ISSN 1070-4280, Russian Journal of Organic Chemistry, 2014, Vol. 50, No. 2, pp. 298–300. © Pleiades Publishing, Ltd., 2014.
Original English Text © S.A. Shipilovskikh, A.E. Rubtsov, 2014, published in Zhurnal Organicheskoi Khimii, 2014, Vol. 50, No. 2, pp. 305–307.

SHORT COMMUNICATIONS

Iminofurans Chemistry. Decyclization of Ethyl 2-[2-Oxo-5-phenylfuran-3(2*H*)-ylideneamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate under the Action of Aliphatic Amines

S. A. Shipilovskikh and A. E. Rubtsov

Perm State University, Perm, 614990 Russia
e-mail: rubtsov@psu.ru

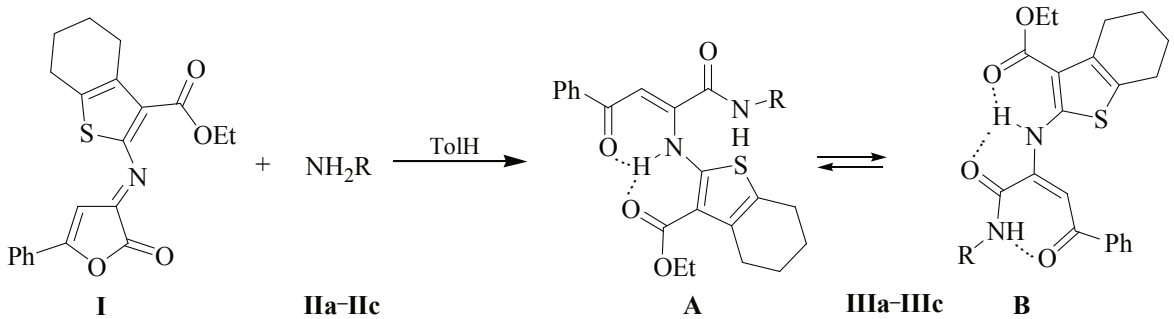
Received September 11, 2013

DOI: 10.1134/S1070428014020286

Publications on compounds containing in the structure 3-imino-3*H*-furan-2-one are scarce [1]. We formerly developed a simple preparation method for a series of ethyl 2-[5-aryl-2-oxofuran-3(2*H*)-ylideneamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylates through an intramolecular cyclization of (*Z*)-4-aryl-4-oxo-2-[3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-ylamino]but-2-enoic acids under the action of acetic anhydride [2]. At the same time this rare type of furan-2-one derivatives is promising in view of the high reactivity and possible biologic action. The introduction into the structure of a thiophene substituent [3–5] at the imine nitrogen atom even more increases the promising qualities of these compounds. Moreover, it has been shown that the proper (*Z*)-4-aryl-4-oxo-2-[3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]-thiophen-2-ylamino]but-2-enoic acids exhibit the biological activity exceeding the activity of drugs used in medicine [6, 7].

It was shown by an example of 5-aryl-3-arylimino-3*H*-furan-3-one that in reaction with anilines the furan ring suffered opening giving amides of 4-aryl-4-oxo-2-arylaminobut-2-enoic acids [8]. In the molecule of ethyl 2-[2-oxo-5-phenylfuran-3(2*H*)-ylideneamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**I**) at least two obvious sites are present for nucleophilic attack with aliphatic amines.

The reaction of ethyl 2-[2-oxo-5-phenylfuran-3(2*H*)-ylideneamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (**I**) with amines **IIa–IIc** in an inert aprotic solvent afforded the corresponding ethyl 2-[(*Z*)-3-oxo-3-phenyl-1-(carbamoyl)-prop-1-enylamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylates **IIIa–IIIc**.



I **IIa–IIc** **A** **IIIa–IIIc** **B**

R = Et (**a**), Bn (**b**), Cy (**c**).

As a result of the study of the reaction it was established that the attack of the amino group was directed at the carbon atom of the lactone carbonyl group of compound **I** and resulted in the products of the decyclization of the furan ring. The ester group under the reaction conditions is not involved into the reaction with amines. Compounds **IIIa**–**IIIc** are crystalline substances.

We registered ^{1}H NMR spectra of compounds **IIIa**–**IIIc** in DMSO-d_6 and $CDCl_3$. It was established that compounds **IIIa**–**IIIc** when dissolved in DMSO-d_6 existed in form **A** characterized by the presence of a singlet at 13.19–13.25 ppm corresponding to the proton of NH group involved in a strong intramolecular hydrogen bond, of proton signal of group NHCO at 8.99–9.62 ppm , and of proton of CH group at 6.25–6.35 ppm.

In $CDCl_3$ solutions compounds **IIIa**–**IIIc** are present in two forms **A** and **B**. The existence of two forms in this case evidently is due to the higher thermodynamic stability of form **B** originating from the formation of several intramolecular hydrogen bonds which are destroyed under the action of more polar DMSO-d_6, and the energy gain becomes prevailing for the solvated form **A**. It was formerly shown by an example of 4-aryl-4-oxo-2-arylaminobut-2-enoic acids derivatives [8–12] that in DMSO-d_6 solution two forms *Z*- and *E*- were present and predominantly *Z*-form existed in chloroform due to stronger stabilization by six-membered intramolecular hydrogen bond between the hydrogen of the amino group in the position *2* and the carbonyl group C^4=O. In compounds **IIIa**–**IIIc** the presence of a bulky substituent at the nitrogen atom and of an additional carbonyl group leads to an opposite effect.

In the ^{1}H NMR spectrum taken in $CDCl_3$ form **A** is characterized by the presence of a singlet at 13.19–13.25 ppm corresponding to the proton of NH group involved in a strong intramolecular hydrogen bond, by a proton signal of group NHCO at 6.26–7.17 ppm, and by a singlet of proton of CH group at 7.07–7.11 ppm. Form **B** gives rise to a singlet of the proton of NH group at 12.28–12.32 ppm, a singlet of proton of CH group at 6.11–6.18 ppm, and a signal of the amide group proton at 12.43–12.97 ppm. This downfield location of the amide group signal is apparently due to the weakening of the N–H bond because of the increase in its acidic character originating from two effects of the same direction: withdrawing the electron density from the oxygen atom of the amide carbonyl at the formation of the hydrogen bond with the hydrogen atom of the amino group at the C^2 atom and involvement of the hydrogen atom of the amide group into the hydrogen bond with the carbonyl C^4=O.

Ethyl 2-[(*Z*)-3-oxo-3-phenyl-1-(ethylcarbamoyl)-prop-1-enylamino]-4,5,6,7-tetrahydro-benzo[*b*]thiophene-3-carboxylate (IIIa). To a solution of 0.079 g of ethylamine hydrochloride (**IIa**) and 0.04 g (1 mmol) of sodium hydroxide in 0.5 mL of H_2O was added a solution of 0.381 g (1 mmol) of compound **I** in 3 mL of anhydrous toluene, and the mixture was stirred at room temperature for 24 h. The separated precipitate was filtered off and recrystallized from 2-propanol. Yield 0.339 g (75%), orange crystals, t.decomp. 155–156°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3332 (NH), 1664 (CONH, COOEt), 1603, 1579, 1513. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.19 t (3H, CH_3, *J* 6.9 Hz), 1.39 t (3H, CH_3, *J* 7.2 Hz), 1.74 m (4H, CH_2), 2.61 m (2H, CH_2), 2.74 m (2H, CH_2), 3.30 q.d (2H, CH_2N, *J* 6.9, 5.7 Hz), 4.39 q (2H, CH_2O, *J* 7.2 Hz), 6.30 s (1H, CH), 7.62 m ($3H_{arom}$), 8.06 d ($2H_{arom}$, *J* 7.1 Hz), 9.09 t (1H, NH, *J* 5.7 Hz), 13.24 s (1H, NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, form **A** (47%): 1.29 m (3H, CH_3), 1.38 m (3H, CH_3), 1.74–2.84 m (8H, CH_2), 3.15 m (2H, CH_2N), 4.39 m (2H, CH_2O), 6.81 br.t (1H, NH), 7.09 s (1H, CH), 7.52 m ($3H_{arom}$), 7.87 d ($2H_{arom}$, *J* 7.1 Hz), 13.38 s (1H, NH); form **B** (53%): 1.29 m (3H, CH_3), 1.38 m (3H, CH_3), 1.74–2.84 m (8H, CH_2), 3.15 m (2H, CH_2N), 4.39 m (2H, CH_2O), 6.11 s (1H, CH), 7.52 m ($3H_{arom}$), 7.98 d ($2H_{arom}$, *J* 7.1 Hz), 12.29 s (1H, NH), 12.46 br.t (1H, NH). Found, %: C 64.74; H 6.10; N 6.57. $C_{23}H_{26}N_2O_4S$. Calculated, %: C 64.77; H 6.14; N 6.57.

Ethyl 2-[(*Z*)-1-(benzylcarbamoyl)-3-oxo-3-phenylprop-1-enylamino]-4,5,6,7-tetrahydrobenzo[*b*]-thiophene-3-carboxylate (IIIb). A solution of 0.381 g (1 mmol) of compound **I** and 0.107 g (1 mmol) of benzylamine (**IIb**) in 3 mL of anhydrous toluene was stirred at 70°C for 2 h. On cooling the reaction mixture to –5°C the separated precipitate was filtered off and recrystallized from 2-propanol. Yield 0.31 g (64%), orange crystals, t.decomp. 176–176°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3341(NH), 1662 (CONH, COOEt), 1600, 1578, 1511. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.39 t (3H, CH_3, *J* 6.9 Hz), 1.75 m (4H, CH_2), 2.51 m (2H, CH_2), 2.73 m (2H, CH_2), 4.39 q (2H, CH_2O, *J* 6.9 Hz), 4.46 d (2H, CH_2N, *J* 6 Hz), 6.35 s (1H, CH), 7.37 m ($5H_{arom}$), 7.59 m ($3H_{arom}$), 8.05 d ($2H_{arom}$, *J* 6.9 Hz), 9.62 t (1H, NH, *J* 6 Hz), 13.19 s (1H, NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, form **A** (54%): 1.34 t (3H, CH_3, *J* 7.5 Hz), 1.72 m (4H, CH_2), 2.48 m (2H, CH_2), 2.65 m (2H, CH_2), 4.32 q (2H, CH_2O, *J* 7.5 Hz), 4.61 d (2H, CH_2N, *J* 5.4 Hz), 7.11 s

(1H, CH), 7.17 br.t (1H, NH), 7.35 m ($3H_{arom}$), 7.77 d ($2H_{arom}$, *J* 7.1 Hz), 13.25 s (1H, NH); form **B** (46%): 1.39 t (3H, CH_3, *J* 7.5 Hz), 1.82 m (4H, CH_2), 2.71 m (2H, CH_2), 2.82 m (2H, CH_2), 4.42 q (2H, CH_2O, *J* 7.5 Hz), 4.71 d (2H, CH_2N, *J* 5.4 Hz), 6.15 s (1H, CH), 7.52 m ($3H_{arom}$), 7.95 d ($2H_{arom}$, *J* 7.1 Hz), 12.32 s (1H, NH), 12.97 br.t (1H, NH). Found, %: C 68.84; H 5.80; N 5.77. $C_{28}H_{28}N_2O_4S$. Calculated, %: C 68.83; H 5.78; N 5.73.

Ethyl 2-[(*Z*)-3-oxo-3-phenyl-1-(cyclohexylcarbamoyl)prop-1-enylamino]-4,5,6,7-tetrahydrobenzo[*b*]-thiophene-3-carboxylate (IIIc) was similarly obtained from compound **I** and amine **IIc**. Yield 0.236 g (49%), orange crystals, t.decomp. 193–194°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3258 (NH), 1708 (COOEt), 1667 (CONH), 1605, 1577, 1511. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.37 m (4H, CH_2), 1.39 t (3H, CH_3, *J* 7.4 Hz), 1.51–1.94 m (8H, CH_2), 2.63 m (2H, CH_2), 2.75 m (2H, CH_2), 3.72 m (1H, CHN), 4.41 q (2H, CH_2O, *J* 7.4 Hz), 6.25 s (1H, CH), 7.62 m ($3H_{arom}$), 8.03 d ($2H_{arom}$, *J* 7.1 Hz), 8.99 d (1H, NH, *J* 7.5 Hz), 13.25 s (1H, NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm, form **A** (49%): 1.17–2.84 m (21H, CH_2), 3.94 m (2H, CHN), 4.18 m (2H, CH_2O), 6.26 br.d (1H, NH), 7.07 s (1H, CH), 7.52 m ($3H_{arom}$), 7.99 d ($2H_{arom}$, *J* 6.9 Hz), 13.15 s (1H, NH); form **B** (51%): 1.17–2.84 m (21H, CH_2, CH_3), 3.94 m (2H, CH_2N), 4.18 m (2H, CH_2O), 6.18 s (1H, CH), 7.52 m ($3H_{arom}$), 7.93 d ($2H_{arom}$, *J* 6.9 Hz), 12.29 s (1H, NH), 12.43 d (1H, NH, *J* 6.6 Hz). Found, %: C 67.44; H 6.70; N 5.87. $C_{27}H_{32}N_2O_4S$. Calculated, %: C 67.47; H 6.71; N 5.83.

IR spectra were recorded on a spectrophotometer FSM-1202 from pellets with KBr. ^1H NMR spectra were registered on a spectrometer Varian-Mercury Plus-300 (operating frequency 300 MHz), internal reference TMS. Elemental analysis was carried out on an instrument Leco CHNS-932. The chemical purity of compounds and the reaction progress was monitored by TLC on Sorbfil plates, eluent ethyl ether–benzene–acetone, 10 : 9 : 1, spots visualized under UV irradiation and in iodine vapor. Melting (decomposition) points were measured on devices PTP-2 and SMP40.

In the study we used commercially available ethylamine hydrochloride, cyclohexylamine, and benzylamine Fluka®; solvents toluene and 2-propanol were of "chemically pure" grade. Compound **I** was synthesized as described in [2].

ACKNOWLEDGMENTS

The study was carried out under a financial support of the Russian Foundation for Basic Research (grants nos. 12-03-31739 and 14-03-96016).

REFERENCES

1. Zalesov, V.V. and Rubtsov, A.E., *Chem. Heterotsikl. Comp.*, 2004, p. 133.
2. Shipilovskikh, S.A., Rubtsov, A.E., and Zalesov, V.V., *Chem. Heterocycl. Comp.*, 2009, p. 658.
3. Bello, Forero, J.S., Jones, J. Jr., and Silva, F.M., *Curr. Org. Synth.*, 2013, vol. 10, p. 347.
4. Puterová, Z., Krutošíková, A., and Végh, D., *Nova Biotechnologica.*, 2009, vol. 9, no. 2, p. 167.
5. Puterová, Z., Krutošíková, A., and Végh, D., *Arcivoc*., 2010, vol. i, p. 209.
6. Shipilovskikh, S.A., Rubtsov, A.E., Makhmudov, R.R., and Zalesov, V.V., RF Patent 2389724, 2008.
7. Makhmudov, R.R., Rubtsov, A.E., and Shipilovskikh, S.A., RF Patent 2485112, 2012.
8. Rubtsov, A.E. and Zalesov, V.V., *Russ. J. Org. Chem*., 2007, vol. 43, p. 739.
9. Igidov, N.M., Rubtsov, A.E., Tyuneva, A.V., Zalesov, V.V., Borodin, A.Yu., and Bukanova, E.V., *Russ. J. Org. Chem*., 2009, vol. 45, p. 716.
10. Rubtsov, A.E. and Zalesov, V.V., *Russ. J. Org. Chem*., 2003, vol. 39, p. 918.
11. Shapet'ko, N.N., Khatipov, S.A., Andreichikov, Yu.S., Kozlov, A.P., and Ryabova, V.V., *Zh. Obshch. Khim*., 1985, vol. 55, p. 661.
12. Yakimovich, S.I., and Zerova, I.V., *Zh. Org. Khim*., 1978, vol. 14, p. 42.