Stereoselective Decomposition of Pyrazolines Containing Trifluoromethyl Groups

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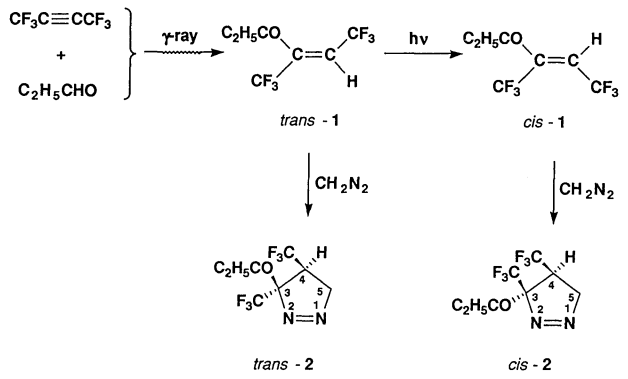
Synopsis. The reaction of (*Z*)- and (*E*)-6,6,6-trifluoro-4-trifluoromethyl-4-hexen-3-ones (**1**) with diazomethane afforded the corresponding *cis*- and *trans*-pyrazolines (**2**), respectively. Photochemical and thermal decompositions of the *r*-3, *t*-4-bis(trifluoromethyl)pyrazoline gave selectively *r*-1, *t*-2-bis(trifluoromethyl)-1-propionylcyclopropane (**3**) and 3,4-bis(trifluoromethyl)-2-ethyl-4,5-dihydrofuran (**4**). On the other hand, those transformations of the *r*-3,*c*-4-isomer of the pyrazoline gave a mixture of the *r*-1, *c*-2-isomer of **3**, **4**, and 4,5-bis(trifluoromethyl)-5-hexen-3-one (**5**).

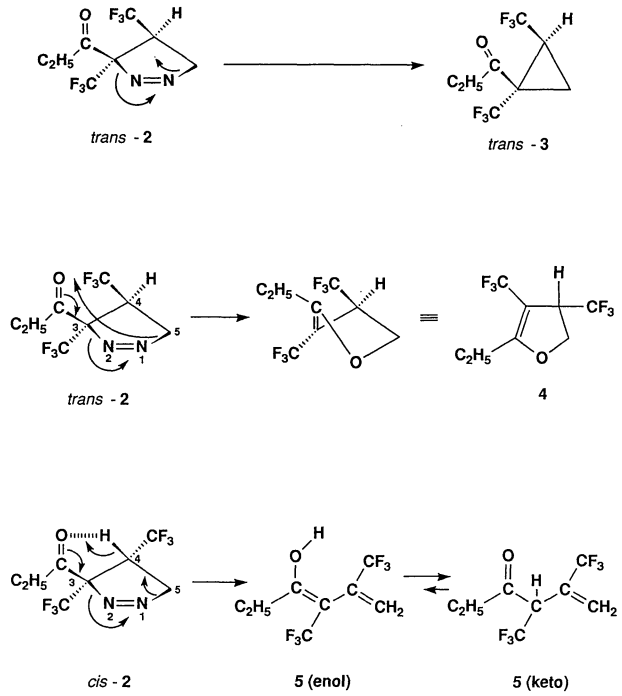
Since cyclopropanes are one of the most important intermediates for the synthesis of medicines, due to their highly strained structure, the introduction of a trifluoromethyl group into such molecules is of interest. Several methods, such as reactions of olefins with carbenes,[1-3] and organomercury compounds,[4] as well as the decomposition of pyrazolines[5,6] have been reported for the synthesis of (trifluoromethyl)cyclopropanes. We wish to report here on the synthesis of pyrazolines obtained from *cis*- and *trans*-6,6,6-trifluoro-4-trifluoromethyl-4-hexen-3-ones (*cis*-**1** and *trans*-**1**),[7] as well as their decomposition reactions to give cyclopropanes containing two trifluoromethyl groups.



Scheme 1.

The reaction of **1** with diazomethane at ambient temperature induced a 1,3-dipolar addition reaction to give 3,4-bis(trifluoromethyl)-3-propionylpyrazoline (**2**) quantitatively (Scheme 1). The stereoselectivity of this reaction concerning two trifluoromethyl groups was determined on the basis of the ^{19}F NMR spectra (the coupling constant of the F atom between trifluoromethyl groups at the 3- and 4-positions: *cis*, J=11.7 Hz; *trans*, J=1.3 Hz).

Though both *cis*- and *trans*-pyrazolines **2** were stable in the dark at room temperature, they easily decomposed at higher temperature or under UV irradiation. The



Scheme 2.

Table 1. Decomposition of 3,4-Bis(trifluoromethyl)-3-propionylpyrazolines (**2**)

Pyrazoline	Method	Total time	Yield/%			
		min	*trans*-**3**	*cis*-**3**	**4**	**5**
trans-**2**	Pyrolysis	90	47	0.9	52	0
trans-**2**	Photolysis	100	80	2.2	18	0
cis-**2**	Pyrolysis	90	4.4	54	11	31
cis-**2**	Photolysis	100	0.3	94	1.3	4.3

results of the decompositions of **2** are summarized in Table 1. Both photochemical and thermal decompositions of *trans*-**2** gave stereoselectively *r*-1,*t*-2-bis(trifluoromethyl)-1-propionylcyclopropane (*trans*-**3**) and 3,4-bis(trifluoromethyl)-2-ethyl-4,5-dihydrofuran (**4**). Those of *cis*-**2** afforded mainly a mixture of *cis*-**3**, **4**, and 4,5-bis(trifluoromethyl)-1-hexen-3-one (**5**).

Concerning the mechanism of decomposition of 1-pyrazolines, three processes (such as a 1,3-diradical, a zwitterionic intermediate, and an electrocyclic process) were proposed; the decomposition of pyrazoline bearing α-electron withdrawing groups is not yet completely understood.[8]

Although a plausible reaction mechanism for the stereoselective formation of **3**,**4**, and **5** is shown in Scheme 2, a diradical or zwitterionic mechanism can not be excluded, since the formation of **4** can also be explained by the ionic intermediate process. Regarding the formation of **5** from the *cis*-**2** isomer, an intramolecular hydrogen bond between the hydrogen on the C-4 carbon and the carbonyl oxygen seems to assist to give an enol form of **5**, which then tautomerizes to the keto form of **5**, as shown in Scheme 2.

Experimental

Instruments. IR spectra were recorded on a Hitachi 285H grating infrared spectrophotometer. ^{1}H NMR (90 MHz) spectra were measured with a Hitachi R22 spectrometer with tetramethylsilane used as an internal reference. ^{19}F NMR (56.45 MHz) spectra were measured with a Hitachi R20B spectrometer; positive δ values appear downfield from the external reference, trifluoroacetic acid. All NMR spectra were measured in carbon tetrachloride by an external lock. Mass spectra were measured with a Hitachi RMU-7 spectrometer.

Synthesis of 6,6,6-Trifluoro-4-trifluoromethyl-4-hexen-3-one (1). (*E*)-6,6,6-Trifluoro-4-trifluoromethyl-4-hexen-3-one (*trans*-**1**) was prepared by the γ-ray induced addition reaction of hexafluoro-2-butyne with propionaldehyde. UV irradiation of the *trans*-**1** gave (*Z*)-6,6,6-trifloro-4-trifluoromethyl-4-hexen-3-one (*cis*-**1**).[7]

Synthesis of 3,4-Bis(trifluoromethyl)-3-propionyl-4,5-dihydro-3*H*-pyrazole (2). To an ether solution (30 mL) of *trans*-**1** (2.50 g, 11.4 mmol), was added an ether solution of diazomethane cooled with ice, which was allowed to stand at ambient temperature for 30 min. After evaporating the solvent, pure *r*-3,*t*-4-bis(trifluoromethyl)-3-propionylpyrazoline (*trans*-**2**) was obtained in 98% yield (2.91 g).

trans-**2**: n_D^{20} 1.3860; IR (neat) 1741 (C=O), 1572 (N=N); ^{1}H NMR δ=1.01 (t, J=7.2 Hz, CH_3), 2.56 (q, J=7.2 Hz, CH_2), 3.0—3.6 (m, $CHCF_3$), 4.90 (br s, CH_2N=N), 4.98 (br s, CH_2N=N); ^{19}F NMR δ=7.2 (q, J=1.3 Hz), 14.5 (dq, J=9.0 and 1.3 Hz).

r-3,*c*-4-Bis(trifluoromethyl)-3-propionylpyrazoline (*cis*-**2**) was obtained quantitatively using a similar procedure.

cis-**2**: n_D^{20} 1.3879; IR (neat) 1739 (C=O), 1565 (N=N); ^{1}H NMR δ=1.07(t, J=7.0 Hz, CH_3), 2.83 (q, J=7.0 Hz, CH_2), 3.1—3.7 (m, $CHCF_3$), 4.72 (br s, CH_2N=N); ^{19}F NMR δ=12.6 (q, J=11.7 Hz), 13.8 (q, J=11.7 Hz).

Decomposition of Pyrazolines 2. 1) Pyrolysis: In a flask equipped with a Dimroth condenser was placed *trans*-**2** (13.23 g, 31.35 mmol), which was heated at 140 °C. After a reaction, volatile products were evaporated. The resulting products were isolated using a preparative gas chromatograph.

2) Photolysis: Into a quartz ampoule (diameter: 10 mm) was placed *trans*-**2** (13.23 g, 31.35 mmol), which was irradiated at room temperature using a high-pressure mercury lamp (distance: 6—10 cm) under a nitrogen atmosphere. After a reaction was complete, volatile products were evaporated. The resulting products were isolated using a preparative gas chromatograph.

r-1,*t*-2-Bis(trifluoromethyl)-1-propionylcyclopropane (*trans*-**3**): Bp 127 °C; n_D^{20} 1.3522; d_4^{20} 1.322; IR (neat) 1735 (C=O); ^{1}H NMR δ=1.10 (t, J=7.4 Hz, CH_3), 1.4—1.7 (m, $CHCF_3$), 1.9—2.4 (m, ring CH_2), 2.73 (q, J=7.4 Hz, CH_2); ^{19}F NMR δ=11.8 (s), 16.3 (d, J=6.0 Hz); MS m/z 234 (M^+). Found: C, 40.99; H, 3.47%. Calcd for $C_8H_8OF_6$: C, 41.04; H, 3.44%.

r-1,*c*-2-Bis(trifluoromethyl)-1-propionylcyclopropane (*cis*-**3**): Bp 135 °C; n_D^{20} 1.3590; d_4^{20} 1.357; IR (neat) 1723 (C=O); ^{1}H NMR δ=1.09 (t, J=7.5 Hz, CH_3), 1.3—2.5 (m, $CHCF_3$), 1.86 (br s, ring CH_2), 2.87 (q, J=7.5 Hz, CH_2); ^{19}F NMR δ=18.7 (d, J=4.6 Hz), 18.7 (s); MS m/z 234 (M^+). Found: C, 40.95; H, 3.53%. Calcd for $C_8H_8OF_6$: C, 41.04; H, 3.44%.

3,4-Bis(trifluoromethyl)-2-ethyl-4,5-dihydrofuran (**4**): Bp 137 °C; n_D^{20} 1.3628; d_4^{20} 1.338; IR (neat) 1674 (C=C); ^{1}H NMR δ=1.14 (t, J=7.0 Hz, CH_3), 2.40 (q, J=7.0 Hz, CH_2), 3.5—3.9 (m, $CHCF_3$), 4.39 (br s, ring CH_2), 4.54 (br s, ring CH_2); ^{19}F NMR δ=5.1 (dq, J=7.3 and 4.8 Hz), 21.8 (q, J=4.8 Hz). Found: C, 40.52; H, 3.34%. Calcd for $C_8H_8OF_6$: C, 41.04; H, 3.44%.

4,5-Bis(trifluoromethyl)-1-hexen-3-one (**5**): Bp 130 °C; n_D^{20} 1.3525; IR (neat) 1743 (C=O), 1662 (C=C); ^{1}H NMR δ=1.10 (t, J=7.2 Hz, CH_3), 2.56 (q, J=7.2 Hz, CH_2), 4.05 (q, J=8.2 Hz, $CHCF_3$), 6.03 (s, CH), 6.13 (s, CH); ^{19}F NMR δ=9.0 (s), 12.2 (d, J=8.2 Hz).

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