ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 6, pp. 1243–1245. © Pleiades Publishing, Ltd., 2014.
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LETTERS TO THE EDITOR

Cycloaddition and Cyclocondensation of Methyl 2-(4,4-Dimethyl-2,6-dioxocyclohexylidene)-3,3,3-trifluoropropionate

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Received November 5, 2013

Keywords: methyl trifluoropyruvate, dimedone, cyanamines, primary amines, cycloaddition, cyclocondensation

DOI: 10.1134/S1070363214060310

The information on heterocyclization of methyl trifluoropyruvate ylides is limited to transformations of fluorinated 4-ethylidene-2,4-dihydro-3-ones in cycloaddition [1–4] and cyclocondensation [4–6], despite the fact that methyl trifluoropyruvate imines have been widely studied in such transformations [7–12].

The purpose of this work was to develop the method for obtaining methyl triftorpiruvate ylides and to study cyclocondensation and cycloaddition reactions of newly prepared methyl 2-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3,3,3-trifluoropropionate with the primary amines.

Methyl 2-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3,3,3-trifluoropropionate **III** was synthesized in 88% yield by condensation of 5,5-dimethylcyclohexane-1,3-dione **I** with methyl trifluoropyruvate **II**. The reaction was carried out by successively adding dione **II** and $SOCl_2$ to a mixture of dimedone **I** and pyridine in benzene. The ^{19}F NMR spectrum of the resulting ylide **III** contained the singlet signal of CF_3-group at 18.68 ppm, which was characteristic of trifluoromethyl-containing ylides [1].

In the aza-Diels–Alder reaction with cyanamines ylide **III** was less reactive than acyl imines of hexafluoroacetone and methyl trifluoropyruvate that reacted with cyanamines with heat evolution [7, 8]. The reaction of ylide **III** with cyanamines **IVa** and **IVb** proceeded at boiling equimolar mixture of the reagents in benzene for 2 h to produce the corresponding tetrahydrobenzoxazines **VIa** and **VIb** in a 74 and 78% yield, respectively.

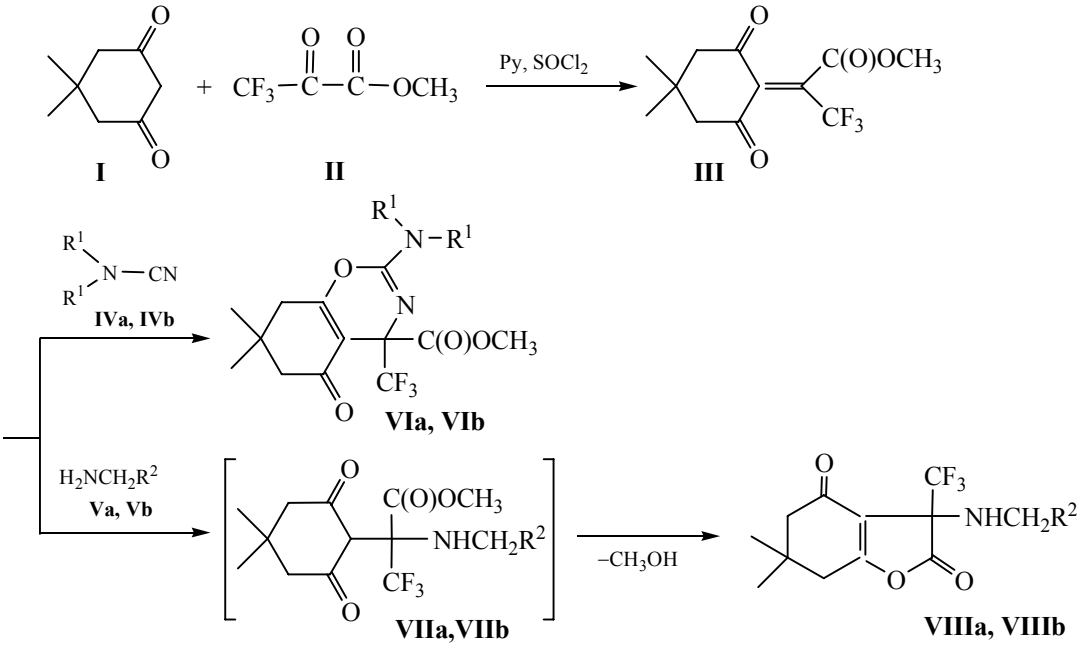
The addition of the primary amines **Va** and **Vb** to ylide **III** proceeded with heat evolution at the highly electrophilic C=C bond to give compounds **VIIa** and **VIIb**. The latter were converted under heating into 3,5,6,7-tetrahydro-1-benzofuran-2,4-diones **VIIIa** and **VIIIb** in a 76 and 82% yield, respectively (Scheme 1).

The synthesized 1,3-benzoxazines **VI** and 3,5,6,7-tetrahydro-1-benzofuran-2,4-diones **VIII** are colorless crystalline substances. The ^{19}F NMR spectra of **III** contained the singlet signal of CF_3-group at 18.7 ppm, whereas in the spectra of **VI** and **VIII** this signal appears in the ranges of 0.73–0.79 and 16.01–16.33 ppm, respectively.

In summary, we synthesized a new highly reactive trifluoromethyl-containing ylide, methyl 2-(4,4-dimethyl-2,6-dioxocyclohexylidene)-3,3,3-trifluoropropionate. The latter can be successfully used as a heterodiene in the Diels–Alder reaction, and as a bis-electrophile in the cyclocondensation, which can be considered as a preparative method for the synthesis of *N*-substituted 3-amino-3-(trifluoromethyl)-3,5,6,7-tetrahydro-1-benzofuranones.

5,5-Dimethylcyclohexane-1,3-dione **I**, methyl trifluoropyruvate **II**, dialkylcyanamines **IVa** and **IVb**,

Scheme 1.



IV, VI, R^1 = Me (**a**), Et (**b**), **V, VII, VIII**, R^2 = C_6H_5 (**a**), pyrid-3-yl (**b**).

amines **Va** and **Vb** (Aldrich) were used without prepurification.

Methyl 2-(4,4-dimethyl-2,6-dioxocyclohexylidene-3,3,3-trifluoropropionate (III). To a solution of 0.1 mol of compound **I** and 0.2 mol of pyridine in 100 mL of benzene were successively added with stirring at 20°C 0.1 mol of compound **II**, 0.1 mol of $SOCl_2$. After 2 h the reaction mixture was filtered and evaporated. Yield 24.6 g (88%), colorless oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 s (6H, Me), 2.71 s (2H, CH_2), 2.76 s (2H, CH2), 3.86 s (3H, MeO). ^{19}F NMR spectrum ($CDCl_3$): δ_F 18.68 ppm. Found, %: C 51.57; H 4.49. $C_{12}H_{13}F_3O_4$. Calculated, %: C 51.80; H 4.71.

Methyl 2-(dimethylamino)-7,7-dimethyl-5-oxo-4-(trifluoromethyl)-5,6,7,8-tetrahydro-4*H*-1,3-benzoxazine-4-carboxylate (VIa). A mixture of 10 mmol of **III** and 10 mmol of **IVa** in 10 mL of benzene was heated at 80°C for 2 h. After cooling, benzene was removed. The residue was recrystallized from hexane. Yield 2.7 g (78%), mp 132–134°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.11 s (3H, Me), 1.14 s (3H, Me), 2.33 s (2H, CH_2), 2.46 s (2H, CH_2), 2.97 s (6H, MeN), 3.79 s (3H, MeO). ^{19}F NMR spectrum ($CDCl_3$): δ_F 0.73 ppm. Found, %: C 51.58; H 5.69; N 8.25. $C_{15}H_{19}F_3N_2O_4$. Calculated, %: C 51.72; H 5.50; N 8.04.

Methyl 2-(diethylamino)-7,7-dimethyl-5-oxo-4-(trifluoromethyl)-5,6,7,8-tetrahydro-4*H*-1,3-benzoxazine-4-carboxylate (VIb) was obtained similarly. Yield 2.8 g (74%), mp 197–199°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.02–1.25 m (12H, Me), 2.34 s (2H, CH2), 2.45 s (2H, CH2), 3.23–3.45 m (4H, $MeCH_2$), 3.79 s (3H, MeO). ^{19}F NMR spectrum ($CDCl_3$): δ_F 0.79 ppm. Found, %: C 54.06; H 6.33; N 7.25. $C_{17}H_{23}F_3N_2O_4$. Calculated, %: C 54.25; H 6.16; N 7.44.

3-Benzylamino-6,6-dimethyl-3-(trifluoromethyl)-3,5,6,7-tetrahydro-1-benzofuran-2,4-dione (VIIIa). To a solution of 10 mmol of **III** in 10 mL of DMF was added with stirring 10 mmol of **Va**. The reaction mixture was stirred at 90°C for 2 h, then cooled and poured into 50 mL of water. The precipitate was separated and recrystallized from 50% ethanol. Yield 2.7 g (76%), mp 201–203°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.88 s (3H, Me), 1.01 s (3H, Me), 1.63 d (1H, CH_2, *J* 11.7 Hz), 1.88 d (1H, CH_2, *J* 11.7 Hz), 2.24 d (1H, CH_2, *J* 13.5 Hz), 2.64 d (1H, CH_2, *J* 13.5 Hz), 4.25 d (2H, CH_2, J_{AB} 14.4 Hz), 6.53 s (1H, NH), 6.82–7.06 m (5H, Ph). ^{19}F NMR spectrum (DMSO-d_6): δ_F 16.01 ppm. Found, %: C 61.43; H 5.29; N 4.11. $C_{18}H_{18}F_3NO_3$. Calculated, %: C 61.19; H 5.13; N 3.96.

6,6-Dimethyl-3-[(pyridin-3-yl)amino]-3-(trifluoromethyl)-3,5,6,7-tetrahydro-1-benzofuran-2,4-

dione (VIIIb) was obtained similarly. Yield 2.9 g (82%), mp 128–130°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.96 s (3H, Me), 1.07 s (3H, Me), 1.95 d (2H, CH_2, J_{AB} 13.7 Hz), 2.38 d (1H, CH_2, J 14.1 Hz), 2.84 d (1H, CH_2, J 13.7 Hz), 4.58 d (2H, CH_2, J_{AB} 16.4 Hz), 7.00 s (1H, NH), 7.31 d. d (1H, CHAr, J 4.5, 1.6 Hz), 7.40 d (1H, CHAr, J 7.8 Hz), 7.40 t. d (1H, CHAr, J 7.8, 1.6 Hz), 8.52 d (1H, CHAr, J 4.5 Hz). ^{19}F NMR spectrum (DMSO-d_6): δ_F 16.33 ppm. Found, %: C 57.46; H 4.63; N 7.75. $C_{17}H_{17}F_3N_2O_3$. Calculated, %: C 57.63; H 4.84; N 7.91.

The ^{1}H and ^{19}F NMR spectra were registered on a Bruker DPX 200 spectrometer operating at 200.13 and 188.29 MHz, internal reference TMS, external reference CF_3COOH, respectively. Melting points were determined using glass capillaries.

ACKNOWLEDGMENTS

This work was performed within the Programs "Development of methods for obtaining chemical substances and new materials" and "Medical and biomedical chemistry" of the Department of Chemistry and Materials Science of the Russian Academy Sciences. The work was financially supported by the Russian Foundation for Basic Research (grant no. 11-03-00496-a).

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