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LETTERS TO THE EDITOR

N-(2,6-Dioxacyclohexyl)-2,2,2-triflouoro-1-trifluoromethylethylamides in Cyclocondensation with Primary Amines

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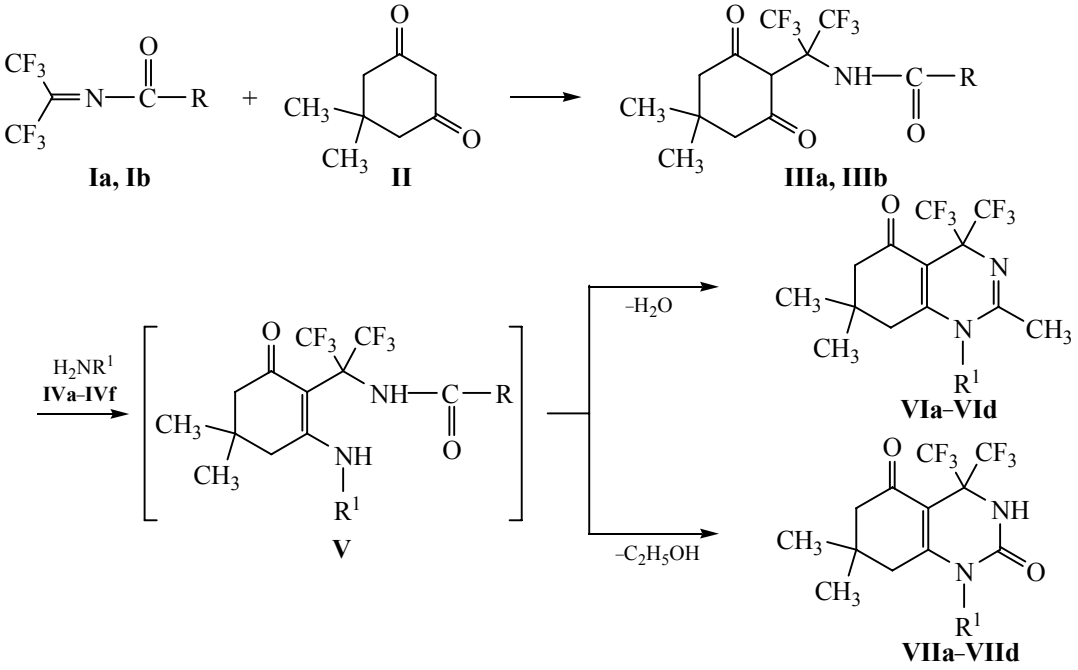
The data we have obtained on a sufficiently large number of examples on the cyclocondensation of the hexafluoroacetone *N*-acylimines with 1,3-binucleophilic reagents [1–6] made it possible to develop a new approach to the synthesis of bis(trifluoromethyl)-containing six-membered heterocycles.

In this study we obtained the previously unknown 1,5-biselectrophilic reagents **III** based on the hexafluoroacetone *N*-acylimines (**Ia, Ib**) and dimedone (**II**), and studied their transformation in the cyclocondensation reaction with primary amines **IVa–IVe**.

Hexafluoroacetone acetylimine **Ia** and ethoxycarbonylimine **Ib** react in the presence of catalytic amounts of triethylamine with dimedone **II** exothermically, forming the products of amidoalkylation **IIIa**, **IIIb** in 86 and 84% yield, respectively. The presence



I, III, V, R = Me (**a**), OEt (**b**); **IV**, R = Bu (**a**), 4-$MeOC_6H_4$ (**b**), 2-$ClC_6H_4CH_2$ (**c**), 4-$FC_6H_4CH_2$ (**d**), pyridin-3-ylmethyl (**e**), furan-2-ylmethyl (**f**); **VI**, Bu (**a**), 2-$ClC_6H_4CH_2$ (**b**), 4-$FC_6H_4CH_2$ (**c**), pyridin-3-ylmethyl (**d**); **VII**, Bu (**a**), 4-$MeOC_6H_4$ (**b**), pyridin-3-ylmethyl (**c**), furan-2-ylmethyl (**d**).

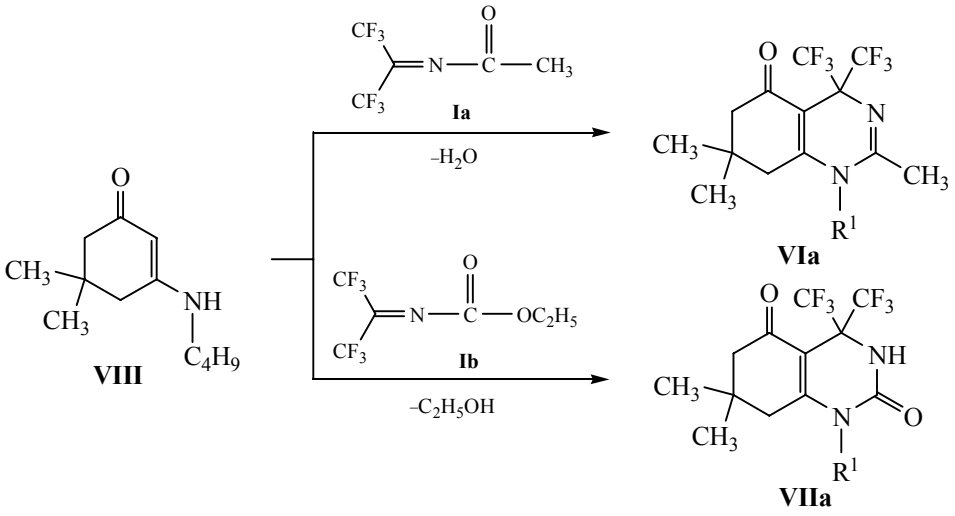
in the molecules of compounds **IIIa**, **IIIb** of two electrophilic sites allows us regarding them as a 1,5-bis-electrophiles able to enter into cyclocondensation with primary amines.

Indeed, the reaction of **IIIa** or **IIIb** with an amine **IVa–IVe** in boiling benzene leads to two types of heterocyclic compounds, depending on the nature of compounds **IIIa**, **IIIb**: 4,6,7,8-tetrahydro-1*H*-quinazolin-5-ones (**VIa–VId**) and 4,6,7,8-tetrahydro-1*H*-quinazoline-2,5-diones (**VIIa–VIId**), according to the following synthetic algorithm:

The primary products in the reaction of compounds **IIIa, IIIb** with amines are apparently the alkylated enamines **V**, which undergo heterocyclization to quinazolin-5-ones **VIa–VId** and quinazoline-2,5-dione **VIIa–VIId** with the elimination of water or ethanol, respectively.

Compounds **IIIa, IIIb, VIa–VId** and **VIIa–VIId** are crystalline solids, formed with a yield of 73–86% and having a characteristic signals in the ^{19}F NMR spectra. Thus, the signals of CF_3 group appear at the 10–11 ppm for **IIIa, IIIb**, 5.1–5.7 ppm for **VIa–VId,** and 4.3–4.6 ppm for **VIIa–VIId**.

Compounds **VId** and **VIId** were obtained by authentic syntheses from 3-butylamino-5,5-dimethylcyclohex-2-enone **VIII** and hexafluoroacetone acetylimine (**Ia**) or ethoxycarbonylimine(**Ib**) at reflux in benzene in the presence of catalytic amounts of triethylamine.



Thus, we have synthesized new 1,5-biselectrophilic reagents, *N*-(2,6-dioxocyclohexyl)-2,2,2-trifluoro-1-trifluoromethylethylamides, which enter the cyclocondensation with primary amines to form trifluoromethyl-containing 4,6,7,8-tetrahydro-1*H*-quinazolin-5-ones.

***N*-[1-(4,4-Dimethyl-2,6-dioxocyclohexyl)-2,2,2-trifluoro-1-trifluoromethylethyl]acetamide (IIIa)**. To a solution of 5 mmol of compound **Ia** and 0.1 g of triethylamine in 10 ml of benzene at 20ºC was added while stirring 5 mmol of compound **II**. The reaction mixture was stirred for 2 h at 20ºC, the precipitate was crystallized from 50% EtOH. Yield 1.5 g (86%), mp 181–183ºC. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.02 s (6H, Me); 1.87 s [3H, MeC(O)]; 2.25 s (4H, CH_2) 2.35 m (1H, CH); 8.16 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 11.14 s. Found, %: C 44.75; H 4.51; N 4.22. $C_{13}H_{15}F_6NO_3$. Calculated, %: C 44.96; H 4.35; N 4.03.

Ethyl *N*-[1-(4,4-Dimethyl-2,6-dioxocyclohexyl)-2,2,2-trifluoro-1-trifluoromethylethyl]carbamoate (IIIb) was obtained similarly. Yield 1.6 g (84%), mp 79–81ºC. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.13 s (6H, Me); 1.28 t (3H, $OCH_2C\underline{H}_3$, J 7.3 Hz), 2.20 m (1H, CH) ; 2.42 s (2H, CH_2); 2.57 s (2H, CH_2) 3.4 q (2H, $OC\underline{H}_2CH_3$, J 7 .3 Hz); 6.44 s (1H, NH) ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 10.66 s. Found, %: C 44.32; H 4.75; N 3.94. $C_{14}H_{17}F_6NO_4$. Calculated, %: C 44.57; H 4.54; N 3.71.

4,4-Bis(trifluoromethyl)-1-butyl-2,7,7-trimethyl-4,6,7,8-tetrahydro-1*H*-quinazolin-5-one (VIa). *a*. A solution of 5 mmol of **IIIa,** 5 mmol of **IVa**, and 0.1 g of triethylamine in 20 ml of benzene was refluxed for 2 h, benzene was evaporated, and the residue was

crystallized from 50% EtOH. Yield 1.4 g (73%), mp 130–132°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.01 m (3H, Me, *J* 7.4 Hz), 1.12 s (6H, Me); 1.40 m (2H, CH_2), 1.55 m (2H, CH_2), 2.33 s (5H, Me + CH_2); 2.47 s (2H, CH_2), 3.64 m (2H, CH_2). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 5.17 s. Found, %: C 53.31; H 5.52; N 7.48. $C_{17}H_{22}F_6N_2O$. Calculated, %: C 53.17; H 5.77; N 7.29.

b. A solution of 5 mmol of **Ia**, 5 mmol of **VIII**, and 0.1 g of triethylamine in 20 ml of benzene was refluxed for 2 h, benzene was evaporated, and the residue was crystallized from 50% EtOH. Yield 1.3 g (67%).

4,4-Bis(trifluoromethyl)-2,7,7-trimethyl-1-(2-chlorobenzyl)-4,6,7,8-tetrahydro-1*H*-quinazolin-5-one VIb) was obtained similarly to **VIa** (method *a*). Yield 1.7 g (75%), mp 121–122°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.99 s (6H, Me); 2.23 s (3H, Me); 2.34 m (4H, CH_2); 4.91 s (2H, CH_2), 7.2 m (1H, CH_{Ar}); 7.36 m (2H, CH_{Ar}); 7.48 m (1H, CH_{Ar}). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 5.57 s. Found, %: C 53.31; H 4.52; N 6.48. $C_{20}H_{19}ClF_6N_2O$. Calculated, %: C 53.05 H 4.24; N 6.19.

4,4-Bis(trifluoromethyl)-2,7,7-trimethyl-1-(4-fluorobenzyl)-4,6,7,8-tetrahydro-1*H*-quinazolin-5-one (VIc) was obtained similarly to **VIa** (method *a*). Yield 1.7 g (78%), mp 171–172°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.00 s (6H, Me); 2.28 s (3H, Me); 2.32 s (2H, CH_2); 2.39 s (2H, CH_2); 4.88 s (2H, CH_2), 7.12 m (4H CH Ar). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 5.66 s (3F, CF_3), –35.58 m (1F, CF_{Ar}) Found, %: C 55.23; H 4.18; N 6.71. $C_{20}H_{19}F_7N_2O$. Calculated, %: C 55.05; H 4.39; N 6.42.

4,4-Bis(trifluoromethyl)-1-(pyridin-3-yl)methyl-2,7,7-trimethyl-4,6,7,8-tetrahydro-1*H*-quinazolin-5-one (VId) was obtained similarly to **VIa** (method *a*). Yield 1.6 g (76%), mp 138–140°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.99 s (6H, Me); 2.28 s (3H, Me); 2.31 s (2H, CH_2); 2.38 s (2H , CH_2); 4.95 s (2H, CH_2), 7.42 m (2H CH_{Ar}); 8.51 g (1H, CH_{Ar}, *J* 1.6 Hz), 8.64 d.d (1H, CH_{Ar}, J_1 5.1 Hz, J_2 1.6 Hz). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 5.67 s. Found, %: C 54.68; H 4.28; N 10.27. $C_{19}H_{19}F_6N_3O$. Calculated, %: C 54.42; H 4.57; N 10.02.

4,4-Bis(trifluoromethyl)-1-butyl-2,7,7-trimethyl-4,6,7,8-tetrahydro-1*H*-quinazolin-2,5-dione (VIIa) *a*. **VIIa** was obtained as **VIa** (method *a*). Yield 1.5 g (78%), mp 117–119°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.97 m (3H, Me, *J* 7.2 Hz), 1.13 s (6H, Me); 1.37 m (2H, CH_2), 1.56 m (2H, CH_2), with 2.34 (2H, CH_2); 2,55 s (2H, CH_2), 3.77 m (2H, CH_2, *J* 8.6 Hz); 6.16 s (1H, NH). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 4.31 s. Found, %: C 49.51; H 5.02; N 7.12. $C_{16}H_{20}F_6N_2O_2$. Calculated, %: C 49.74; H 5.22; N 7.25.

b. A solution of 5 mmol of **Ib**, 5 mmol of **VIII**, and 0.1 g of triethylamine in 20 ml of benzene was refluxed for 2 h, benzene was evaporated, and the residue was crystallized from 50% EtOH. Yield 1.2 g (62%).

4,4-Bis(trifluoromethyl)-1-(4-methoxyphenyl)-2,7,7-trimethyl-4,6,7,8-tetrahydro-1*H*-quinazolin-2,5-dione (VIIb) was obtained similarly to **VIa** (method *a*). Yield 1.6 g (73%), mp 211–213°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.99 s (6H, Me); 2,12 s (2H, CH_2); 2,33 s (2H, CH_2); 3.86 s (3H, MeO); 6.06 s (1H, NH); 6.97–7.12 m (4H, CH_{Ar});. ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 4.39 s. Found, %: C 52.04; H 4.02; N 6.22. $C_{19}H_{18}F_6N_2O_3$. Calculated, %: C 52.30; H 4.16; N 6.42.

4,4-Bis(trifluoromethyl)-1(-pyridin-3-yl)methyl-2,7,7-trimethyl-4,6,7,8-tetrahydro-1*H*-quinazolin-5-one (VIIc) was obtained similarly to **VIa** (method *a*). Yield 1.6 g (76%), mp 202–204°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.98 s (6H, Me); 2.31 s (2H, CH_2); 2.41 s (2H, CH_2); 5.10 s (2H, CH_2); 6.44 s (1H, NH); 7.34 m (1H CH Ar); 7.52 d (1H, CH_{Ar}, *J* 8.1 Hz), 8.51 d (1H, CH_{Ar}, *J* 1.9 Hz), 8.60 d.d (1H, CH_{Ar}, J_1 4.9 Hz, J_2 1.9 Hz). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 4.60 s. Found, %: C 51.52; H 4.22; N 10.22. $C_{18}H_{17}F_6N_3O_2$. Calculated, %: C 51.31; H 4.07; N 9.97.

4,4-Bis(trifluoromethyl)-2,7,7-trimethyl-1-(furan-2-yl)methyl-4,6,7,8-tetrahydro-1*H*-quinazolin-2,5-dione (VIId) was obtained similarly to **VIa** (method *a*). Yield 1.5 g (73%), mp 243–245°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1,08 s (6H, Me); 2.34 s (2H, CH_2); 2.72 s (2H, CH_2); 5.01 s (2H, CH_2); 6.16 s (1H, NH); 6.29 d.d (1H, CH_{Ar}, J_1 3.3 Hz, J_2 0.9 Hz), 6.36 m (1H, CH_{Ar}) 7.37 d.d (1H, CH_{Ar}, J_1 1.9 Hz, J_2 0.6 Hz). ^{19}F NMR spectrum (DMSO-d_6), δ_F, ppm: 4.40 s. Found, %: C 49.52; H 4.12; N 6.65. $C_{17}H_{16}F_6N_2O_3$. Calculated, %: C 49.76;H 3.93; N 6.83.

The ^{1}H and ^{19}F NMR spectra were recorded on a Bruker DPX 200 spectrometer at a frequency of 200.13 and 188.29 MHz relative to tetramethylsilane (internal reference) and CF_3COOH (external reference), respectively. Melting points were deter-

mined in glass capillaries. Hexafluoroacetone acetylimine **Ia** and ethoxycarbonylimine **Ib** were synthesized according to procedure [7]. Dimedone **II** and amines **IVa–IVf** (Aldrich) were used without pretreatment.

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REFERENCES

1. Sokolov, V.B., Aksinenko, A.Yu., Epishina, T.A., Goreeva, T.V., and Martynov, I.V., *Izv. Akad. Nauk, Ser. Khim*., 2005, no. 2, p. 462.
2. Sokolov, V.B. and Aksinenko, A.Yu., *Izv. Akad. Nauk, Ser. Khim*., 2005, no. 6, p. 1470.
3. Sokolov, V.B. and Aksinenko, A.Yu., *Izv. Akad. Nauk, Ser. Khim*., 2005, no. 6, p. 1474.
4. Sokolov, V.B., Aksinenko, A.Yu., Pushin, A.N., and Martynov, I.V., *Izv. Akad. Nauk, Ser. Khim*., 2005, no. 7, p. 1694.
5. Sokolov, V.B., Aksinenko, A.Yu., Epishina, T.A., Goreva, T.V., and Martynov, I.V., *Izv. Akad. Nauk, Ser. Khim*., 2005, no. 12, p. 1755.
6. Sokolov, V.B., Aksinenko, A.Yu., Epishina, T.A., Goreva, T.V., and Martynov, I.V., *Izv. Akad. Nauk, Ser. Khim*., 2005, no. 4, p. 845.
7. Sokolov, V.B. and Aksinenko, A.Yu., *Izv. Akad. Nauk, Ser. Khim*., 1998, no. 4, p. 748.