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SHORT COMMUNICATIONS

Reactions of 2-Perfluoroacylcycloalkanones with Benzoylhydrazine

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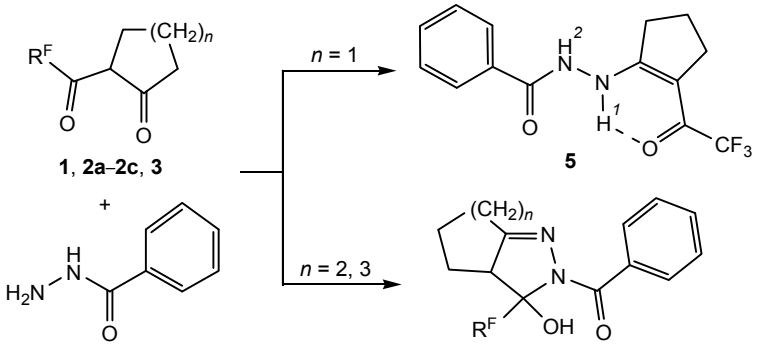
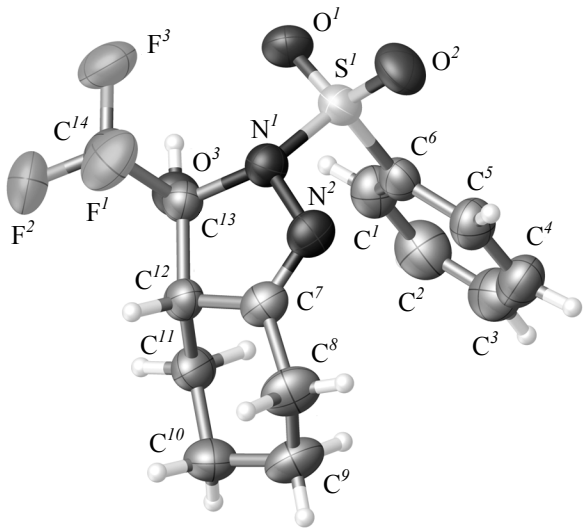
Reactions of aromatic acids hydrazides with trifluoromethyl-containing 1,3-diketones may result in condensation products involving both carbonyl groups [1–9]. We report here on the structure of reaction products between 2-perfluoroacylcycloalkanones and benzoylhydrazine. The structure of compounds was established using ^{1}H and ^{13}C NMR spectra, elemental analysis, and X-ray diffraction (XRD) study. The reactions proceed with a 100% regioselectivity and regardless of the carbocycle size and the length of the perfluoroalkyl group the condensation products are formed involving the carbocyclic carbonyl group. The size of the carbocycle governs the structure of the condensation products **5**–**7**.

Reaction product formed from 2-perfluoroacylcyclopentanone **1** and benzoylhydrazine **4** has a conjugated enehydrazine structure. It is confirmed by the presence in the ^{1}H NMR spectrum recorded in $CDCl_3$ of two signals in the downfield region at 10.75 and 8.66 ppm belonging to the protons of groups NH^1 and NH^2. The presence in the ^{13}C NMR spectrum taken in $CDCl_3$ of a quartet signal at 173.68 ppm ($^2J_{CF}$ 34.1 Hz) corresponding to the carbon atom of the trifluoroacetyl group proves the reaction occurrence at the carbocyclic carbonyl group of diketone **1**. The condensation products of perfluoroacylcyclohexanones **2a**–**2c** and **3** with benzoylhydrazine **4** are the derivatives of 5-hydroxy-2-pyrazolines **6a**–**6c** and **7** as is confirmed by the NMR data and by the comparison of the obtained results with the spectral characteristics of condensation products obtained from aliphatic perfluoroalkyl-containing 1,3-diketones with benzoylhydrazine [3, 5, 10]. For instance, in the ^{13}C NMR spectrum of compound **6a** taken in $CDCl_3$ the quartet at 92.28 ppm ($^2J_{CF}$ 33.6 Hz) corresponds to the carbon atom in the position *3* of the pyrazoline ring linked to the trifluoromethyl group. In the ^{1}H NMR spectrum of compound **6a** in keeping with the bicyclic structure a doublet of doublets is observed at 3.14 ppm (J 12.3, 3.6 Hz) demonstrating the axial orientation of the proton at the *chair*-like geometry of the cyclohexane ring. The existence of a single set of signals in the



n = 1 (**1**), 2 (**2**, **6**), 3 (**3**, **7**); **2**, **6**, R^F = CF_3 (**a**), C_2F_5 (**b**), C_3F_7 (**c**).

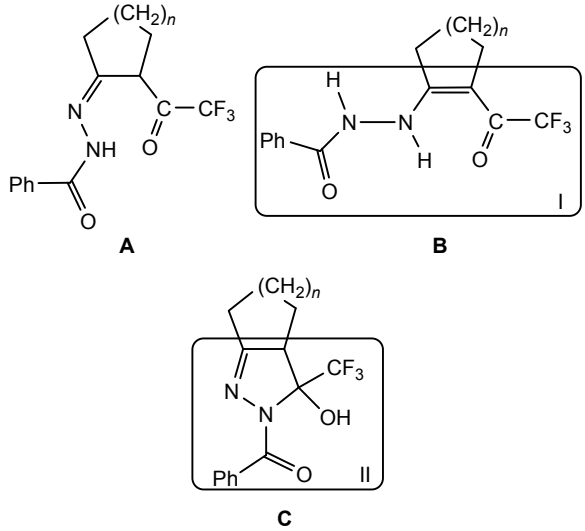


Structure of 2-(phenylsulfonyl)-3-(trifluoromethyl)-3,3a,4,5,6,7-hexahydro-2*H*-indazol-3-ol (**8**) according to X-ray diffraction data

NMR spectra of compound **6a** shows that forms only one of the possible diastereomers. 5-Hydroxy-2-pyrazoline structure of the compounds was proved by XRD analysis by an example of compound **8** prepared by the reaction of 2-perfluoroacylcyclohexanone with *p*-toluenesulfonic acid hydrazide (see the figure).

The cyclohexane ring is present in the chair conformation, the pyrazoline ring exists in strongly flattened *envelope* conformation with the maximum deviation of atoms from the plane of 4°. The hydroxy group is located in the pseudoaxial position, and the trifluoromethyl group has the pseudoequatorial orientation. The planes of the benzenesulfonyl substituent and the pyrazoline ring form an angle of 47.1°. The spectral characteristics of compounds **8** and **6**, **7** are in sufficiently good agreement. The appearance of the NMR spectra of compounds **5–8** does not change with time, the enehydrazine and bicyclic structure is retained. It has been shown formerly that in the series of condensation products of perfluoroalkyl-containing 1,3-diketones $MeCOCH_2COR^F$ with benzoylhydrazine with the growing length of the perfluoroalkyl chain the probability grows of the appearance in the solution along with compounds of 5-hydroxy-2-pyrazoline structure also of tautomers with the conjugated enehydrazine structure [11]. Yet the condensation products **6a–6c** of benzoylhydrazine with 2-perfluoroacylcyclohexanones **2a–2c** possesses a bicyclic structure and form as a single diastereomer. Compounds **5**, **6a**, and **7** react with nickel acetate in aqueous ammonia in the form of linear enehydrazine to afford a complex $NiL{\cdot}NH_3$ containing the four-coordinate nickel atom [12].

Quantum-chemical calculations [DFT, B3LYP 6-31G(d)] for compounds **5** and **6a** were carried out considering three most probable tautomeric forms: hydrazone **A**, enehydrazine **B**, and 5-hydroxy-2-pyrazoline **C**.



The comparison of the values of free Gibbs energies (ΔG) showed that the tautomer stability of the 2-trifluoroacetylcyclopentanone derivative **5** decreased in the series **B** > **C** > **A**, and in its homolog compound **6a**, in the series **C** > **B** > **A**. The hydrazone form **A** in both cases proved to be the least feasible (see the table). Thus the calculation data are consistent with the experiment: compound **5** has the enehydrazine structure **B**, compound **6a**, 5-hydroxy-2-pyrazoline

Comparison of Gibbs free energies of tautomers **A**, **B**, and **C** of compounds **5** and **6a**

Compound no.	$\Delta G_{C\text{-}B}$, kcal mol^{-1}		$\Delta G_{C\text{-}A}$, kcal mol^{-1}		$\Delta G_{B\text{-}A}$, kcal mol^{-1}	
	vacuum	$CHCl_3$	vacuum	$CHCl_3$	vacuum	$CHCl_3$
5	–4.54	–6.99	3.52	1.68	8.05	8.67
6a	5.80	1.76	14.95	12.98	9.15	11.22

structure **C**. The found succession is reproduced also by the calculations taking into account the effect of the solvent ($CHCl_3$, polarized continuum model). For structures **B** and **C** we analyzed the Kohn–Sham molecular orbital diagrams, bond orders, and effective charges on the atoms. The comparison of these characteristics of enehydrazine and cyclic forms of compounds **5** and **6a** showed the identity of the electronic structure of fragments I and II in both homologs.

Thus the performed calculations suggest that the higher stability of enehydrazine tautomer of compound **5** and 5-hydroxy-2-pyrazoline tautomer of compound **6a** is governed by the interactions between the carbocycle and the fragments I and II.

Reaction of 2-perfluoroacylcycloalkanones with benzoylhydrazine. General procedure. To a solution of 3 mmol of 2-perfluoroacylcycloalkanone in 5 mL of ethanol was added dropwise at stirring a solution of 3 mmol of benzoylhydrazine in 3 mL of ethanol. The mixture was stirred for 1 h. On removing the solvent the residue was recrystallized from ethanol.

***N′*-2-[(2,2,2-Trifluoroacetyl)cyclopent-1-enyl]-benzhydrazide (5).** Yield 0.850 g (95%), mp 187–188°C. ^{1}H NMR spectrum, δ, ppm: 1.93 t (2H, CH_2, *J* 7.3 Hz), 2.73 t (2H, CH_2, *J* 7.3 Hz), 2.80 t (2H, CH_2, *J* 7.3 Hz), 7.49 t (2H, H_{Ph}, *J* 7.5 Hz), 7.60 t (1H, H_{Ph}, *J* 7.5 Hz), 7.84 d (2H, H_{Ph}, *J* 7.6 Hz), 8.66 br.s (1H, NH), 10.75 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 21.90 (CH_2), 28.62 (CH_2), 32.09 (CH_2), 102.58 (C=<u>C</u>CO), 118.14 q (CF_3, J_{CF} 287.8 Hz), 127.94, 129.09, 131.46, 133.06 (C_{Ph}), 167.37 (HN<u>C</u>=C), 173.68 ($COCF_3$, $^2J_{CF}$ 34.1 Hz), 177.00 (COPh). Found, %: C 56.18; H 4.41; N 9.36. $C_{14}H_{13}F_3N_2O_2$. Calculated, %: C 56.38; H 4.39; N 9.39.

(3-Hydroxy-3-(trifluoromethyl)-3,3a,4,5,6,7-hexahydro-2*H*-indazol-2-yl)phenylketone (6a). Yield 0.870 g (93%), mp 121–122°C. ^{1}H NMR spectrum, δ, ppm: 1.45 m (2H, CH_2), 1.75 m (2H, CH_2), 2.01 m (2H, CH_2), 2.25 m (1H, CH), 2.66 m (1H, CH), 3.14 d.d (1H, $C^{3a}H$, *J* 12.3, 6.3 Hz), 6.78 br.s (1H, OH), 7.45 m (2H, H_{Ph}), 7.54 m (1H, H_{Ph}), 7.90 d (2H, H_{Ph}, *J* 8.0 Hz). ^{13}C NMR spectrum, δ, ppm: 24.19 (CH_2), 26.04 (CH_2), 26.55 (CH_2), 28.15 (CH_2), 52.64 ($C^{3a}H$), 92.28 q (C^3, $^2J_{CF}$ 33.6 Hz), 124.24 q (CF_3, J_{CF} 285.9 Hz), 128.24, 130.60, 132.53, 133.69 (C_{Ph}), 161.21 (C^{7a}), 169.63 (COPh). Found, %: C 57.57; H 4.81; N 8.86. $C_{15}H_{15}F_3N_2O_2$. Calculated, %: C 57.69; H 4.84; N 8.97.

[3-Hydroxy-3-(1,1,2,2,2-pentafluoroethyl)-3,3a,4,5,6,7-hexahydro-2*H*-indazol-3-yl]phenylketone (6b). Yield 0.521 g (48%), mp 108–109°C. ^{1}H NMR spectrum, δ, ppm: 1.36–1.57 m (2H, CH_2), 1.77 q.d (1H, CH, *J* 12.4, 2.9 Hz), 1.96–2.09 m (3H, CH_2, CH), 2.24 t.d (1H, CH, *J* 13.1, 5.8 Hz), 2.66 br.d.d (1H, CH, *J* 14.2, 3.7 Hz), 3.24 d.d (1H, $C^{3a}H$, *J* 12.4, 5.8 Hz), 7.01 br.s (1H, OH), 7.46 t (2H, H_{Ph}, *J* 6.9 Hz), 7.55 m (1H, H_{Ph}, *J* 6.9 Hz), 7.89 br.d (2H, H_{Ph}, *J* 7.2 Hz). ^{13}C NMR spectrum, δ, ppm: 24.30 (CH_2), 26.28 (CH_2), 26.60 (CH_2), 28.18 (CH_2), 53.30 ($C^{3a}H$), 93.26 t (C^3, $^2J_{CF}$ 25.0 Hz), 112.00–122.00 m (C_2F_5), 128.27, 130.55, 132.60, 133.74 (C_{Ph}), 161.68 (C^{7a}), 173.17 (COPh). Found, %: C 52.91; H 4.14; N 7.71. $C_{16}H_{15}F_5N_2O_2$. Calculated, %: C 53.04; H 4.17; N 7.73.

[3-(1,1,2,2,3,3,3-Heptafluoropropyl)-3-hydroxy-3,3a,4,5,6,7-hexahydro-2*H*-indazol-3-yl]phenylketone (6c). Yield 0.519 g (42%), mp 132–134°C. ^{1}H NMR spectrum, δ, ppm: 1.36–1.57 m (2H, CH_2), 1.77 q.d (1H, CH, *J* 12.7, 2.9 Hz), 1.96–2.11 m (3H, CH_2, CH), 2.25 m (1H, CH, *J* 13.1, 5.8 Hz), 2.66 br.d (1H, CH, *J* 12.4 Hz), 3.21 d.d (1H, $C^{3a}H$, *J* 12.4, 5.9 Hz), 7.09 br.s (1H, OH), 7.45 br.t (2H, H_{Ph}, *J* 7.1 Hz), 7.54 t (1H, H_{Ph}, *J* 7.2 Hz), 7.89 d (2H, H_{Ph}, *J* 7.2 Hz). ^{13}C NMR spectrum, δ, ppm: 24.32 (CH_2), 26.24 (CH_2), 26.55 (CH_2), 28.21 (CH_2), 53.53 ($C^{3a}H$), 94.06 q (C^3, $^2J_{CF}$ 25.6 Hz), 108.00–122.00 m (C_3F_7), 128.27, 130.54, 132.60, 133.75 (C_{Ph}), 161.68 (C^{7a}), 173.17 (COPh). Found, %: C 49.65; H 3.77; N 6.53. $C_{17}H_{15}F_7N_2O_2$. Calculated, %: C 49.52; H 3.67; N 6.79.

[3-Hydroxy-3-(trifluoromethyl)-3a,4,5,6,7,8-hexahydrocyclohepta[*c*]pyrazol-2(3*H*)-yl]phenylketone (7). Yield 0.635 g (65%), mp 96°C. ^{1}H NMR spectrum, δ, ppm: 1.41–1.92 m (7H, CH), 2.07 m (1H, CH), 2.58 m (2H, CH_2), 3.34 d.d (1H, $C^{3a}H$, *J* 9.5, 3.8 Hz), 6.79 br.s (1H, OH), 7.44 br.t (2H, H_{Ph}, *J* 7.3 Hz), 7.54 t (1H, H_{Ph}, *J* 7.3 Hz), 7.90 d (2H, H_{Ph}, *J* 7.3 Hz). ^{13}C NMR spectrum, δ, ppm: 25.50 (CH_2), 25.95 (CH_2), 28.482 (CH_2), 30.01 (CH_2), 30.35 (CH_2), 54.91 ($C^{3a}H$), 93.03 q (C^3, $^2J_{CF}$ 32.2 Hz), 124.17 q (CF_3, J_{CF} 286.7 Hz), 128.19, 130.60, 132.46, 133.65 (C_{Ph}), 163.64 (C^{8a}), 171.90 (COPh). Found, %: C 58.76; H 5.19; N 8.52. $C_{16}H_{17}F_3N_2O_2$. Calculated, %: C 58.89; H 5.25; N 8.58.

2-(Phenylsulfonyl)-3-(trifluoromethyl)-3a,4,5,6,7-hexahydro-2*H*-indazol-3-ol (8). Yield 0.710 g (68%), mp 159–160°C. ^{1}H NMR spectrum, δ, ppm: 1.20 br.s (1H, CH), 1.39 br.s (2H, CH_2), 1.94 br.m (2H, CH_2),

2.16 br.t.d (1H, CH, *J* 13.4, 5.1 Hz), 2.67 br.d (1H, CH, *J* 13.1 Hz), 3.04 d.d (1H, $C^{3a}H$, *J* 11.6, 5.8 Hz), 4.93 br.s (1H, OH), 7.55 br.t (2H, H_{Ph}, *J* 8.0 Hz), 7.65 t (1H, H_{Ph}, *J* 7.3 Hz), 7.98 d (2H, H_{Ph}, *J* 8.0 Hz). ^{13}C NMR spectrum, δ, ppm: 23.94 (CH_2), 25.95 (CH_2), 26.32 (CH_2), 28.11 (CH_2), 53.65 ($C^{3a}H$), 93.65 q (C^3, $^2J_{CF}$ 32.9 Hz), 123.28 q (CF_3, J_{CF} 285.2 Hz), 128.58 ($2C_{Ph}$), 129.20 ($2C_{Ph}$), 133.97 (C_{Ph}), 138.52 (C_{Ph}), 161.90 (C^{7a}). Found, %: C 48.16; H 4.30; N 7.98. $C_{14}H_{15}F_3N_2O_3S$. Calculated, %: C 48.27; H 4.34; N 8.04.

X-ray diffraction analysis of compound **8**. $C_{14}H_{15}F_3N_2O_3S$. M_{calc} 348.34. Space group $P2_{1/n}$, *a* 13.0433, *b* 8.2753, *c* 15.2962 Å, α 90, β 109.9890, γ 90°, *V* 1551.6 $Å^3$, *Z* 4, T 293 K, d_{calc} 1.491 g/cm^3, measured reflections 13714 (2849 independent), R_{all} 0.0484, *wR* 0.0920. The structure was solved by the direct method and refined first in isotropic, then in anisotropic approximation using SHELXL software [13]. The hydrogen atoms were placed in geometrically calculated positions and refined using a *riding* model.

^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker DPX-300 (300.13 and 75.47 MHz) in $CDCl_3$. Elemental analysis was carried out on an instrument MKh-1321 (70 eV). XRD experiment was performed on a diffractometer SMART 1000 CCD (MoK_α-radiation, graphite monochromator, ω-scanning). The reaction progress was monitored by TLC on Silufol UV-254 plates. 2-Perfluoroacylcycloalkanones were prepared by procedure [14].

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