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Synthesis of 1,1,1-trifluorobut-3-yn-2-ones and their reactions with N-nucleophiles

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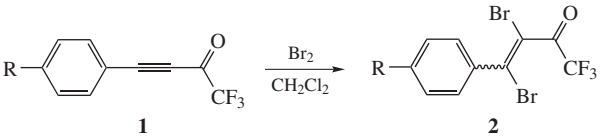
Bromination of 4-aryl-1,1,1-trifluorobut-3-yn-2-ones gives 4-aryl-3,4-dibromo-1,1,1-trifluorobut-3-en-2-ones whose reactivity towards N-nucleophiles (hydrazine and ethylenediamine) was investigated.

The importance of fluorinated compounds for medicinal chemistry can be hardly overestimated.[1] Among them, trifluoromethylated pyrazoles (*e.g.*, Celecoxib) are important type of pharmacologically relevant compounds.[2–5]

α,β-Unsaturated trifluoromethyl ketones are the versatile building blocks for the synthesis of various fluorinated molecules, especially heterocyclic ones.[6] Heterocyclization of trifluoromethyl-containing building blocks (for example, enones or 1,3-diketones) with hydrazines[7] is a common access to trifluoromethylated pyrazoles. Here, we report the synthesis of novel fluorinated building blocks, α,β-dibromo-CF_3-enones, and their reactions with hydrazine and ethylenediamine.

The presence of three electrophilic centers (trifluoroacetyl group, activated double bond and carbon adjacent with halogens) in the structure of α,β-dibromo-CF_3-enones led us to expect high activity of these compounds towards nucleophiles to open wide possibilities of incorporating a trifluoromethyl group into target compounds with the desired position of CF_3 group. Heterocycles of various sizes can be prepared using these building blocks depending on the nature of binucleophiles (1,2-, 1,3- and 1,4-binucleophiles).

CF_3-ynones **1** were prepared from lithiated terminal alkynes and ethyl trifluoroacetate.[8] Their bromination in CH_2Cl_2 afforded α,β-dibromo-CF_3-enones **2** in almost quantitative yields (Scheme 1).[†] The reaction was stereoselective and gave mixtures of *E*,*Z*-isomers in which content of a major isomer reached 80% (the ratio of the isomers was determined by ^{1}H NMR for **1b–e** or ^{19}F NMR for **1a**). The configuration of isomers was not assigned. Compounds **2** with both electron-donating and electron-withdrawing substituents in the phenyl ring were thus prepared.



1 **2**

a R = H, 92%, 80:20
b R = Cl, 97%, 75:25
c R = MeO, 95%, 72:28
d R = Bu^t, 92%, 77:23
e R = Me, 93%, 79:21

Scheme 1

[†] ^{1}H (400.1 MHz), ^{13}C (100.6 MHz) and ^{19}F (376.3 MHz) NMR spectra in $CDCl_3$ were recorded on a Bruker AVANCE 400 MHz spectrometer. IR spectra were recorded on ThermoNicolet IR 200. The GC/MS analyses were performed with a Shimadzu GCMS-QP5050A instrument (EI, 70 eV). ESI-MS spectra were measured with a MicroTOF Bruker Daltonics instrument.

α,β-Dibromo-CF_3-enones **2** *(general procedure).* 1 M solution of Br_2 in CH_2Cl_2 (5.1 ml) was added dropwise to a solution of the corresponding CF_3-ynone **1** (0.005 mol) in CH_2Cl_2 (10 ml) on cooling with water bath. After stirring for 0.5 h, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (silica gel, 230–400 Mesh, hexane–CH_2Cl_2, 3:1). All of products **2a–e** were obtained as yellowish viscous oils and as mixtures of isomers which were not resolved. Isomer ratios are specified in Scheme 1.

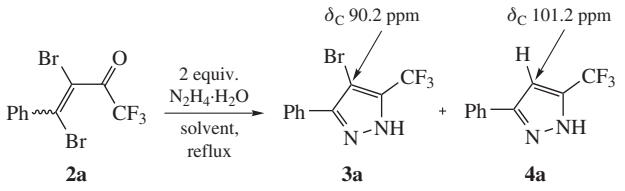
3,4-Dibromo-1,1,1-trifluoro-4-phenylbut-3-en-2-one **2a**. Yield 1.792 g (92%). For the mixture of isomers: IR (neat, ν/cm^{-1}): 1589 (C=C), 1745 (C=O). ^{1}H NMR, δ: 7.34–7.56 (m, 5H, Ph). ^{13}C NMR, δ: 105.0, 113.7, 114.8 (q, CF_3, *J* 291.9 Hz), 124.6, 128.6, 128.8, 130.5, 130.9, 136.5, 137.2, 138.0, 179.9 (q, C=O, *J* 38.7 Hz). ^{19}F NMR, δ: –74.0 (major), –73.8 (minor).

3,4-Dibromo-4-(4-chlorophenyl)-1,1,1-trifluorobut-3-en-2-one **2b**. Yield 1.905 g (97%). Major isomer: ^{1}H NMR, δ: 7.27 (d, 2H, Ar, *J* 8.6 Hz), 7.36 (d, 2H, Ar, *J* 8.6 Hz). ^{13}C NMR, δ: 114.4, 114.9 (q, CF_3, *J* 291.9 Hz), 129.2, 130.0, 135.6, 136.7, 137.2, 179.5 (q, C=O, *J* 38.3 Hz). ^{19}F NMR, δ: –73.9. Minor isomer: ^{1}H NMR, δ: 7.44 (d, 2H, Ar, *J* 8.7 Hz), 7.48 (d, 2H, Ar, *J* 8.7 Hz). ^{13}C NMR, δ: 105.7, 114.9 (q, CF_3, *J* 291.9 Hz), 123.3, 129.0, 130.3, 134.8, 179.4 (q, C=O, *J* 39.1 Hz). ^{19}F NMR, δ: –73.8.

3,4-Dibromo-1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-en-2-one **2c**. Yield 1.840 g (95%). Major isomer: ^{1}H NMR, δ: 3.82 (s, 3H, MeO), 6.88 (d, 2H, Ar, *J* 8.8 Hz), 7.29 (d, 2H, Ar, *J* 8.8 Hz). ^{13}C NMR, δ: 55.3, 112.4, 114.8 (q, CF_3, *J* 292.3 Hz), 114.2, 129.6, 130.7, 138.6, 161.7, 180.4 (q, C=O, *J* 38.4 Hz). ^{19}F NMR, δ: –73.8. Minor isomer: ^{1}H NMR, δ: 3.86 (s, 3H, MeO), 6.96 (d, 2H, Ar, *J* 8.9 Hz), 7.53 (d, 2H, Ar, *J* 8.9 Hz). ^{13}C NMR, δ: 103.5, 113.8, 114.8 (q, CF_3, *J* 291.9 Hz), 124.9, 128.2, 130.8, 161.2, 179.8 (q, C=O, *J* 38.4 Hz). ^{19}F NMR, δ: –73.6.

*3,4-Dibromo-4-(4-*tert*-butylphenyl)-1,1,1-trifluorobut-3-en-2-one* **2d**. Yield 1.908 g (92%). Major isomer: ^{1}H NMR, δ: 1.33 (s, 9H, Bu^t), 7.28 (d, 2H, Ar, *J* 8.5 Hz), 7.40 (d, 2H, Ar, *J* 8.5 Hz). ^{13}C NMR, δ: 31.0, 34.9, 113.0, 114.8 (q, CF_3, *J* 292.3 Hz), 125.8, 128.7, 134.3, 138.5, 154.7, 180.2 (q, C=O, *J* 38.3 Hz). ^{19}F NMR, δ: –73.9. Minor isomer: ^{1}H NMR, δ: 1.37 (s, 9H, Bu^t), 7.47 (d, 2H, Ar, *J* 8.9 Hz), 7.51 (d, 2H, Ar, *J* 8.9 Hz). ^{13}C NMR, δ: 31.1, 35.0, 104.2, 114.8 (q, CF_3, *J* 291.1 Hz), 124.9, 125.5, 128.8, 133.3, 154.1, 179.8 (q, C=O, *J* 38.7 Hz). ^{19}F NMR, δ: –73.7.

*3,4-Dibromo-1,1,1-trifluoro-4-(*p*-tolyl)but-3-en-2-one* **2e**. Yield 1.736 g (93%). Major isomer: ^{1}H NMR, δ: 2.38 (s, 3H, Me), 7.19 (d, 2H, Ar, *J* 8.2 Hz), 7.25 (d, 2H, Ar, *J* 8.2 Hz). ^{13}C NMR, δ: 21.3, 113.0, 114.6 (q, CF_3, *J* 292.3 Hz), 128.8, 129.5, 134.5, 138.5, 141.6, 180.2 (q, C=O, *J* 38.7 Hz). ^{19}F NMR, δ: –73.9. Minor isomer: ^{1}H NMR, δ: 2.43 (s, 3H, Me), 7.27 (d, 2H, Ar, *J* 8.2 Hz), 7.46 (d, 2H, Ar, *J* 8.2 Hz). ^{13}C NMR, δ: 21.4, 104.3, 125.0, 128.8, 129.2, 133.5, 141.0. Other signals are identical to those of major isomer. ^{19}F NMR, δ: –73.7.



Scheme 2

Table 1 Reaction of **2a** with hydrazine hydrate in different solvents.

Solvent	Yield of **3a** + **4a** (%)	Yield of **3a** (%)	**3a**:**4a** ratio
THF	36	27	76:24
BuOH	68	58	86:14
EtOH	95	77	81:19
EtOH[a]	75	64	86:14
EtOH[b]	50	40	82:18
Toluene	97	85	87:13
MeOH	72	56	77:23
Pr^{i}OH	25	22	87:13
AcOH	20	16	80:20
CF_3CH_2OH	35	31	89:11
NEt_3	15	6	41:59
$CHCl_3$	61	46	75:25

[a] 1 equiv. of $N_2H_4·H_2O$ and 1 equiv. of AcONa. [b] 1 equiv. of $N_2H_4·H_2O$ and 1 equiv. of NEt_3.

We assumed that treatment of α,β-dibromo-CF_3-enones with hydrazine hydrate should afford the corresponding 3-bromo-2-trifluoromethylpyrazoles. Using compound **2a** as a model, we found that the highest yields (up to 85%, ^{19}F NMR monitoring) of the target bromopyrazole **3a** were achieved in boiling ethanol or toluene (Scheme 2, Table 1).‡ Surprisingly, in all cases a formation of pyrazole **4a** containing no bromine atom (up to 25%) also occurred. Structures of both products were confirmed by GC-MS (molecular ions with *m*/*z* 212 for H-pyrazole **4a** and doublet with *m*/*z* 290, 292 for bromopyrazole **3a**). Additionally ^{1}H, ^{13}C and ^{19}F NMR spectra of **3a** and **4a** are in total agreement with published ones. The most characteristic are signals of C^3 carbons in the pyrazole ring (C–Br of **3a**, 90.2 ppm and C–H of **4a**, 101.2 ppm).

We suppose that pyrazole **4a** is formed through the halophilic mechanism including an attack of a nucleophile to a bromine atom of reactant **2a**. Steric hindrance caused by bromine atoms in compound **2a** at the double bond creates difficulties for nucleophile attack at the double bond (Michael addition) as well as at the carbonyl group. To confirm this assumption, we performed DFT (B3LYP) quantum-chemical calculations and estimated charges on atoms in molecules of **2a**, which showed that the *Z* isomer was more stable by 0.23 kcal mol^{-1} but the difference was very small. The analysis of atomic charges (Mulliken and Levden) showed that both bromine atoms have a localized positive charge (Figure 1). Consequently, the calculations confirmed our assumption about the possibility of halophilic reaction for dibromoenones **2**.

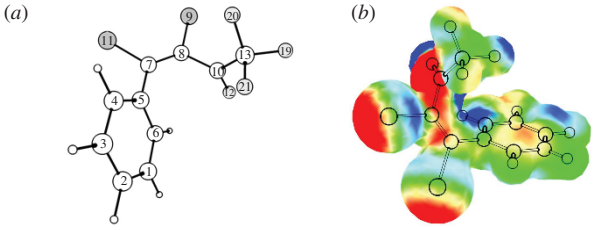
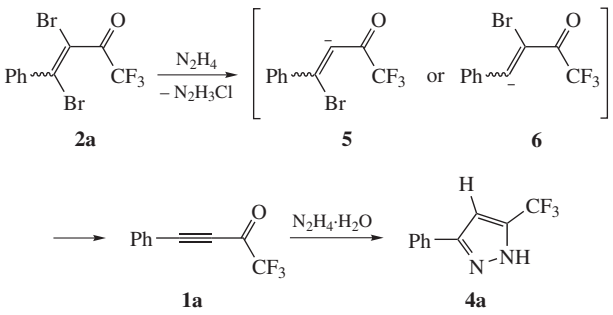


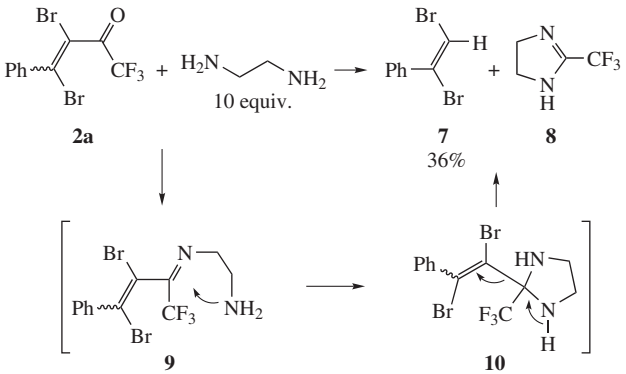
Figure 1 (*a*) The optimized geometry of enone **2a** and (*b*) the diagram of the electrostatic potential of the molecule.

Halophilic attack of hydrazine hydrate, which is also strong reducing agent, on bromine atom in **2a** gives intermediate anions **5** or **6**, which are transformed into acetylenic ketone **1a** by elimination of bromide. The subsequent reaction of **1a** with hydrazine hydrate affords pyrazole **4a**. This is confirmed by the presence of traces of acetylene **1a** in the reaction mixture (*m*/*z* 198, GC-MS, the signal at –77.8 ppm in ^{19}F NMR spectrum). Moreover, heterocyclization of similar ynones with hydrazine hydrate to pyrazoles is known.[9]



Scheme 3

Compound **2a** also reacted unusually with ethylenediamine§ to form *E*-α,β-dibromostyrene **7** and 2-trifluoromethylimidazoline **8** as a result of C–C bond cleavage. The possible mechanism includes an attack of ethylenediamine to the carbonyl group to produce trifluoromethylimine **9**, which cyclizes into trifluoro-



Scheme 4

‡ *Reaction of compound* **2a** *with hydrazine hydrate*. A mixture of compound **2a** (1.0 mmol) and hydrazine hydrate (2.0 mmol) in appropriate solvent (2 ml, see Table 1) was stirred at reflux for 10–12 h. The volatiles were evaporated *in vacuo*, the residue was purified by column chromatography on silica gel (eluent, hexane–CH_2Cl_2, 1:2). The pyrazoles **3a** and **4a** were not separated. NMR data of **3a**[11] and **4a**[12] are consistent with those in the literature.

*4-Bromo-5-(trifluoromethyl)-3-phenyl-1*H*-pyrazole* **3a**. ^{1}H NMR, δ: 7.48–7.83 (m, 5H, Ar), 14.39 (br. s, 1H, NH). ^{13}C NMR, δ: 88.8, 122.1 (q, CF_3, *J* 291.9 Hz), 126.8, 127.8, 129.0, 129.7, 139.9 (q, *C*CF_3, *J* 36.1 Hz), 142.5. ^{19}F NMR, δ: –61.9.

*5-(Trifluoromethyl)-3-phenyl-1*H*-pyrazole* **4a**: ^{1}H NMR, δ: 7.48–7.83 (m, 5H, Ar), 14.09 (br. s, 1H, NH). ^{13}C NMR, δ: 101.0, 117.0, 118.4 (q, CF_3, *J* 291.9 Hz), 125.6, 127.8, 129.1, 129.3, 135.8 (q, *C*CF_3, *J* 36.1 Hz), 144.0. ^{19}F NMR, δ: –61.3.

§ *Reaction of compound* **2a** *with ethylenediamine*. A mixture of compound **2a** (1.0 mmol) and ethylenediamine (1.0 ml) was kept at room temperature for 12 h. The volatiles were evaporated *in vacuo*, the residue was purified by column chromatography on silica gel (eluent, hexane–CH_2Cl_2, 1:1) to afford 0.094 g (36%) of *E*-α,β-dibromostyrene **7** as a colorless oil. ^{1}H NMR, δ: 6.81 (s, 1H, =CH), 7.36–7.54 (m, Ar) (*cf.* ref. 13).

methylimidazolidine **10**, followed by cleavage of the C–C bond to furnish compounds **7** and **8**. Similar examples of cleavage of C–C bonds were described for unsaturated compounds bearing electron-withdrawing substituents in reactions with ethylenediamine.[10] However, a significant difference with the published data should be noted. In the case of compound **2a** the cleavage of single C–C bond is observed, whereas previously formal cleavage of multiple C–C bonds proceeded.

In conclusion, synthesis of previously unknown α,β-dibromo-CF_3-enones by bromination of CF_3-ynones was elaborated. Their reactivity towards N-nucleophiles was examined, which opens prospects to new useful fluorinated compounds.

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