ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 6, pp. 1180–1182. © Pleiades Publishing, Ltd., 2012.
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LETTERS TO THE EDITOR

Hexafluoroacetone and Methyl Trifluoropyruvate Acylimines in the Cyclocondensation with Amides

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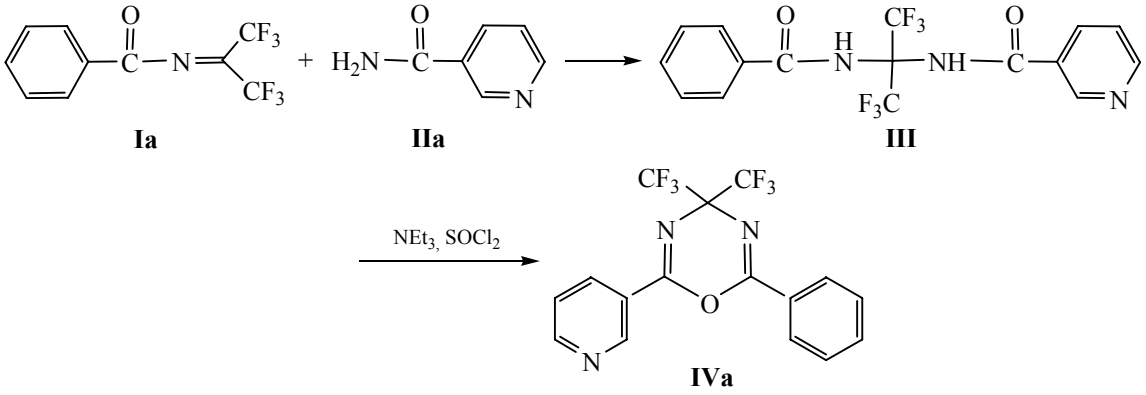
Received November 28, 2011

DOI: 10.1134/S1070363212060266

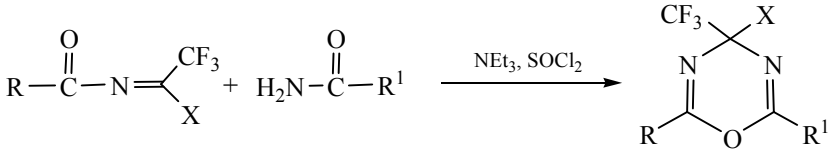
Fluorinated 1,3,5-oxadiazines comprise a promising class of biologically active substances, including, for example, effective insecticides and fungicides of a general action [1]. There are two approaches to the synthesis of these compounds. The first is based on the Diels–Alder aza-reaction of acylimines with hexafluoroacetone or methyl trifluoropyruvate with nitriles [2, 3] or cyanamines [4–7]. The second route is dehydration under rigid conditions (heating in oleum) of amidals derived from the hexafluoroacetone perfluoroacylimines and amides of perfluorocarboxylic acids [8]. Thus, the availability of the 1,3,5-oxadiazines through the cycloaddition reaction is determined primarily by the availability of nitriles, and their synthesis by the dehydration in rigid conditions is applicable to a limited number of amides, in particular, to the amides of perfluorocarboxylic acids. The aim of this study was to expand the possibilities of cyclocondensation reactions of hexafluoroacetone and methyl trifluoropyruvate acylimines with carboxylic amides to produce a variety of 1,3,5-oxadiazines containing one or two trifluoromethyl groups. A prerequisite for this research were the data we obtained in the course of systematic studies of the behavior of N-substituted hexafluoroacetone and methyl trifluoropyruvate imines in cyclocondensation reactions with 1,3-binucleophiles, including the use of a system of pyridine–thionyl chloride as a dehydrating agent [9].

The cyclocondensation of hexafluoroacetone and methyl trifluoropyruvate acylimines **Ia–Id** with carboxylic amides **IIa–IIf** occurs in two stages: the addition of amide **II** to the highly electrophilic C=N bond of acylamine **I** followed by dehydration of the resulting amidal to form 1,3,5-oxadiazine **IV**.



Ia **IIa** **III** **IVa**

In the cyclocondensation of the hexafluoroacetone benzoylimine **Ia** and nicotinamide **IIa** individual product of amidoalkylation **III** was isolated and characterized. Oxadiazines **IVb–IVf** were obtained by one-pot process adding amide **IIa–IIf**, triethylamine and thionyl chloride to a solution of acylimine **Ib–Id** in DMF.

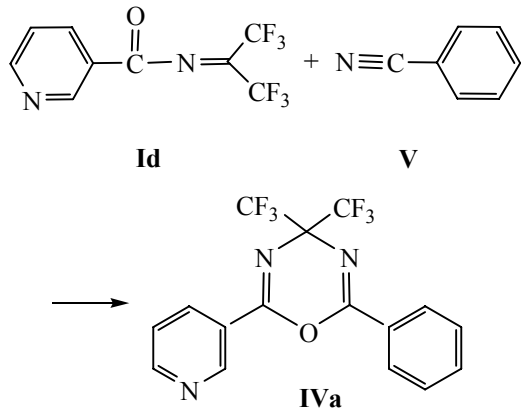


Ib–Id **IIa–IIf** **IVb–IVf**

I: X = CF_3, R = 3-ClC_6H_5 (**b**), Furyl (**c**); X = C(O)OCH_3, R = 4-FC_6H_5 (**d**); **II**: R^1 = C_6H_5 (**a**), 2-$CH_3C_6H_5$ (**b**), 3-$CH_3C_6H_5$ (**d**), 3-$CH_3OC_6H_5$ (**e**), Pyridin-4-yl (**f**); **IV**: X = CF_3, R = 3-ClC_6H_5, R^1 = 2-$CH_3C_6H_5$ (**b**), Pyridin-4-yl (**c**); R = Furyl, R^1 = 3-$CH_3OC_6H_5$ (**d**); X = C(O)OCH_3, R = 4-FC_6H_5, R^1 = C_6H_5 (**e**), 2-$CH_3C_6H_5$ (**f**).

The synthesized 1,3,5-oxadiazines **IVa–IVf** were obtained in yields of 66–78% as crystalline substances. Their composition and structure were proved by elemental analysis and ^1H and ^{19}F NMR spectroscopy. The ^{19}F NMR spectra include characteristic signals in the range from 0 to –1 ppm for **IVa–IVd** and from –1 to –2 ppm for **IVe** and **IVf**.

The 1,3,5-oxadiazine **IVa** was obtained also by authentic synthesis from the imine **Id** and benzonitrile **V** by heating equimolar mixture of the components at 150°C in a closed volume for 5 h.



Id **V** **IVa**

Thus, we have developed a convenient preparative method for the synthesis of biologically active trifluoromethyl-containing oxadiazines based on cyclocondensation of hexafluoroacetone and methyl trifluoropyruvate acylimines with amides.

***N*-(Benzoylamino-2,2,2-trifluoro-1-trifluoromethylethyl)nicotinamide (III)**. To a solution of 5 mmol of compound **Ia** in 10 ml of DMF while stirring at 20ºC was added 5 mmol of compound **IIa**. The reaction mixture was stirred for 8 h at 20ºC, poured into 50 ml of H_2O, the precipitate formed was separated and crystallized from 50% EtOH. Yield 1.7 g (87%), mp 105–106ºC. ^1H NMR spectrum (DMSO-d_6) δ, ppm: 7.23–7.59 m (4H, CHAr); 7.61–7.85 m (3H, CHAr + NH); 8.01 d.t (1H, CHAr, J_1 7.9 Hz, J_2 1.6 Hz), 8.67 g d (1H, CHAr, J_1 5.1 Hz, J_2 1.6 Hz), 8.99 d (1H, CHAr, J 2.1 Hz), 9.34 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6) δ_F, ppm: 3.84 s. Found, %: C 49.35; H 2.62; N 10.92. $C_{16}H_{11}F_6N_3O_2$. Calculated, %: C 49.12; H 2.83; N 10.74.

2-Phenyl-6-pyridin-3-yl-4,4-bis(trifluoromethyl)-4*H*-1,3,5-oxadiazine (IVa). *a*. To a solution of 3 mmol of compound **Ia** and 6 mmol of triethylamine in 10 ml of DMF while stirring at 0ºC was added 3 mmol of $SOCl_2$. The reaction mixture was stirred for 2 h at 20ºC, poured into 50 ml of H_2O, the precipitate was crystallized from hexane. Yield 0.8 g (71%), mp 108–110ºC. ^1H NMR spectrum (DMSO-d_6) δ, ppm: 7.45–7.76 m (4H, CHAr); 8.22 d (2H, CHAr, J 8.6 Hz), 8.52 d (1H, CHAr, J 7.9 Hz), 8.84 d.d (1H, CHAr, J_1 5.1 Hz, J_2 2.0 Hz), 9.33 d (1H, CHAr, J 2.0 Hz). ^{19}F NMR spectrum (DMSO-d_6) δ_F, ppm: –0.42 s. Found, %: C 51.67; H 2.25; N 11.42. $C_{16}H_9F_6N_3O$. Calculated, %: C 51.49; H 2.43; N 11.26.

b. A mixture of 3 mmol of compound **Id** and 3 mmol of compound **V** was heated in a closed vessel for 6 h at 150ºC, then the reaction mixture was crystallized from hexane. Yield 0.7 g (63.5%), mp 108–110ºC.

2-(3-Chlorophenyl)-6-*o*-tolyl-4,4-bis(trifluoromethyl)-4*H*-1,3,5-oxadiazine (IVb). To a solution of 5 mmol of compound **Ib** in 10 ml of DMF while stirring at 20ºC was added 5 mmol of compound **IIb**. The reaction mixture was stirred for 8 h at 20ºC, then 10 mmol of triethylamine was added, and at 0ºC, 5 mmol of $SOCl_2$. The stirring was continued for 2 h at 20ºC, then the mixture was poured into 50 ml of H_2O, the precipitate formed was separated and crystallized from hexane. Yield 1.3 g (62%), mp 91–93ºC. ^1H NMR spectrum (DMSO-d_6) δ, ppm: 2.69 s (3H, Me); 7.35–7.60 m (4H, CHAr); 7.65 d (1H, CHAr, J 8.2 Hz), 7.92 d (1H, CHAr, J 7.4 Hz), 8.8 d (1H, CHAr, J 7.5 Hz); 8.16 s (1H, CHAr). ^{19}F NMR spectrum (DMSO-d_6) δ_F, ppm: –0.48 s. Found, %: C 51.21; H 2.83; N 6.87. $C_{18}H_{11}ClF_6N_2O$. Calculated, %: C 51.39; H 2.64; N 6.66.

2-(3-Chlorophenyl)-6-pyridin-4-yl-4,4-bis(trifluoromethyl)-4*H*-1,3,5-oxadiazine (IVc) was obtained similarly to compound **IVb**. Yield 1.4 g (69%), mp 81–82°C. ^{1}H NMR spectrum (DMSO-d_6) δ, ppm: 7.55 t (1H, CHAr, *J* 8.1 Hz), 7.68 d (1H, CHAr, *J* 8.1 Hz); 7.96–8,24 m (4H, CHAr) , 8.93 d (2H, CHAr, *J* 6.5 Hz). ^{19}F NMR spectrum (DMSO-d_6) δ_F, ppm: –0.56 s. Found, %: C 47.31; H 1.79; N 10.09. $C_{16}H_8ClF_6N_3O$. Calculated, %: C47.14; H 1.98; N 10.31.

2-(2-Furyl)-6-(3-methoxyphenyl)-4,4-bis(trifluoromethyl)-4*H*-1,3,5-oxadiazine (IVd) was obtained similarly to compound **IVb**. Yield 1.2 g (62%), mp 73–75°C. ^{1}H NMR spectrum (DMSO-d_6) δ, ppm: 3.88 s (3H, MeO); 7.62 m (1H, CHAr); 7.19 d.d (1H, CHAr, J_1 8.7 Hz, J_2 2.2 Hz), 7.45 t (1H, CHAr, *J* 7.9 Hz), 7.50–7.62 m (2H, CHAr); 7.73 d (1H, CHAr, *J* 7.3 Hz); 7.95 s (1H, CHAr). ^{19}F NMR spectrum (DMSO-d_6) δ_F, ppm: –0.53 s. Found, %: C 48.81; H 2.36; N 7.32. $C_{16}H_{10}F_6N_2O_3$. Calculated, %: C48.99; H 2.57; N 7.14.

Methyl 2-(4-fluorophenyl)-6-phenyl-4-trifluoromethyl)-4*H*-1,3,5-oxadiazine-4-carboxylate (IVe) was obtained similarly to compound **IVb**. Yield 1.2 g (63%), mp 161–162°C. ^{1}H NMR spectrum (DMSO-d_6) δ, ppm: 3.72 s (3H, CH_3O), 7.12 t (2H, CHAr, *J* 8.8 Hz), 7.36–7.57 m (3H, CHAr); 7.99–8.17 m (4H, CHAr). ^{19}F NMR spectrum (DMSO-d_6) δ_F, ppm: –1.19 s (3F), –27.36 m (1F). Found, %: C 56.65; H 3.32; N 7.54. $C_{18}H_{12}F_4N_2O_3$. Calculated, %: C 56.85; H 3.18; N 7.37.

Methyl 2-(4-fluorophenyl)-6-*m*-tolyl-4-trifluoromethyl)-4*H*-1,3,5-oxadiazine-4-carboxylate (IVf) was obtained similarly to compound **IVb**. Yield 1.1 g (56%), mp 102–104°C. ^{1}H NMR spectrum (DMSO-d_6) δ, ppm: 2.38 s (3H, Me); 3.78 s (3H, MeO); 7.01–7.22 m (2H, CHAr); 7.34 m (2H, CHAr); 7.87 m (2H, CHAr); 8.02–8.18 m (2H, CHAr). ^{19}F NMR spectrum (DMSO-d_6) δ_F, ppm: –1.21 s (3F); –27.40 m (1F). Found, %: C 57.62; H 3.41; N 7.33. $C_{19}H_{14}F_4N_2O_3$. Calculated, %: C 57.87; H 3.58; N 7.10.

^{1}H and ^{19}F NMR spectra were taken on a Bruker DPX 200 spectrometer at the operating frequencies 200.13 and 188.29 MHz, relative to internal tetramethylsilane or external CF_3COOH, respectively. Melting points were determined in glass capillaries. Hexafluoroacetone and methyl trifluoropyruvate acylamines **Ia–Id** were synthesized by the method of [7]. Initial amides **IIa–IIf** (Aldrich) were used without pretreatment.

ACKNOWLEDGMENTS

This work was supported by the Program "Medical and Biomedical Chemistry" of Russian Academy of Sciences, Material Sciences Division.

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