ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 10, pp. 1728–1730. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © V.B. Sokolov, A.Yu. Aksinenko, T.A. Epishina, T.V. Goreva, 2012, published in Zhurnal Obshchei Khimii, 2012, Vol. 82, No. 10, pp. 1724–1726.

Fluoro-Containing 4-Ethylidene-2,4-dihydropyrazol-3-ones in the Diels–Alder Reaction with Cyclopentadiene and Cyanamines

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Received August 1, 2011

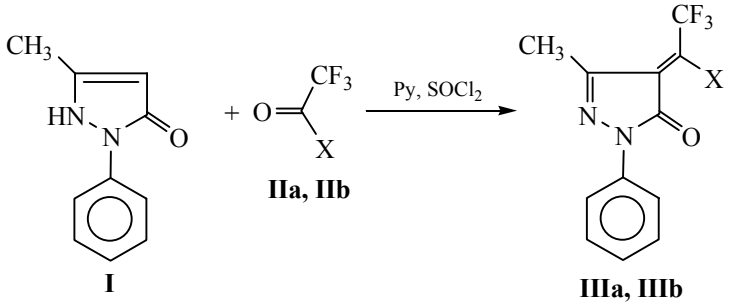
Abstract—The fluorinated 4-ethylidene-2,4-dihydropyrazol-3-ones act as heterodienes and dienophiles in the Diels–Alder reaction with amines and cyclopentadiene to give 1,4-dihydropyrazolo[4,3-*e*]-1,3-oxazines and spirobicyclo[2.2.1]hept-5-ene-2,4'-pyrazolones, respectively.

DOI: 10.1134/S1070363212100155

The heterodienes derived from hexafluoroacetone and methyl trifluoropyruvate like acylimines are known to act in the Diels–Alder reaction as the electron-excessive heterodienes in the cycloaddition with dienophiles and as the electron deficient dienophiles in the reactions with dienes [1–7]. So, hexafluoroacetone acylimines and methyl trifluoropyruvate react with the electron-releasing dienophiles, like aldehydes and ketones [2], ketenes [8, 9], sulfoxides [10], nitriles [11], cyanamines [3, 4, 7, 12]. They also react as the electron-deficient dienophiles with dienes, like cyclopentadiene [6, 7, 13] and 1,3-butadiene [5].

The aim of this research is the study of the Diels–Alder reaction of trifluoromethyl heterodienes and ylides derived from 5-methyl-2-phenyl-1,2-dihydropyrazol-3-one **I**, hexafluoroacetone **IIa** and methyl trifluoropyruvate **IIb**, with cyanamines and cyclopentadiene resulting in six-membered heterocycles and spirobicyclo[2.2.1]hept-5-enes containing dihydropyrazolone fragment, which is a substructural cluster of certain drug molecules. [14]

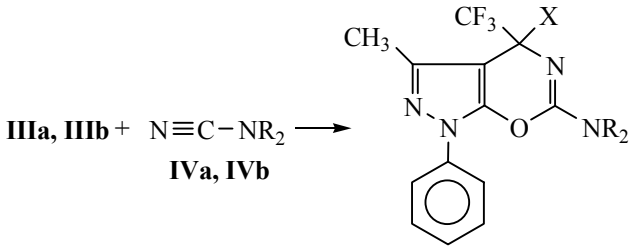
The fluorinated 4-ethylidene-2,4-dihydropyrazol-3-ones [15] were obtained by a modified one-pot method including the sequential addition of pyridine, hexafluoroacetone **IIa**, or methyl trifluoropyruvate **IIb** and $SOCl_2$ to a suspension of 5-methyl-2-phenyl-1,2-dihydropyrazol-3-one **I** in benzene.



I **IIa, IIb** **IIIa, IIIb**

II, III, X = CF_3 (**a**), $C(O)OCH_3$ (**b**).

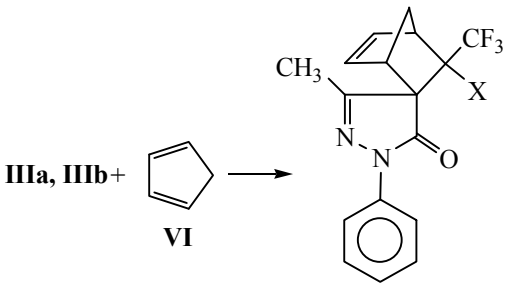
Compared with hexafluoroacetone, acylimines, and methyl trifluoropyruvate, heterodienes **IIIa** and **IIIb** are less reactive in the [2+4]-cycloaddition reaction with cyanamines **IVa** and **IVb**. So, to complete the reaction of compounds **IIIa** and **IIIb** with **IVa** and **IVb** boiling is required of the equimolar mixture of reagents in benzene over 5 h. The reaction results in the corresponding dihydropyrazolo[4,3-*e*]-1,3-oxazines **Va–Vd**.



Va–Vd

IV, R = CH_3 (**a**), $CH_2CH_2OCH_2CH_2$ (**b**); **V**, X = CF_3, R = CH_3 (**a**), $CH_2CH_2OCH_2CH_2$ (**b**); X = $C(O)OCH_3$, R = CH_3 (**c**), $CH_2CH_2OCH_2CH_2$ (**d**).

The fluorinated 4-ethylidene-2,4-dihydropyrazol-3-ones **IIIa** and **IIIb** react as dienophiles with cyclopentadiene at 20°C in benzene to form spirobicyclo[2.2.1]heptenes **VIIa** and **VIIb** in 77 and 74% yields, respectively.



VIIa, VIIb

VII, X = CF_3 (**a**), $C(O)OCH_3$ (**b**).

The synthesized dihydropyrazolo[4,3-*e*]-1,3-oxazines **Va–Vd** and spirobicyclo[2.2.1]heptenes **VIIa** and **VIIb** are crystalline solids. Their composition and structure were proved by the elemental analysis, ^{1}H NMR and ^{19}F NMR spectroscopy. In the ^{19}F NMR spectra there are the characteristic singlet signals at 1.5–2.5 (**Va–Vd**) and 1.6 ppm (**VIIb**) or the quartets of the nonequivalent trifluoromethyl groups at 18.7 and 21.5 ppm (**VIIb**).

Thus, we developed promising reagents for the Diels–Alder reaction, the fluorinated 4-ethylidene-2,4-dihydropyrazol-3-ones, which act as 1,3-heterodienes and dienophiles in the considered transformations.

EXPERIMENTAL

The ^{1}H NMR and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer operating at 200.13 and 188.29 MHz relative to internal tetramethylsilane and external CF_3COOH, respectively. The melting points were determined in a glass capillary. The initial 5-methyl-2-phenyl-1,2-dihydropyrazol-3-one **I**, hexafluoroacetone **IIa**, methyl triftorpiruvate **IIb**, cyanamines **IVa** and **IVb**, cyclopentadiene **VI** (Aldrich) were used without previous purification

5-Methyl-2-phenyl-4-[2,2,2-trifluoro-1-(trifloromethyl)ethylidene]-2,4-dihydro-3*H*-pyrazol-3-one (IIIa). To a suspension of 0.05 mol of compound **I** in 50 ml of benzene were subsequently added 0.1 mol of pyridine and 0.05 mol of compound **IIa** while stirring at 20°C. The reaction mixture was stirred for 1 h till dissolution of the precipitate. Then 0.05 mol of $SOCl_2$ was added. The mixture was stirred for 1 h, filtered, and concentrated. The residue was recrystallized from hexane. Yield 12.3 g (76%), mp 75–77°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.28 q (3H, CH_3, J_{HF} 3.0 Hz), 7.13 t (1H, CH_{Ar}, J 7.3 Hz), 7.29 t (2H, CH_{Ar}, J 7.3 Hz), 7.69 d (2H, CH_{Ar}, J 7.3 Hz). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: 18.76 q (J_{FF} 10.3 Hz), 21.46 q.q (J_{FF} 10.3, J_{FH} 2.8 Hz). Found, %: C 48.26; H 2.25; N 8.43. $C_{13}H_8F_6N_2O$. Calculated, %: C 48.46; H 2.50; N 8.69.

Methyl 3,3,3-trifluoro-2-(3-methyl-5-oxo-1-phenyl-1,5-dihydro-4*H*-pyrazol-4-ylidene)propionate (IIIb) was prepared similarly. Yield 12.8 g (82%), mp 110–111°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.30 q (3H, CH_3, J_{HF} 1.9 Hz), 3.90 s (3H, CH_3O), 7.11 t (1H, CH_{Ar}, J 7.2 Hz), 7.29 t (2H, CH_{Ar}, J 7.2 Hz), 7.69 d (2H, CH_{Ar}, J 7.2 Hz). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: 21.54 q (J_{FH} 1.9 Hz). Found, %: C 53.61; H 3.76; N 8.72. $C_{14}H_{11}F_3N_2O_3$. Calculated, %: C 53.85; H 3.55; N 8.97.

Dimethyl (3-methyl-1-phenyl-4,4-bistrifluoromethyl-1,4-dihydropyrazolo[4,3-*e*]-1,3-oxazin-6-yl)-amine (Va). A solution of 0.01 mol of compound **III** and 0.01 mol of compound **IVa** in 20 ml of benzene was refluxed for 5 h. Then the solvent was evaporated, and the residue was recrystallized from hexane. Yield 3.5 g (89%), mp 140–142°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.26 s (3H, Me), 3.11 s (6H, MeN), 7.32 t (1H, CH_{Ar}, J 7.2 Hz), 7.48 t (2H, CH_{Ar}, J 7.2 Hz), 7.70 d (2H, CH_{Ar}, J 7.2 Hz). ^{19}F NMR spectrum ($CDCl_3$): δ_F 2.70 ppm. Found, %: C 48.71; H 3.88; N 14.53. $C_{16}H_{14}F_6N_4O$. Calculated, %: C 48.99; H 3.60; N 14.28.

5-Methyl-2-phenyl-4-[2,2,2-trifluoro-1-(methylamino)-1-(trifluoromethyl)ethyl]-1,2-dihydro-3*H*-pyrazol-3-one (Vb) was prepared similarly. Yield 3.7 g (85%), mp 138–140°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.30 s (3H, CH_3), 3.58 m (4H, CH_2N), 3.70 m

(4H, CH_2O), 7.33 t (1H, CH_{Ar}, *J* 7.2 Hz), 7.50 t (2H, CH_{Ar}, *J* 7.2 Hz), 7.68 d (2H, CH_{Ar}, *J* 7.2 Hz). ^{19}F NMR spectrum ($CDCl_3$): δ_F 0.21 ppm. Found, %: C 49.67; H 3.92, N 12.71. $C_{18}H_{16}F_6N_4O_2$. Calculated, %: C 49.48; H 3.71; N 12.90.

Methyl 6-dimethylamino-3-methyl-1-phenyl-4-trifluoromethyl-1,4-dihydropyrazolo[4,3-*e*]-1,3-oxazine-4-carboxylate (Vc) was prepared similarly. Yield 3.0 g (76%), mp 80–81°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.21 s (3H, Me), 3.11 s (6H, MeN), 3.73 s (3H, MeO), 7.29 t (1H, CH_{Ar}, *J* 7.2 Hz), 7.47 t (2H, CH_{Ar}, *J* 7.2 Hz), 7.71 d (2H, CH_{Ar}, *J* 7.2 Hz). ^{19}F NMR spectrum ($CDCl_3$): δ_F 1.73 ppm. Found, %: C 53.21; H 4.69, N 14.41. $C_{17}H_{17}F_3N_4O_3$. Calculated, %: C 53.40; H 4.48; N 14.65.

Methyl 3-methyl-6-morpholin-4-yl-1-phenyl-4-trifluoromethyl-1,4-dihydropyrazolo[4,3-*e*]-1,3-oxazine-4-carboxylate (Vd) was prepared similarly. Yield 3.5 g (83%), mp 130–131°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.20 s (3H, Me), 3.55 m (4H, CH_2N), 3.71 m (4H, CH_2O), 3.79 s (3H, MeO), 7.30 t (1H, CH_{Ar}, *J* 7.3 Hz), 7.48 t (2H, CH_{Ar}, *J* 7.3 Hz), 7.67 d (2H, CH_{Ar}, *J* 7.3 Hz). ^{19}F NMR spectrum ($CDCl_3$): δ_F 1.52 ppm. Found, %: C 53.51; H 4.69, N 13.41. $C_{19}H_{19}F_3N_4O_4$. Calculated, %: C 53.77; H 4.51; N 13.20.

5'-Methyl-2'-phenyl-3,3-bis(trifluoromethyl)-spiro(bicyclo[2.2.1]hept-5-ene-2,4'-pyrazol)-3'(2'*H*)-one (VIIa). To a solution of 0.01 mol of compound **IIIa** in 20 ml of benzene was added 0.01 mol of compound **VI** at 20°C. The reaction mixture was stirred for 1 h and concentrated. The residue was recrystallized from hexane. Yield 3.0 g (77%), mp 100–102°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.71 d (1H, *J* 10.4 Hz), 2.07 q (3H, MeC, J_{HF} 3.1 Hz), 3.12 br.s (1H), 3.31 d (1H, *J* 10.4 Hz), 3.42 br. s (1H), 6.52 m (1H), 6.76 m (1H), 7.16 m (1H, CH_{Ar}, *J* 8.4 Hz), 7.38 t (2H, CH_{Ar}, *J* 8.4 Hz), 7.78 d (2H, CH_{Ar}, *J* 8.4 Hz). ^{19}F NMR spectrum ($CDCl_3$), δ_F, ppm: 18.70 m (3F), 21.51 m (3F). Found, %: C 55.50; H 3.89, N 7.43. $C_{18}H_{14}F_6N_2O$. Calculated, %: C 55.68; H 3.63; N 7.21.

5'-Methyl-2'-phenyl-3-trifluoromethyl-3-methoxycarbonylspiro(bicyclo[2.2.1]hept-5-ene-2,4'-pyrazol)-3'(2'*H*)-one (VIIb) was prepared similarly. Yield 2.8 g (74%), mp 76–78°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.71 d (1H, *J* 10.4 Hz), 2.07 s (3H, MeC), 3.12 br.s (1H), 3.31 d (1H, *J* 10.4 Hz), 3.42 br.s (1H), 3.68 s (3H, MeO), 6.52 m (1H), 6.76 m (1H), 7.16 m (1H, CH_{Ar}, *J* 8.4 Hz), 7.38 t (2H, CH_{Ar}, *J* 8.4 Hz), 7.78 d (2H, CH_{Ar}, *J* 8.4 Hz). ^{19}F NMR spectrum ($CDCl_3$): δ_F 16.12 ppm. Found, %: C 60.15; H 4.32, N 7.63. $C_{19}H_{17}F_3N_2O$. Calculated, %: C 60.32; H 4.53; N 7.40.

ACKNOWLEDGMENTS

This work was supported by the Programme "Biomolecular and Medicinal Chemistry" of the Department of Chemistry and Materials Science of the Russian Academy of Sciences.

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