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CHEMISTRY OF IMINOFURANS 3.* SYNTHESIS AND INTRAMOLECULAR CYCLIZATION OF (*Z*)-4-ARYL-2-[3-(ETHOXYCARBONYL)-4,5,6,7-TETRAHYDROBENZO[*b*]THIOPHEN-2-YLAMINO]-4-OXOBUTEN-2-OIC ACIDS

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(Z)-4-Aryl-2-[3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylamino]-4-oxobuten-2-oic acids, which exist in the enamino keto form in solutions, were synthesized by the action of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate on 4-aryl-2-hydroxy-4-oxobuten-2-oic acids. Under the influence of acetic anhydride the obtained acids undergo cyclization to ethyl 2-(5-aryl-2-oxofuran-3(2H)-ylideneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylates.

Keywords: amino acids, 4-aryl-2-hydroxy-4-oxobuten-2-oic acids, 3-imino-3H-furan-2-ones, Gewald thiophene, cyclization.

Compounds containing 3-imino-3H-furan-2-one in their structure are represented in the literature by a few examples of their preparation [2]. Earlier we proposed a simple method for the production of a series of N-substituted 5-aryl-3-imino-3H-furan-2-ones by the intramolecular cyclization of N-substituted 2-amino-4-aryl-4-oxobuten-2-oic acids by the action of acetic anhydride [3]. At the same time, the rare type of 2-furanone derivatives seemed extremely promising from the standpoint of high reactivity and the possible presence of biologically active compounds in a series of furan derivatives, while the introduction of a thiophene substituent [4] into the structure at the imine nitrogen atom increases the prospects of the compounds even further. The aim of the present work was the synthesis of N-substituted 5-aryl-3-imino-3H-furan-2-ones combining two different heterocycles in their structure.

Initially, 4-aryl-2-[3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-ylamino]-4-oxobuten-2-oic acids **3a**-**h** were synthesized by the reaction of 4-aryl-2-hydroxy-4-oxobuten-2-oic acids **1a**-**h** with ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **2** (Table 1).

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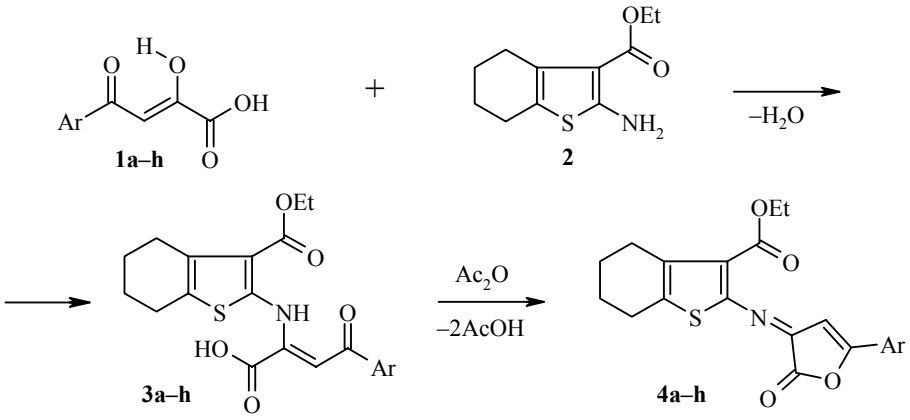

1, **3, 4 a** Ar = Ph, **b** Ar = 4-MeC_6H_4, **c** Ar = 4-$MeOC_6H_4$, **d** Ar = 4-$EtOC_6H_4$, **e** Ar = 4-FC_6H_4, **f** Ar = 4-ClC_6H_4, **g** Ar = 4-BrC_6H_4, **h** Ar = 2,4-$(MeO)_2C_6H_3$

The IR spectra of the acids **3a-h** contain a broad band for the stretching vibrations of the NH group (3410-3380) and absorption bands for the stretching vibrations of the ester and carboxy groups (1715-1701 and 1668-1665 cm^{-1}).

TABLE 1. The Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			Decomp. points, °C	Yield, %
		C	N	S		
3a	$C_{21}H_{21}NO_5S$	63.12 63.14	3.52 3.51	8.03 8.03	189-190	88
3b	$C_{22}H_{23}NO_5S$	64.04 63.90	3.41 3.39	7.79 7.75	188-189	72
3c	$C_{22}H_{23}NO_6S$	61.68 61.52	3.24 3.26	7.42 7.47	186-187	85
3d	$C_{23}H_{25}NO_6S$	62.32 62.29	3.15 3.16	7.22 7.23	172-173	90
3e	$C_{21}H_{20}FNO_5S$	60.45 60.42	3.34 3.36	7.65 7.68	181-182	85
3f	$C_{21}H_{20}ClNO_5S$	58.15 58.13	3.19 3.23	7.41 7.39	176-177	83
3g	$C_{21}H_{20}BrNO_5S$	52.70 52.73	2.95 2.93	6.72 6.70	172-173	82
3h	$C_{23}H_{25}NO_7S$	60.09 60.12	2.99 3.05	6.95 6.98	183-184	93
4a	$C_{21}H_{19}NO_4S$	66.13 66.12	3.63 3.67	8.45 8.41	190-192	86
4b	$C_{22}H_{21}NO_4S$	66.83 66.82	3.59 3.54	8.09 8.11	154-156	63
4c	$C_{22}H_{21}NO_5S$	64.22 64.22	3.37 3.40	7.76 7.79	144-145	68
4d	$C_{23}H_{23}NO_5S$	64.95 64.92	3.29 3.29	7.58 7.54	177-180	41
4e	$C_{21}H_{18}FNO_4S$	63.18 63.15	3.47 3.51	7.99 8.03	186-187	48
4f	$C_{21}H_{18}ClNO_4S$	60.64 60.65	3.33 3.37	7.73 7.71	155-157	40
4g	$C_{21}H_{18}BrNO_4S$	54.75 54.79	3.03 3.04	6.98 6.97	165-167	45
4h	$C_{23}H_{23}NO_6S$	62.53 62.57	3.13 3.17	7.25 7.26	161-164	74

The ^{1}H NMR spectra of compounds **3a-h** (Table 2) contain signals for the protons of both fragments of the initial molecules. A characteristic feature is the presence of a singlet signal at 12.7-12.8 ppm for the proton of the NH group involved in a hydrogen bond.

We studied the intramolecular cyclization of the acids **3a-h** in boiling acetic anhydride and established that ethyl 2-(5-aryl-2-oxofuran-3(2H)-ylideneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylates **4a-h** are formed in the reaction (Tables 1 and 2).

TABLE 2. The Spectral Characteristics of Compounds **3a** and **4a-h**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
3a	3131 (br., NH), 1708 (COO)	12.78 (1H, s, NH); 7.76 (5H, m, arom.); 6.52 (1H, s, C=CH); 4.32 (2H, q, *J* = 6.9, OCH$_2$CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.33 (3H, t, *J* = 6.9, OCH$_2$CH$_3$)
3b	3442 (br., NH), 1715 (COO)	12.75 (1H, s, NH); 7.61 (4H, m, arom.); 6.51 (1H, s, C=CH); 4.32 (2H, q, *J* = 6.9, OCH$_2$CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 2.38 (3H, s, CH$_3$); 1.33 (3H, t, *J* = 6.9, OCH$_2$CH$_3$)
3c	3412 (br., NH), 1712 (COO)	12.75 (1H, s, NH); 7.5 (4H, m, arom.); 6.51 (1H, s, C=CH); 4.31 (2H, q, *J* = 6.9, OCH$_2$CH$_3$,); 3.85 (3H, s, OCH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.33 (3H, t, *J* = 6.9, OCH$_2$CH$_3$)
3d	3416 (br., NH), 1701 (COO)	12.70 (1H, s, NH); 7.50 (4H, m, arom.); 6.51 (1H, s, C=CH); 4.32 (2H, q, *J* = 6.9, OCH$_2$CH$_3$); 4.18 (2H, q, *J* = 6.8, OCH$_2$CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.33 (3H, t, *J* = 6.9, OCH$_2$CH$_3$); 1.35 (3H, t, *J* = 6.8, OCH$_2$CH$_3$)
3e	3412 (br., NH), 1707 (COO)	12.79 (1H, s, NH); 7.75 (4H, m, arom.); 6.52 (1H, s, C=CH); 4.31 (2H, q, *J* = 6.9, OCH$_2$CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.33 (3H, t, *J* = 6.9, OCH$_2$CH$_3$)
3f	3412 (br., NH), 1701 (COO)	12.79 (1H, s, NH); 7.78 (4H, m, arom.); 6.50 (1H, s, C=CH); 4.32 (2H, q, *J* = 6.9, OCH$_2$CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.33 (3H, t, *J* = 6.9, OCH$_2$CH$_3$)
3g	3402 (br., NH), 1701 (COO)	12.79 (1H, s, NH); 7.81 (4H, m, arom.); 6.49 (1H, s, C=CH); 4.32 (2H, q, *J* = 6.9, OCH$_2$CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.33 (3H, t, *J* = 6.9, OCH$_2$CH$_3$)
3h	3392 (br., NH), 1670 (br.)	12.58 (1H, s, NH); 7.3 (4H, m, arom.); 6.57 (1H, s, C=CH); 4.31 (2H, q, *J* = 6.9, OCH$_2$CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.32 (3H, t, *J* = 6.9, OCH$_2$CH$_3$)
4a	1796 (CO$_{lact}$), 1715 (COOEt), 1607 (C=N)	7.5 (5H, m, arom.); 7.31 (1H, s, C=CH); 4.3 (2H, q, *J* = 6.8, OCH$_2$CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.39 (3H, t, *J* = 6.8, OCH$_2$CH$_3$)
4b	1794 (CO$_{lact}$), 1716 (COOEt), 1607 (C=N)	7.8 (4H, m, arom.); 7.19 (1H, s, C=CH); 4.28 (2H, q, *J* = 6.8, OCH$_2$CH$_3$); 2.4 (3H, s, CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.31 (3H, t, *J* = 6.8, OCH$_2$CH$_3$)
4c	1796 (CO$_{lact}$), 1697 (COOEt), 1610 (C=N)	7.6 (4H, m, arom.); 7.12 (1H, s, C=CH); 4.3 (2H, q, *J* = 6.8, OCH$_2$CH$_3$); 3.85 (3H, s, OCH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.31 (3H, t, *J* = 6.8, OCH$_2$CH$_3$)
4d	1800 (CO$_{lact}$), 1694 (COOEt), 1609 (C=N)	7.4 (3H, m, arom.); 7.02 (1H, s, C=CH); 4.27 (2H, q, *J* = 6.8, OCH$_2$CH$_3$); 4.17 (2H, q, *J* = 6.8, OCH$_2$CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.35 (3H, t, *J* = 6.8, OCH$_2$CH$_3$); 1.29 (3H, t, *J* = 6.8, OCH$_2$CH$_3$)
4e	1804 (CO$_{lact}$), 1707 (COOEt), 1610 (C=N)	7.75 (4H, m, arom.); 7.26 (1H, s, C=CH); 4.3 (2H, q, *J* = 6.8, OCH$_2$CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.3 (3H, t, *J* = 6.8, OCH$_2$CH$_3$)
4f	1793 (CO$_{lact}$), 1711 (COOEt), 1607 (C=N)	7.9 (4H, m, arom.); 7.32 (1H, s, C=CH); 4.3 (2H, q, *J* = 6.8, OCH$_2$CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.28 (3H, t, *J* = 6.8, OCH$_2$CH$_3$)
4g	1796 (CO$_{lact}$), 1711 (COOEt), 1611 (C=N)	7.9 (4H, m, arom.); 7.31 (1H, s, C=CH); 4.3 (2H, q, *J* = 6.8, OCH$_2$CH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.28 (3H, t, *J* = 6.8, OCH$_2$CH$_3$)
4h	1785 (CO$_{lact}$), 1719 (COOEt), 1609 (C=N)	7.4 (3H, m, arom.); 7.02 (1H, s, C=CH); 4.2 (2H, q, *J* = 6.8, OCH$_2$CH$_3$); 4.03(3H, s, OCH$_3$); 3.89 (3H, s, OCH$_3$); 3.0-1.5 (8H, m, (CH$_2$)$_4$); 1.28 (3H, t, *J* = 6.8, OCH$_2$CH$_3$)

The IR spectra of compounds **4a-h** contain a band for the stretching vibrations of the lactone carbonyl of the furan ring (1793-1804), a band for the absorption of the ester carbonyl (1694-1715), and a band for the absorption of the C=N bond (1607-1611 cm^{-1}). The ^1H NMR spectra of compounds **4a-h** do not contain signals for the proton of the amino group, but a singlet for the methine proton (H-4) of the heterocycle is observed in the more downfield region (7.02-7.32 ppm) compared with the singlet of the methine proton of the initial acids. The downfield position of the singlet for the methine proton of the furan ring of compounds **4** may be due to its screening by the bulky heterocyclic substituent at the imine nitrogen atom.

EXPERIMENTAL

The IR spectra were obtained in vaseline oil on an FSM-1201 instrument. The ^1H NMR spectra were recorded in DMSO-d_6 on a Varian-Mercury +300 instrument (300 MHz) with TMS as internal standard. The chemical purity of the compounds and the end of the reaction were monitored by TLC on Silufol UV-254 plates in the 10:9:1 ether–benzene–acetone system. The decomposition points were determined on a PTP-2 instrument.

(*Z*)-4-Aryl-2-[3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-ylamino]-4-oxo-buten-2-oic Acids (3). To a solution of the respective 4-aryl-2-hydroxy-4-oxobuten-2-oic acid (0.5 g, 0.01 mol) in ethanol (10 ml) we added a solution of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate **2** (0.01 mol) in ethanol (10 ml). The mixture was left at room temperature for 24 h. The precipitate was filtered off and recrystallized from acetonitrile.

Ethyl 2-(5-Aryl-2-oxofuran-3(2H)-ylideneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylates 4a-h. A solution of the respective acid **3a-h** (0.01 mol) in acetic anhydride (8 ml) was boiled for 1 h. The precipitate that separated after cooling was filtered off, washed with anhydrous ether, and recrystallized from anhydrous toluene.

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