubstituted pyrazolines in high yields (see Table 1, entries *7* and *8*). It should be noted that neither *Z* nor *E* configuration of the double bond affected the reaction outcome. Thus, dimethyl fumarate (*E*-**5f**) and diethyl maleate (*Z*-**5g**) gave the corresponding pyrazolines in almost quantitative yields. If the double bond is substituted with electron-donating or phenyl group along with the electron-withdrawing moiety, the reaction either failed to proceed or proceeded very slowly. This observation was made when the following substrates were involved in the reaction: styrene (**5h**), ethyl vinyl ether (**5i**), ethyl cinnamate (**5j**), benzylideneacetone (**5k**), chalcone (**5l**), and cyclohex-2-en-1-one (**7**). In the case of maleic anhydride (**8**), resinification of the reaction mixture occurred.



5h—l

5: R^1 = H, R^2 = Ph (**h**), OEt (**i**); R^1 = Ph, R^2 = CO_2Et (**j**), C(O)Me (**k**), C(O)Ph (**l**)



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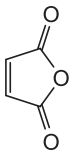

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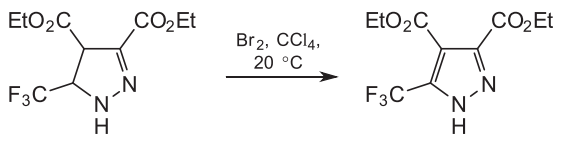
As it was noted above, trifluoromethyl-substituted pyrazole carboxylic acids are the important building blocks for drug design. To demonstrate the synthetic potential of the suggested approach, we realized the oxidative aromatization of one of the synthesized fluorinated pyrazolines to the corresponding pyrazole. Oxidation of pyrazoline **3g** with bromine in tetrachloromethane gave pyrazole **6b** in 82% yield (Scheme 4).

Scheme 4



3g **6b** (82%)

In summary, we developed a new method for the synthesis of trifluoromethyl-substituted pyrazolines by the [3+2] cycloaddition reaction. In the present work, we used trifluoroacetaldehyde *N*-tosylhydrazone (**1**) as a precursor of CF_3CHN_2, which, in turn, is necessary as a dipole that reacted with the electron-deficient alkenes. It was found that trifluoroacetaldehyde *N*-tosylhydrazone (**1**) in the presence of *N*,*N*-diisopropylethylamine and calcium oxide reacted with alkenes bearing the electron-withdrawing groups to give 5-(trifluoromethyl)pyrazolines in high yields. The reaction proceeded under mild conditions and tolerated a wide variety of the substituents. Although not all alkenes react with hydrazone under the described conditions, this reagent shows significant advantages over trifluorodiazoethane, mainly in regard of the stability of the reagent, simplicity of its synthesis, and simplicity of the protocol. We also demonstrated that the synthesized pyrazolines can be easily transformed to the fluorinated pyrazoles that are the promising building blocks for the synthesis of pharmaceutical agents.

Experimental

NMR spectra were recorded on a Bruker instrument (operating frequencies of 400 (^{1}H), 100 (^{13}C), and 376 MHz (^{19}F)). The ^{1}H NMR shifts are reported relative to the residual solvent ($CHCl_3$) signal (δ_H 7.27), the ^{13}C NMR shifts are given relative to the central line of the $CDCl_3$ signal (δ_H 77.36). The $^{13}C\{^1H\}$ NMR spectra were recorded with complete proton decoupling. The ^{19}F NMR chemical shifts are reported relative to $CFCl_3$ as an external standard. High resolution electrospray mass spectrometry was performed on a TripleTOF 5600+ instrument (AB Sciex, Canada). The starting compounds are commercially available unless stated otherwise. Trifluoroacetaldehyde *N*-tosylhydrazone (**1**) was synthesized as earlier described.[25] Ethyl acetate was distilled prior to use. Tetrahydrofuran was distilled over sodium metal in the presence of benzophenone under nitrogen. Dichloromethane was dried by distillation over P_2O_5. The reaction course was monitored by TLC using Merck TLC silica gel 60 F_{254} aluminum sheets. The spots of the compounds were visualized under UV light (λ = 254 nm) or using a potassium permanganate aqueous solution. Silica gel (230—400 mesh, particle size of 40—63 μm) was used for column chromatography.

Synthesis of 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles 3a—d (general procedure). To a solution of trifluoroacetaldehyde tosylhydrazone (**1**) (133 mg, 0.5 mmol), the appropriate alkene (0.8 mmol), and Pr^i_2NEt (33 mg,

0.25 mmol) in ethyl acetate (3 mL), CaO (56 mg, 1 mmol) was added and the mixture was stirred at room temperature for 16 h. After the reaction completion, the precipitate was filtered off and the filtrate was concentrated *in vacuo*. The product was purified by silica gel column chromatography if required.

Methyl 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole-3-carboxylate (3a) was synthesized from methyl acrylate (**5a**) without additional purification. Yield 97% (95 mg). Colorless solid, m.p. 119—122 °C. ^{1}H NMR ($CDCl_3$), δ: 6.69 (br.s, 1 H, NH); 4.42 (m, 1 H, $CHCF_3$); 3.82 (s, 3 H, OCH_3); 3.24 (m, 1 H, C<u>H</u>H); 3.12 (m, 1 H, C<u>H</u>H). ^{13}C NMR ($CDCl_3$), δ: 161.9 (s, CO); 142.0 (s, C=N); 124.3 (q, CF_3, J_{CF} = 279.5 Hz); 61.2 (q, CH, J_{CF} = 31.5 Hz); 52.3 (s, OCH_3); 32.1 (s, CH_2). ^{19}F NMR ($CDCl_3$), δ: −77.4 (d, J_{FH} = 6.9 Hz). Physicochemical properties of the synthesized product **3a** are in agreement with those published earlier.[30]

Ethyl 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole-3-carboxylate (3b) was synthesized from ethyl acrylate (**5b**) without additional purification. Yield 99% (104 mg). Colorless oil, m.p. 63—65 °C. ^{1}H NMR ($CDCl_3$), δ: 6.57 (br.s, 1 H, NH); 4.42 (m, 1 H, $CHCF_3$); 4.30 (q, 2 H, OCH_2, ^3J = 7.1 Hz); 3.22 (m, 1 H, C<u>H</u>H); 3.12 (m, 1 H, C<u>H</u>H); 1.33 (t, 3 H, CH_3, ^3J = 7.1 Hz). ^{13}C NMR ($CDCl_3$), δ: 161.5 (s, CO); 142.4 (s, C=N); 124.4 (q, CF_3, J_{CF} = 279.5 Hz); 61.5 (s, OCH_2); 61.2 (q, CH, J_{CF} = 31.5 Hz); 32.2 (s, CH_2); 14.1 (s, CH_3). ^{19}F NMR ($CDCl_3$), δ: −77.3 (d, J_{FH} = 6.9 Hz). Physicochemical properties of the synthesized product **3b** are in agreement with those published earlier.[31]

5-Trifluoromethyl-4,5-dihydro-1*H*-pyrazole-3-carbonitrile (3c) was synthesized from acrylonitrile (**5c**) without additional purification. Yield 95% (77 mg). Colorless solid, m.p. 90—93 °C. ^{1}H NMR ($CDCl_3$), δ: 6.66 (br.s, 1 H, NH); 4.48 (m, 1 H, $CHCF_3$); 3.24 (m, 1 H, C<u>H</u>H); 3.11 (m, 1 H, C<u>H</u>H). ^{13}C NMR ($CDCl_3$), δ: 123.3 (s, CN); 124.7 (q, CF_3, J_{CF} = 279.7 Hz); 113.1 (s, C=N); 60.7 (q, CH, J_{CF} = 31.5 Hz); 34.1 (s, CH_2). ^{19}F NMR ($CDCl_3$), δ: −77.5 (d, J_{FH} = 6.9 Hz). Physicochemical properties of the synthesized product **3c** are in agreement with those published earlier.[30]

3-Acetyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (3d) was synthesized from methyl vinyl ketone (**5d**). The product was purified by silica gel column chromatography (EtOAc—petroleum ether, 1 : 3). Yield 68% (62 mg). ^{1}H NMR ($CDCl_3$), δ: 6.61 (br.s, 1 H, NH); 4.40 (m, 1 H, $CHCF_3$); 3.19—3.03 (m, 2 H, CH_2); 2.41 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$), δ: 193.8 (s, CO); 150.0 (s, C=N); 124.4 (q, CF_3, J_{CF} = 279.5 Hz); 61.4 (q, CH, J_{CF} = 31.5 Hz); 30.6 (s, CH_2); 25.4 (s, CH_3). ^{19}F NMR ($CDCl_3$), δ: −77.4 (d, J_{FH} = 6.9 Hz). Physicochemical properties of the synthesized product **3d** are in agreement with those published earlier.[32]

Synthesis of 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles 3e—g (general procedure). A solution of trifluoroacetaldehyde tosylhydrazone (**1**) (160 mg, 0.6 mmol), the appropriate alkene (0.5 mmol), and Pr^i_2NEt (33 mg, 0.25 mmol) in ethyl acetate (3 mL) was stirred at room temperature for 16 h. After the reaction completion, the volatiles were removed *in vacuo*. The product was purified by silica gel column chromatography if required.

3-Phenylsulfonyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (3e) was purified by silica gel column chromatography (EtOAc—petroleum ether, 1 : 3). Yield 50% (69 mg). Colorless liquid. ^{1}H NMR ($CDCl_3$), δ: 7.94 (m, 2 H, Ar); 7.69 (m, 1 H, Ar); 7.58 (m, 2 H, Ar); 6.50 (br.s, 1 H, NH); 4.48 (m, 1 H, $CHCF_3$); 3.31 (m, 1 H, C<u>H</u>H); 3.11 (m, 1 H, C<u>H</u>H). ^{13}C NMR ($CDCl_3$), δ: 150.6 (s, C=N); 137.8 (s, Ar); 134.4 (s, Ar); 129.4 (s, Ar); 128.3 (s, Ar); 123.9 (q, CF_3, J_{CF} = 279.5 Hz); 62.1 (q, <u>C</u>CF_3, J_{CF} = 32.0 Hz); 31.8 (s, CH_2). ^{19}F NMR ($CDCl_3$), δ: −77.2 (d, J_{FH} = 6.9 Hz). Physicochemical properties of the synthesized product **3e** are in agreement with those published earlier.[33]

Dimethyl 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole-3,4-dicarboxylate (3f) was synthesized from dimethyl fumarate (*E*-**5f**) without additional purification. Yield 99% (125 mg). Colorless solid, m.p. 89—91 °C. ^{1}H NMR ($CDCl_3$), δ: 7.15 (br.s, 1 H, NH); 4.67 (m, 1 H, $CHCF_3$); 4.13 (d, 1 H, CHC(O), ^3J = 7.9 Hz); 3.80 (s, 3 H, OCH_3); 3.76 (s, 3 H, OCH_3). ^{13}C NMR ($CDCl_3$), δ: 169.0 (s, CO); 161.2 (s, CO); 138.6 (s, C=N); 123.6 (q, CF_3, J_{CF} = 279.5 Hz); 65.7 (q, <u>C</u>HCF_3, J_{CF} = 32.2 Hz); 53.2 (s, OCH_3); 52.4 (s, OCH_3); 50.3 (s, <u>C</u>HC(O)). ^{19}F NMR ($CDCl_3$), δ: −80.8 (d, J_{FH} = 6.9 Hz). Physicochemical properties of the synthesized product **3f** are in agreement with those published earlier.[34]

Diethyl 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole-3,4-dicarboxylate (3g) was synthesized from diethyl maleate (*Z*-**5g**) without additional purification. Yield 99% (125 mg). Colorless liquid. ^{1}H NMR ($CDCl_3$), δ: 6.87 (br.s, 1 H, NH); 4.66 (m, 1 H, $CHCF_3$); 4.23 (m, 5 H, CHC(O), 2 OCH_2); 1.30 (m, 6 H, 2 CH_3). ^{13}C NMR ($CDCl_3$), δ: 168.6 (s, CO); 160.7 (s, CO); 139.6 (s, C=N); 123.7 (q, CF_3, J_{CF} = 279.4 Hz); 65.9 (q, <u>C</u>HCF_3, J_{CF} = 32.1 Hz); 62.5 (s, OCH_2); 61.7 (s, OCH_2); 50.7 (s, <u>C</u>HC(O)); 14.0 (s, CH_3); 13.8 (s, CH_3). ^{19}F NMR ($CDCl_3$), δ: −76.7 (d, J_{FH} = 6.9 Hz). Physicochemical properties of the synthesized product **3g** are in agreement with those published earlier.[34]

3-Trifluoromethyl-1*H*-pyrazole (6a). A solution of trifluoroacetaldehyde tosylhydrazone (**1**) (160 mg, 0.6 mmol), alkene **5e** (84 mg, 0.5 mmol) and Pr^i_2NEt (129 mg, 1 mmol) in ethyl acetate (3 mL) was stirred at room temperature for 16 h. After the reaction completion, the solvent was removed *in vacuo*. Purification of the residue by silica gel column chromatography (EtOAc—petroleum

ether, 1 : 3) afforded 27 mg (40%) of compound **6a** and 34 mg (25%) of product **3e**.

Compound **6a**. Colorless liquid. ^{1}H NMR ($CDCl_3$), δ: 13.60 (br.s, 1 H, NH); 7.72 (s, 1 H, Ar); 6.67 (s, 1 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 142.4 (q, $\underline{C}CF_3$, J_{CF} = 38.0 Hz); 121.5 (q, CF_3, J_{CF} = 268.1 Hz); 130.2 (s, CH); 103.9 (s, CH). ^{19}F NMR ($CDCl_3$), δ: −61.7 (s). Physicochemical properties of the synthesized product **6a** are in agreement with those published earlier.[35]

Diethyl 5-trifluoromethyl-1*H*-pyrazole-3,4-dicarboxylate (6b). To a solution of compound **3g** (100 mg, 0.35 mmol) in CCl_4 (3 mL) cooled to 0 °C, bromine (80 mg, 0.5 mmol) was added. The mixture was stirred at room temperature for 24 h and concentrated *in vacuo*. Purification of the residue by silica gel column chromatography (EtOAc—petroleum ether, 1 : 3) afforded 81 mg (82%) of compound **6b**. Colorless liquid. ^{1}H NMR ($CDCl_3$), δ: 11.7 (br.s, 1 H, NH); 4.44 (q, 2 H, OCH_2, J = 7.1 Hz); 4.41 (q, 2 H, OCH_2, J = 7.1 Hz), 1.40 (t, 3 H, CH_3, J = 7.0 Hz); 1.38 (t, 3 H, CH_3, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$), δ: 161.1 (s, CO); 157.9 (s, CO); 141.7 (q, $\underline{C}CF_3$, J_{CF} = 39.3 Hz); 134.7 (s, $\underline{C}C(O)$); 120.0 (q, J_{CF} = 268.8 Hz); 115.5 (s, $\underline{C}C(O)$); 62.7 (s, CH_2); 62.4 (s, CH_2); 13.9 (s, CH_3); 13.8 (s, CH_3). ^{19}F NMR ($CDCl_3$), δ: −61.7 (s). Physicochemical properties of the synthesized product **6b** are in agreement with those published earlier.[29]

Funding

This work was financially supported by the Russian Science Foundation (Project No. 22-23-00381).

Animal Testing and Ethics

No human or animal subjects were used in this research.

Conflict of Interest

The authors declare no competing interests.

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Received June 5, 2023;
in revised form September 27, 2023;
accepted October 20, 2023