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2-R-5-AR(HET)-5,6-DIHYDRO-7H-[1,2,4]-TRIAZOLO[5,1-*b*][1,3]-THIAZIN-7-ONES

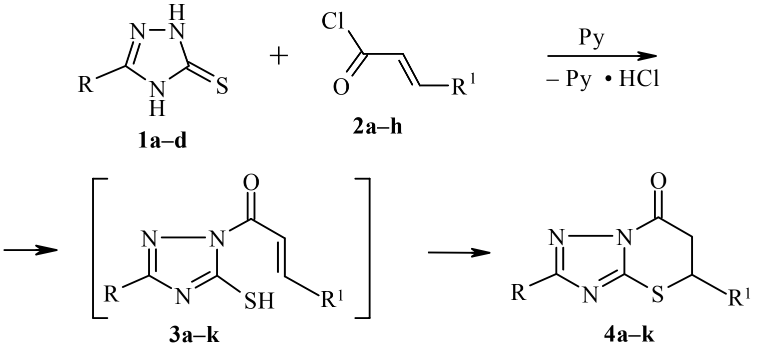
V. N. Britsun and M. O. Lozinskii

A novel method for synthesis of 2-R-5-Ar(Het)-5,6-dihydro-7H-[1,2,4]triazolo[5,1-b][1,3]thiazin-7-ones by condensation of 3-R-4,5-dihydro-1H-1,2,4-triazole-5-thiones with 3-aryl(heteryl)-2-propenoyl chlorides is proposed.

Keywords: 2-R-5-aryl(heteryl)-5,6-dihydro-7H-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones, 3-aryl-(heteryl)-2-propenoyl chlorides, 3-aryl-4,5-dihydro-1H-1,2,4-triazole-5-thiones.

4,5-Dihydro-1H-1,2,4-triazole-5-thione is the starting reagent for synthesis of condensed heterocycles, in particular derivatives of 4H-1,3-thiazin-4-one [1-3]. We know that 1,2,4-triazole-5-thiones are acylated by acid chlorides only at the position 1 [4, 5], while compounds are readily added to the thione group (at 20°C) when they contain an activated multiple bond, such as the methyl ester of propiolic acid [3], acrylic acid [6], or acrylonitrile [7].

We established earlier [8] that when unsubstituted 1,2,4-triazole-5-thione **1a** reacts with cinnamoyl chloride (**2a**), it is not the corresponding 1-acyl-1,2,4-triazole-5-thione **3a** that is formed but rather its cyclization product: 5-phenyl-5,6-dihydro-7H-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-one (**4a**). In this work, we have studied such a reaction for novel examples with participation of 3-aryl-4,5-dihydro-1H-1,2,4-triazole-5-thiones **1b-d** and 3-aryl(heteryl)-2-propenoyl chlorides **2b-h**, where (probably through intermediate acylation products of **3b-k** [9]) we obtain 2-R-5-R^1-5,6-dihydro-7H-[1,2,4]triazolo[5,1-*b*][1,3]-thiazin-7-ones **4b-k**.



1a, **3**, **4 a**–**h** R = H; **1b**, **3**, **4 i** R = Ph; **1c**, **3**, **4 j** R = p-MeOC$_6$H$_4$;
1d, **3**, **4 k** R = p-NO$_2$C$_6$H$_4$; **2–4 a**, **3**, **4 i–k** R^1= Ph; **2–4 b** R^1 = 3,4-(MeO)$_2$C$_6$H$_3$,
c R^1 = p-NO$_2$C$_6$H$_4$, **d** R^1 = p-ClC$_6$H$_4$, **e** R^1 = p-FC$_6$H$_4$, **f** R^1 = 1-naphthyl,
g R^1 = 3,4-methylenedioxyphenyl, **h** R^1 = 2-thienyl

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev 02094; e-mail: iochkiev@ukrpack.net. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1256-1260, August, 2004. Original article submitted February 4, 2002.

The process occurs under mild conditions (boiling in pyridine for 1 h), and compounds **4** are formed in good yields (50%-72%), where when R = H, R^1 = Ar the yield is higher (**4a-g**, 60%-72%) than when R = Ar, R^1 = Ph (**4i-k**, 50%-55%); but when R = H, R^1 = 2-thienyl, product **4h** is obtained in 51% yield.

The composition and structure of the synthesized compounds **4** are confirmed by the elemental analysis results and data from spectral investigation methods (Tables 1 and 2).

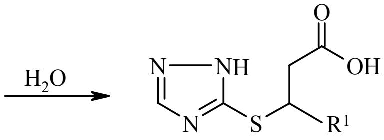
Meaningful proof for the formation of a heterocycle comes from the ^{1}H NMR spectroscopy data. The double bond of the starting 3-aryl-2-propenoyl chloride **2**, the proton signals of which appear in the ^{1}H NMR spectra as two doublets in the 6.80 ppm and 7.50 ppm region, after heterocyclization is converted to the single bond of compounds **4**, with proton signals in the 3.30-5.50 ppm region (an ABX system). Analysis of the lineshape in the ^{13}C NMR spectrum for compound **4a**, obtained without proton decoupling, also supports formation of a six-membered thiazine ring, since the signal for the carbonyl carbon atom (δ 162.92 ppm) appears as a doublet of triplets ($^2J_{CH}$ = 7.1, $^3J_{CH}$ = 4.3 Hz) as a result of spin–spin coupling with the protons of the CH_2CH moiety. In the IR spectra of the products **4a-k**, an absorption band for the C=O group is characteristic (1730-1720 cm^{-1}).

TABLE 1. Characteristics of Synthesized Compounds **4a-k, 5a-h**

Com-pound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	[M$^+$]
		C	H	N			
4a	$C_{11}H_9N_3OS$	57.27 57.14	3.73 3.90	18.33 18.18	163-165	70	231
4b	$C_{13}H_{13}N_3O_3S$	53.45 53.61	4.59 4.47	14.31 14.43	158-160	68	291
4c	$C_{11}H_8N_4O_3S$	47.70 47.83	3.09 2.90	20.02 20.29	200-202	72	276
4d	$C_{11}H_8ClN_3OS$	49.70 49.72	3.23 3.01	15.71 15.82	158-160	68	266
4e	$C_{11}H_8FN_3OS$	52.87 53.01	3.29 3.21	16.64 16.87	140-142	65	249
4f	$C_{15}H_{11}N_3OS$	64.27 64.06	3.77 3.91	15.19 14.95	213-215	67	281
4g	$C_{12}H_9N_3O_3S$	52.47 52.36	3.06 3.27	15.38 15.27	192-193	60	275
4h	$C_9H_7N_3OS_2$	45.53 45.57	2.80 2.95	17.88 17.72	150-153	51	237
4i	$C_{17}H_{13}N_3OS$	66.64 66.45	4.04 4.23	13.85 13.68	170-173	55	307
4j	$C_{18}H_{15}N_3O_2S$	64.23 64.09	4.66 4.45	12.59 12.46	191-193	52	337
4k	$C_{17}H_{12}N_4O_3S$	57.92 57.95	3.66 3.41	15.72 15.91	250-252	50	352
5a	$C_{11}H_{11}N_3O_2S$	53.12 53.00	4.20 4.45	16.71 16.86	143-145	83	249
5b	$C_{13}H_{15}N_3O_4S$	50.62 50.48	4.71 4.89	13.73 13.58	167-169	90	309
5c	$C_{11}H_{10}N_4O_4S$	45.19 44.90	3.21 3.42	18.71 19.04	191-193	86	294
5d	$C_{11}H_{10}ClN_3O_2S$	46.48 46.57	3.34 3.55	14.70 14.81	170-172	94	283
5e	$C_{11}H_{10}FN_3O_2S$	49.53 49.43	3.88 3.77	15.61 15.72	161-163	88	267
5f	$C_{15}H_{13}N_3O_2S$	60.32 60.19	4.23 4.38	14.22 14.04	198-200	91	299
5g	$C_{12}H_{11}N_3O_4S$	49.31 49.14	3.59 3.78	14.20 14.33	181-183	71	293
5h	$C_9H_9N_3O_2S_2$	42.13 42.34	3.28 3.55	16.54 16.46	147-149	75	255

We note that 2-Ar-triazolo[5,1-*b*][1,3]thiazin-7-ones **4i-k** are quite stable compounds, while their analogs **4a-h** which are unsubstituted at the 2 position slowly undergo hydrolysis due to moisture in the air when stored under normal conditions, forming 3-aryl-3-(1H-1,2,4-triazole-5-thio)propanoic acids **5a-h**:

4a–h



5a–h

5 a R^1= Ph, **b** R^1 = 3,4-$(MeO)_2C_6H_3$, **c** R^1 = *p*-$O_2NC_6H_4$, **d** R^1 = *p*-ClC_6H_4, **e** R^1 = *p*-FC_6H_4,
f R^1 = 1-naphthyl, **g** R^1 = 3,4-methylenedioxyphenyl, **h** R^1 = 2-thienyl

We may assume that the 2-aryl-substituted triazolothiazinones **4i-k** are stable compounds because of conjugation of the triazole ring with the aromatic ring at the 2 position. When compounds **4a-h** are recrystallized from aqueous acetic acid or when they are heated with hot water, the hydrolysis rate increases considerably.

The composition and structure of acids **5** are supported by the results of elemental analysis (Table 1) and data from spectral investigation methods. In the ^{1}H NMR spectra of compounds **5**, broadened singlets from protons of the COOH (12.37-12.55 ppm) and NH (14.12-14.23 ppm) groups are characteristic, and in the IR spectra there is a characteristic absorption band for C=O (1680-1720 cm^{-1}).

Thus the reaction of 3-aryl-4,5-dihydro-1H-1,2,4-triazole-5-thiones with 3-aryl(heteryl)-2-propenoyl chlorides is of a general nature, and is a novel and convenient one-step method for synthesis of substituted 5,6-dihydro-7H-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones, allowing us to vary the substituents (Ar, Het) at the positions 2 and 5.

TABLE 2. Spectral Characteristics of Compounds **4a-k, 5a-h**

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
1	2	3
4a*	3100, 1730 (C=O), 1510, 1450, 1410, 1320	3.42 (1H, m, H-6); 3.90 (1H, m, H-6); 5.45 (1H, m, H-5); 7.42-7.51 (5H, m, C_6H_5); 8.31 (1H, s, H-2)
4b	3100, 1730 (C=O), 1600, 1500, 1400, 1310	3.36 (1H, m, H-6); 3.77 (6H, s, $2CH_3O$); 3.89 (1H, m, H-6); 5.40 (1H, m, H-5); 6.99 (2H, m, *o*-, *m*-H_{Ar}); 7.10 (1H, s, *o*-H_{Ar}); 8.28 (1H, s, H-2)
4c	3100, 1730 (C=O), 1540 (N=O), 1500, 1400	3.53 (1H, m, H-6); 3.94 (1H, m, H-6); 5.64 (1H, m, H-5); 7.80 (2H, d, *J* = 9.3, *o*-H_{Ar}); 8.28 (2H, d, *J* = 9.3, *m*-H_{Ar}); 8.32 (1H, s, H-2)
4d	3100, 1720 (C=O), 1590, 1490, 1410, 1360	3.42 (1H, m, H-6); 3.85 (1H, m, H-6); 5.48 (1H, m, H-5); 7.52 (4H, m, *o*-, *m*-H_{Ar}); 8.30 (1H, s, H-2)
4e	3100, 1730 (C=O), 1590, 1510, 1400, 1310	3.50 (1H, m, H-6); 3.85 (1H, m, H-6); 5.43 (1H, m, H-5); 7.25 (2H, t, *J* = 8.1, *o*-H_{Ar}); 7.67 (2H, m, *m*-H_{Ar}); 8.30 (1H, s, H-2)
4f	3000, 1730 (C=O), 1590, 1500, 1390, 1320	3.50 (1H, m, H-6); 4.12 (1H, m, H-6); 6.39 (1H, m, H-5); 7.60-8.01 (6H, m, $C_{10}H_7$); 8.25 (1H, m, $C_{10}H_7$); 8.32 (1H, s, H-2)
4g	3000, 1720 (C=O), 1590, 1510, 1440, 1400, 1310	3.28 (1H, m, H-6); 3.88 (1H, m, H-6); 5.38 (1H, m, H-5); 6.06 (2H, s, OCH_2O), 6.95 (2H, m, *o*- и *m*-H_{Ar}); 7.11 (1H, s, *o*-H_{Ar}); 8.29 (1H, s, H-2)

TABLE 2 (continued)

1	2	3
4h	3200, 1720 (C=O), 1580, 1500, 1400, 1310	3.61 (1H, m, H-6); 3.78 (1H, m, H-6); 5.68 (1H, m, H-5); 7.03 (1H, d. d, $J_1 = 5.1$, $J_2 = 3.0$, H_{Het}-4); 7.18 (1H, d, $J = 3.0$, H_{Het}-3); 7.54 (1H, d, $J = 5.1$, H_{Het}-5); 8.27 (1H, s, H-2)
4i	3200-3000, 1720 (C=O), 1600, 1480, 1430	3.47 (1H, m, H-6); 3.88 (1H, m, H-6); 5.49 (1H, m, H-5); 7.46-8.10 (10H, m, $2C_6H_5$)
4j	3100-3000, 1720 (C=O), 1600, 1480, 1460, 1410	3.38 (1H, m, H-6); 3.83 (3H, s, CH_3O); 3.90 (1H, m, H-6); 5.48 (1H, m, H-5); 7.07 (2H, d, $J = 8.1$, *m*-H_{Ar}); 7.41-7.54 (5H, m, C_6H_5); 8.03 (2H, d, $J = 8.1$, *o*-H_{Ar})
4k	3100-3000, 1720 (C=O), 1590, 1530 (N=O), 1480, 1400	3.44 (1H, m, H-6); 3.95 (1H, m, H-6); 5.56 (1H, m, H-5); 7.41-7.56 (5H, m, C_6H_5); 8.32 (2H, d, $J = 9.1$, *o*-H_{Ar}); 8.39 (2H, d, $J = 9.1$, *m*-H_{Ar})
5a	3300-2800, 1700 (C=O), 1450, 1410, 1360	3.14 (2H, m, CH_2CO); 5.01 (1H, m, SCH); 7.40 (5H, m, C_6H_5); 8.54 (1H, br. s, H-3); 12.44 (1H, br. s, COOH); 14.13 (1H, br. s, NH)
5b	3300, 2900, 2550, 1700 (C=O), 1610, 1520, 1480	3.09 (2H, m, CH_2CO); 3.66 (6H, s, 2 OCH_3); 4.97 (1H, m, SCH); 6.83 (2H, d, $J = 5.1$, *o*-, *m*-H_{Ar}); 7.12 (1H, s, *o*-H_{Ar}); 8.58 (1H, br. s, H-3); 12.38 (1H, br. s, COOH); 14.15 (1H, br. s, NH)
5c	3250, 2900, 2600, 1690 (C=O), 1520, 1500, 1410	3.05 (2H, m, CH_2CO); 5.13 (1H, m, SCH); 7.11 (2H, d, $J = 9.1$, *o*-H_{Ar}); 8.34 (2H, d, $J = 9.1$, *m*-H_{Ar}); 8.48 (1H, br. s, H-3); 12.41 (1H, br. s, COOH); 14.17 (1H, br. s, NH)
5d	3200, 2950, 2500, 1680 (C=O), 1490, 1430, 1370	3.04 (2H, m, CH_2CO); 4.98 (1H, m, SCH); 7.36 (2H, d, $J = 9.2$, *o*-H_{Ar}); 7.42 (2H, d, $J = 9.2$, *m*-H_{Ar}); 8.47 (1H, br. s, H-3); 12.50 (1H, br. s, COOH); 14.20 (1H, br. s, NH)
5e	3200, 2950, 2600, 1700 (C=O), 1660, 1490, 1370	3.09 (2H, m, CH_2CO); 4.99 (1H, m, SCH); 7.15 (2H, t, $J = 7.7$, *o*-H_{Ar}); 7.46 (2H, t, $J = 7.7$, *m*-H_{Ar}); 8.49 (1H, br. s, H-3); 12.55 (1H, br. s, COOH); 14.17 (1H, br. s, NH)
5f	3100-2600, 1720 (C=O), 1500, 1400, 1310	3.36 (2H, m, CH_2CO); 5.84 (1H, m, SCH); 7.57-8.33 (7H, m, $C_{10}H_7$); 8.53 (1H, br. s, H-3); 12.40 (1H, br. s, COOH); 14.23 (1H, br. s, NH)
5g	3100-2600, 1700 (C=O), 1600, 1500, 1430, 1350	3.02 (2H, m, CH_2CO); 4.95 (1H, m, SCH); 6.02 (2H, s, OCH_2O), 6.82 (2H, m, *o*- и *m*-H_{Ar}); 7.01 (1H, s, *o*-H_{Ar}); 8.48 (1H, br. s, H-3); 12.37 (1H, br. s, COOH); 14.23 (1H, br. s, NH)
5h	3200, 2900, 2550, 1710 (C=O), 1530, 1480, 1320	3.07 (2H, m, CH_2CO); 4.94 (1H, m, SCH); 6.92 (1H, d. d, $J_1 = 5.4$, $J_2 = 3.2$, H_{Het}-4); 7.13 (1H, d, $J = 3.2$, H_{Het}-3); 7.58 (1H, d, $J = 5.4$, H_{Het}-5); 8.44 (1H, br. s, H-3); 12.41 (1H, br. s, COOH); 14.15 (1H, br. s, NH)

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* ^{13}C spectrum, δ, ppm: 40.47 (C-6), 42.64 (C-5), 127.52 (C_6H_5), 128.80 (C_6H_5), 129.10 (C_6H_5), 136.66 (C_6H_5), 153.16 (C-2), 156.06 (C-3a), 162.93 (C-7).

EXPERIMENTAL

The NMR spectra were recorded on a Varian-300 (300 MHz (^1H), 75 MHz (^{13}C)) in DMSO-d_6, internal standard TMS. The mass spectra were taken on an MKh-1303; the IR spectra were taken on a UR-20 in KBr disks.

2-R-5-Ar(Het)-5,6-Dihydro-7H-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones (4a-k) (General Procedure). Acid chloride **2** (10 mmol) in benzene (4 ml) was added to a solution of compound **1** (10 mmol) in pyridine (4 ml) at 20°C. The solution was boiled for 1 h under reflux and then cooled, and then water was added. The precipitated product **4** was filtered out, recrystallized from acetic acid, and dried.

3-Ar(Het)-3-(1H-1,2,4-Triazole-5-thio)propanoic Acids (5a-h) (General Procedure). A mixture of water (5 ml) and compound **4a-h** (5 mmol) was held for 24 h at 95°C and then cooled. Product **5** was filtered out, recrystallized from acetic acid, and dried.

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