Reaction of 3,3-dialkyl-6-trifluoromethyl-2,3-dihydro-4-pyrones with hydrazine hydrate

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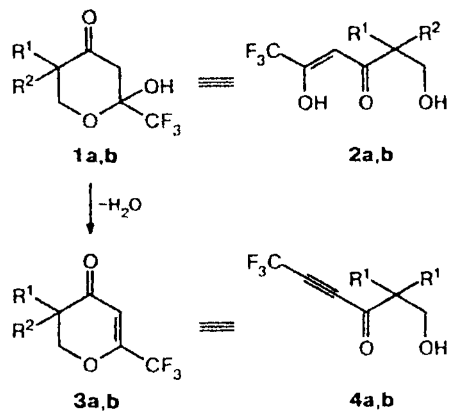
3,3-Dialkyl-2,3-dihydro-6-trifluoromethyl-4-pyrones react with hydrazine hydrate to give 2-hydrazino-2-trifluoromethyl-4-tetrahydropyrone hydrazones. When heated, the latter are transformed into 3(5)-(2-hydroxyethyl)-5(3)-trifluoromethylpyrazoles, while their treatment with HCl in ether leads to 3,3-dialkyl-2,3-dihydro-6-trifluoromethyl-4-pyrone azines.

Key words: hydrazine hydrate, CF_3-containing dihydropyrones; hydrazones, azines, pyrazoles.

In a preceding report,[1] we showed that 5,5-dialkyl-2-hydroxy-2-trifluoromethyl-4-tetrahydropyrones (**1a,b**) are synthetic equivalents of 5-hydroxy-1,3-diketones (**2a,b**) because their behavior in reactions with N-nucleophiles is analogous to that of unsymmetrical fluorine-containing 1,3-diketones described earlier,[2] *viz.*, the attack is mainly directed at the carbonyl group that is not bound to the trifluoromethyl substituent. When distilled *in vacuo* over P_2O_5, tetrahydropyrones **1a,b** are dehydrated to give 3,3-dialkyl-2,3-dihydro-6-trifluoromethyl-4-pyrones (**3a,b**), which contain an activated double bond and easily add ammonia and water.[3]

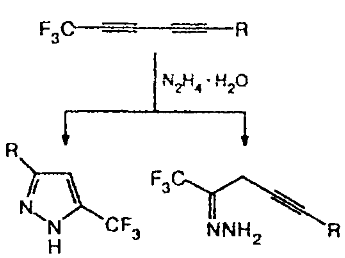
Scheme 1



$R^1 = R^2 = $ Me (**a**)
$R^1 + R^2 = (CH_2)_5$ (**b**)

The present work is devoted to the study of the reaction of dihydropyrones **3a,b** with hydrazine hydrate. In estimating the reactivity of dihydropyrones **3a,b**, we assumed that they can be considered as synthetic equivalents of trifluoropropynyl ketones (**4a,b**) and hence should be more reactive with respect to nucleophiles than tetrahydropyrones **1a,b** and be of interest as new CF_3-containing synthons for various heterocyclic systems with the trifluoromethyl substituent (Scheme 1).

There are no published data about the properties of ketones functionalized with the trifluoropropynyl group, but related compounds, *viz.*, alkyltrifluoromethyldiacetylenes, have been described and their reactions with hydrazine hydrate studied. It was shown[4,5] that, unlike with dialkyldiacetylenes, the reaction products were not only the expected pyrazoles, but also nonconjugated hydrazones.



We established that the reaction of dihydropyrones **3a,b** with an excess of hydrazine hydrate in ethanol at room temperature proceeds simultaneously with both electrophilic centers to give 2-hydrazino-5,5-dimethyl-2-trifluoromethyl-4-tetrahydropyrone hydrazones (**5a,b**)

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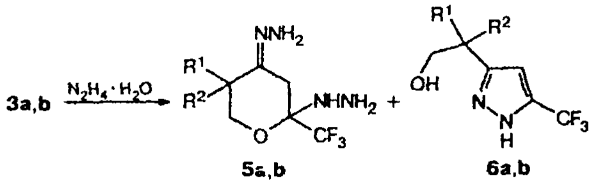
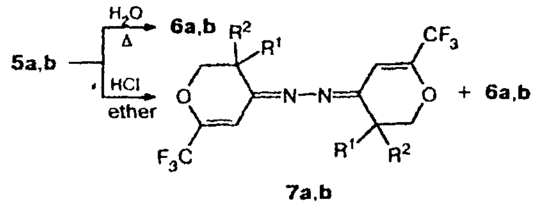
in high yield with an admixture of pyrazoles (**6a,b**) that have also been obtained by us earlier from **1a,b**.[1]



Products **5a,b** are highly reactive. When heated in water or ethanol, they are transformed almost quantitatively into pyrazoles **6a,b**, whereas the action of gaseous hydrogen chloride in ether results in mixtures of pyrazoles **6a,b** and azines (**7a,b**), the latter being isolated in 30% yields.



The structures of compounds **5a,b** and **7a,b** were confirmed by data from elemental analysis and IR, ^1H ^{19}F, and ^{13}C NMR spectroscopy. These data attest that the formation of compounds **5a,b** and **7a,b** is highly stereoselective, although their stereochemistry (*Z,E*-configuration of the C=N bond) was not determined. Two AB systems with the centers at δ 2.66 ($H_2C(3)$, J_{AB} = 15.0 Hz) and 3.70 ($H_2C(6)$, J_{AB} = 11.4 Hz) were observed in the ^1H NMR spectrum of compound **5b**, and the protons of the hydrazino and hydrazono groups appeared as broadened singlets at δ 3.67 and 5.10, respectively (Fig. 1, *a*). The ^{19}F NMR spectrum of this compound exhibits a singlet of the CF_3 group (δ 80.57) and a low-intense signal of the CF_3 group of pyrazole **6b** (δ 99.84), which is present as an admixture with a content varying from 1 to 6%. Compound **5a** also contained pyrazole **6a** (a singlet at δ 99.96, CF_3) as an admixture (3—12%).

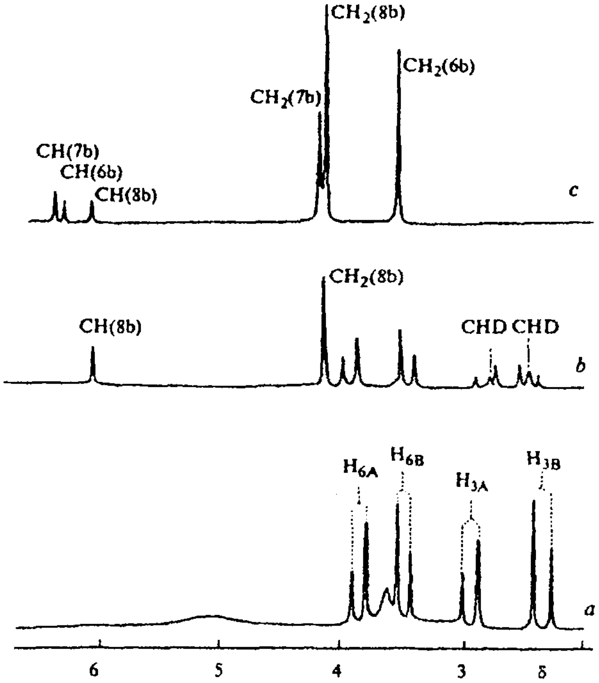
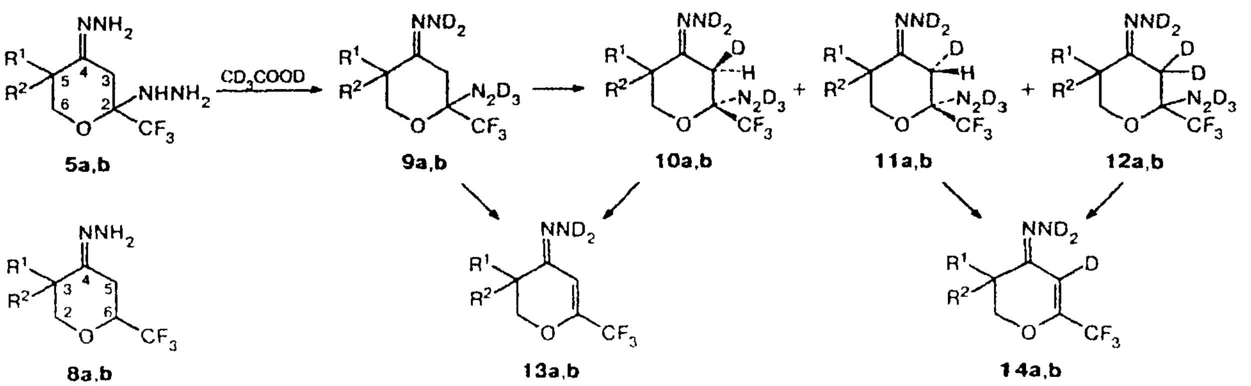


Fig. 1. ^1H NMR: (*a*) hydrazinohydrazone **5b**; (*b*) hydrazinohydrazone **5b** with an excess of CD_3COOD; (*c*) hydrazinohydrazone **5b** with an excess of CD_3COOD three days later.

Along with a multiplet of the aliphatic protons of the cyclohexane ring in the region of δ 1.3—2.0, there are two singlets at δ 4.22 and 6.46 in the ^1H NMR spectrum of azine **7b**, which correspond to the protons of the CH_2 and =CH groups, while the CF_3 group appears in the ^{19}F NMR spectrum as a singlet at δ 89.27.

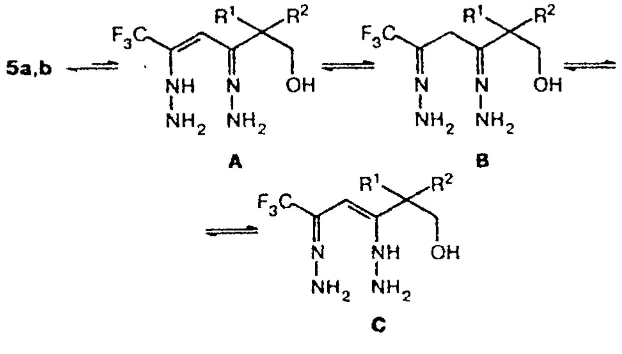
Scheme 2



When an equimolar amount of CD_3COOD is added to a solution of compound **5b** in $CDCl_3$, only the signals for NH protons at δ 3.67 and 5.10 disappear, whereas the addition of an excess of CD_3COOD results in more significant changes. First, the relative integral intensities (RII) of the AB systems of the $H_2C(6)$ and $H_2C(3)$ decreases, RII of the latter decreasing to a greater extent, and two new singlets at δ 2.50 and 2.80 overlap. Second, two other singlets appear in the lower field at δ 4.19 and 6.16 (see Fig. 1, *b*). Compound **5a** undergoes similar changes in the presence of deuterioacetic acid. This can be explained by Scheme 2.

The addition of an excess of CD_3COOD results in deuterium exchange of not only the NH and NH_2 protons (compound **9b**)[*] but also of the $H_2C(3)$ protons, which leads to a decrease in its RII to ~25% of RII of the $H_2C(6)$ group. Singlets at δ 2.50 and 2.80 should be assigned to the nonequivalent protons at position 3 of two diastereomers (**10b**, **11b**), which are formed upon partial deuterium exchange of the $H_2C(3)$ group. Because RII of these signals was also ~25% of those of the $H_2C(6)$ group, one could suggest that the total deuterium exchange of the $H_2C(3)$ group, which yields compound **12b**, was only half completed. The high mobility of the protons of the $H_2C(3)$ group in **5b**, which was also observed for **5a**, can be explained by ring-chain tautomerism, if these compounds are considered to be the cyclic forms of 5-hydroxy-1,3-diketone (**2a,b**) dihydrazones, which exist in equilibrium with the acyclic tautomeric forms (**A**—**C**). The latter cannot be observed in the time scale of NMR spectroscopy, but their existence accounts for rapid deuterium exchange of the $H_2C(3)$ group of the tetrahydropyran ring (Scheme 3).

Scheme 3



The deuteration at position 3 of compound **5b** is accompanied by formation of a new compound that manifests itself by singlets at δ 4.19 and 6.16. Chemical shifts of these signals do not correspond to the CH_2 and =CH groups of azine **7b** and were assigned to the analogous groups of compound **8b** (see Scheme 2), whose content was ~40%. The intensity ratio of these singlets (2 : 0.75) suggests that the formation of hydrazone **8b** involves not only the *N*-deuterated form (**9b**) but also *N,C*-deuterated compounds **10b**—**12b**, which leads to the *N*-deuterated (**13b**) and *N,C*-deuterated form (**14b**) of hydrazone **8b** (see Scheme 2). The ^1H NMR spectrum of compound **5b** in the presence of CF_3COOH exhibits only the singlets of compound **8b** at δ 4.19 (2 H) and 6.28 (1 H).

In the ^1H NMR spectrum recorded immediately after the addition of an excess of CD_3COOD to compound **5a**, the signals for the CH_2 and =CH groups of hydrazone **8a**, which is a mixture of *N*-deuterated and *N,C*-deuterated compounds (**13a**, **14a**) (see Scheme 2), are observed at δ 3.97 and 6.19, their intensity ratio being 2 : 0.72. By analogy with compounds **5a,b**, which are the cyclic forms of 5-hydroxy-1,3-diketone (**2a,b**) dihydrazones, compounds **5a,b** can be considered as the cyclic forms of trifluoropropynyl ketone (**4a,b**) hydrazones and can be expected to be highly reactive.

Thus, in acidic medium, dihydrazones **5a,b** eliminate one hydrazine molecule to give hydrazones **8a,b**, which probably are intermediates in the transformation of compounds **5a,b** into pyrazoles **6a,b** and azines **7a,b**. In the ^1H NMR spectrum recorded three days after the addition of an excess of CD_3COOD to a solution of dihydrazones **5b** in $CDCl_3$, the signals of the initial compound **5b** were absent, but three singlets at δ 3.60, 4.18, and 4.23 corresponding to the methylene groups of pyrazole **6b**,[1] hydrazone **8b**, and azine **7b**, respectively, were observed. Singlets at δ 6.15, 6.38, and 6.47 corresponding to the methyne protons of hydrazone **8b**, pyrazole **6b**, and azine **7b**, respectively, were observed in the low field. These signals were of lower intensity because of partial deuterium exchange. The **8b** : **6b** : **7b** ratio calculated from RII of the methylene groups was ~3 : 2 : 1 (see Fig. 1, *c*).

A more precise time dependence of the reaction mixture composition, which would allow one to evaluate the **5b** → **8b** → **6b** + **7b** transformation rate, was determined from ^{19}F NMR spectra recorded (a) immediately after the addition of an excess of CD_3COOD, (b) 10 min after, and (c) three days after. The following data were obtained: **5b** : **8b** : **6b** : **7b** = (a) 50 : 45 : 5 : 0, (b) 18 : 76 : 6 : 0, and (c) 0 : 46 : 32 : 22, which confirms the participation of compound **8b** in the transformation of **5b** into **6b** and **7b**. The CF_3 groups of compounds **5b**, **8b**, and **6b** are manifested in the spectra (a and b) as singlets at δ 81.17, 89.58, and 99.96, respectively, while two singlets of azine **7b** at δ 89.34 and 89.39, two singlets of hydrazone **8b** at δ 89.52 and 89.58, and a singlet of pyrazole **6b** at δ 99.91 were present in the spectrum (c). The appearance of a double set of signals of different intensity of the CF_3 groups of azine **7b** and hydrazone **8b** is probably due to the fact that the *syn*- and *anti*-forms of compounds **7b** and **8b** exist in thermodynamic equilibrium.

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[*] Compounds **9a,b**—**14a,b** were observed only in the NMR spectrometer tube, while compounds **1a,b**—**8a,b** could be isolated.

Thus, unlike the known tetrahydropyrones **1a,b**,[1] dihydropyrones **3a,b** react with two moles of hydrazine hydrate to give compounds **5a,b**, which can be considered as the cyclic forms of 5-hydroxy-1,3-diketone (**2a,b**) dihydrazones. In acidic medium, these compounds eliminate one hydrazine molecule and are transformed *via* hydrazones **8a,b**, into pyrazoles **6a,b** and azines **7a,b**.

Experimental

IR spectra were recorded on an IKS-29 instrument (Vaseline oil). ^{1}H NMR spectra were recorded in $CDCl_3$ on a Tesla BS-567A spectrometer (100 MHz). ^{19}F and ^{13}C NMR spectra were recorded on a Tesla BS-587A spectrometer (75.3 and 20.1 MHz, respectively). Tetramethylsilane (^{1}H and ^{13}C) and C_6F_6 (^{19}F) were used as the internal standards. Assignment of signals in the ^{13}C NMR spectra was carried out using the DEPT pulse sequence. Mass spectra of azines **7a,b** were obtained on an MS-30 instrument (EI, 70 eV).

Dihydropyrones **3a,b** and pyrazoles **6a,b** were described earlier.[1,3]

2-Hydrazino-5,5-dimethyl-2-trifluoromethyl-4-tetrahydropyrone hydrazone (5a). Hydrazine hydrate (1.0 mL, 1.03 g, 13.0 mmol) was added to dihydropyrone **3a** (1.0 g, 5.1 mmol) in 2 mL of ethanol, and the mixture was left at ~20 °C for 1 d. The crystals that formed were filtered off and recrystallized from ethanol, yield 85%, m.p. 113—114 °C. Found (%): C, 39.96; H, 6.30; N, 23.37. $C_8H_{15}F_3N_4O$. Calculated (%): C, 40.00; H, 6.29; N, 23.32. IR, ν/cm^{-1}: 1605, 1660 (δ NH, NH_2); 1635 (C=N); 3225, 3360 (ν NH, NH_2). ^{1}H NMR, δ: 1.06 (s, 3 H, CH_3); 1.22 (s, 3 H, CH_3); 2.66 (AB system, $\Delta\delta$ = 0.56, 2 H, $H_2C(3)$, J_{AB} = 15.3 Hz); 3.58 (s, 2 H, $H_2C(6)$); 3.7 (br.s, 3 H, $NHNH_2$); 4.6 (br.s, 2 H, $=NNH_2$). ^{19}F NMR, δ: 80.81 (s, CF_3). ^{13}C NMR, δ: 21.68, 22.41 (C(3)); 24.50 (2 CH_3); 37.94 (C(5)); 72.15 (C(6)); 88.38 (q, C(2), $^2J_{C-F}$ = 28.1 Hz); 123.97 (q, CF_3, $^1J_{C-F}$ = 287.5 Hz); 150.52 (C(4)).

6-Hydrazino-6-trifluoromethyltetrahydropyran-3-spirocyclohexan-4-one hydrazone (5b) was obtained from dihydropyrone **3b** by analogy with compound **5a**, yield 89%, m.p. 134—135 °C. Found (%): C, 47.14; H, 7.00; N, 19.73. $C_{11}H_{19}F_3N_4O$. Calculated (%): C, 47.14; H, 6.83; N, 19.99. IR, ν/cm^{-1}: 1645 (C=N); 3230, 3285, 3360 (ν NH, NH_2). ^{1}H NMR, δ: 1.2—2.0 (m, 10 H, cyclohexane ring); 2.66 (AB system, $\Delta\delta$ = 0.58, 2 H, $H_2C(3)$, J_{AB} = 15.0 Hz); 3.70 (AB system, $\Delta\delta$ = 0.35, 2 H, $H_2C(6)$, J_{AB} = 11.4 Hz); 3.67 (br.s, 3 H, $NHNH_2$); 5.10 (br.s, 2 H, $=NNH_2$). ^{19}F NMR, δ: 80.57 (s, CF_3). ^{13}C NMR, δ: 21.18, 21.30 (C(3′), C(5′)); 22.33 (C(3)); 25.85 (C(4′)); 30.31, 31.83 (C(2′), C(6′)); 39.83 (C(5)); 67.77 (C(6)); 87.77 (q, C(2), $^2J_{C-F}$ = 27.5 Hz); 124.18 (q, CF_3, $^1J_{C-F}$ = 289.3 Hz); 146.81 (C(4)).

3,3-Dimethyl-6-trifluoromethyl-2,3-dihydro-4-pyrone azine (7a). Dry hydrogen chloride was passed through a solution of compound **5a** (0.72 g, 3 mmol) in 10 mL of anhydrous ether for 0.5 h. The reaction mixture was neutralized with an aqueous solution of ammonia. Concentration of the aqueous layer gave pyrazole **6a** isolated in 25% yield, which did not give a depression of the melting point with the authentic sample and had the identical IR spectrum. The ethereal solution was dried with anhydrous sodium sulfate, the ether removed, and the residue recrystallized from aqueous ethanol. The yellowish crystals of **7a** were obtained in 30% yield, m.p. 94—95 °C. Found (%): C, 50.28; H, 5.01; N, 7.47. $C_{16}H_{18}F_6N_2O_2$. Calculated (%): C, 50.00; H, 4.72; N, 7.29. IR, ν/cm^{-1}: 1605 (C=C); 1650 (C=N). ^{1}H NMR, δ: 1.26 (s, 6 H, 2 CH_3); 4.04 (s, 2 H, CH_2); 6.48 (s, 1 H, CH=). MS, *m/z* (I_{rel} (%)): 384 $[M]^+$ (27), 383 $[M-H]^+$ (48), 368 $[M-H-Me]^+$ (37), 315 $[M-CF_3]^+$ (29), 248 $[M-136]^+$ (100), 192 $[1/2\ M]^+$ (41), 177 $[1/2\ M-Me]^+$ (30), 163 $[1/2\ M-CHO]^+$ (33), 150 $[1/2\ M-C_3H_6]^+$ (28), 138 $[1/2\ M-C_4H_6]^+$ (42), 95 $[1/2\ M-97]^+$ (45), 81 $[1/2\ M-111]^+$ (42), 69 $[CF_3]^+$ (26).

6-Trifluoromethyl-2,3-dihydropyran-3-spirocyclohexan-4-one azine (7b) was obtained from compound **5b** by analogy with azine **7a**. Pyrazole **6b** was isolated from the aqueous layer in 27% yield (its IR spectrum was identical with that of the authentic sample). Azine **7b** was isolated from the ethereal layer in 29% yield, m.p. 139—140 °C. Found (%): C, 56.81; H, 5.79; N, 5.98. $C_{22}H_{26}F_6N_2O_2$. Calculated (%): C, 56.89; H, 5.64; N, 6.03. IR, ν/cm^{-1}: 1605 (C=C); 1650 (C=N). ^{1}H NMR, δ: 1.3—2.0 (m, 10 H, 2 cyclohexane rings); 4.22 (s, 2 H, CH_2); 6.46 (s, 1 H, CH=). ^{19}F NMR, δ: 89.27 (s, CF_3). MS, *m/z* (I_{rel} (%)): 464 $[M]^+$ (7), 409 $[M-C_4H_7]^+$ (48), 329 $[M-135]^+$ (100), 234 $[1/2\ M+2H]^+$ (85), 232 $[1/2\ M]^+$ (70), 95 $[1/2\ M+2H-139]^+$ (57).

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