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AMINOLYSIS OF 2-ARYL-5-R-5,6-DIHYDRO-7H-[1,2,4]TRIAZOLO[5,1-*b*]1,3]THIAZIN-7-ONES

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We have established that the products of aminolysis of 2-aryl-5-R-5,6-dihydro-7H-[1,2,4]triazolo-[5,1-b][1,3]thiazin-7-ones in boiling ethanol are 3-R-3-(5-aryl-4H-1,2,4-triazol-3-ylsulfanyl)-propanamides, and at 180°C-210°C (depending on the structure of the substituent R): 3-phenyl-4,5-dihydro-1H-1,2,4-triazoline-5-thione and 3-arylacrylamides or 3-(3-aryl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanamides.

Keywords: 3-arylacrylamides, 3-aryl-4,5-dihydro-1H-1,2,4-triazoline-5-thiones, 2-aryl-5-R-5,6-dihydro-7H-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones, 3-(3-aryl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanamides, 3-R-3-(5-aryl-4H-1,2,4-triazol-3-ylsulfanyl)propanamides, aminolysis.

Earlier we proposed a novel method for synthesis of 2,5-diaryl-5,6-dihydro-7H-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones **1a-c** including condensation of 3-aryl-4,5-dihydro-1H-1,2,4-triazoline-5-thiones with 3-arylacryloyl chlorides [1, 2]. 2-Phenyl-5,6-dihydro-7H-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones **1** at 160°C-170°C react with ammonia and aromatic amines and are converted to 3-(5-aryl-4H-1,2,4-triazol-ylsulfanyl)propanamides **2** [3]. We thought it would be of interest to study the reactions of 2,5-diaryl-substituted compounds **1a-c** with primary aliphatic and aromatic amines, and to compare them with analogous conversions of 2-monoaryltriazolothiazinones **1d-f**.

We have established that the direction of their reaction depends on the temperature conditions. Thus for reaction of compounds **1a-c** with aniline, benzylamine, and 3-aminomethylpyridine in boiling ethanol, the reaction products are 3-propanamides **2a-e**. At the same time, aminolysis of the same compounds in boiling amine (180°C-184°C) leads to breakdown of the 1,3-thiazine ring and formation of 3-phenyl-4,5-dihydro-1H-1,2,4-triazoline-5-thione **3** and 3-arylacrylamides **4a-c** (Tables 1, 2).

The same compounds are the result of thermal decomposition of propanamides **2a-3**, which occurs when their solutions in the corresponding amine or in 1,3-dichlorobenzene are boiled (180°C) for 30 min. At the same time, compounds **2a-e** are quite stable when briefly heated to 190°C; for example, amides **2b** and **2d** were recrystallized from benzonitrile with no signs of decomposition.

In the ^{1}H NMR spectra of compounds **2b-e**, due to the presence of a chiral center (3-CH), the signals from the protons of the 3-CH, 2-CH_2, and $NH\underline{CH_2}C_6H_5$ groups appear as multiplets. In the IR spectra of compounds **2** (and also **4** and **5**), we observe the characteristic absorption bands ν_{N-H} in the 3300-3250 cm^{-1} region, $\nu_{C=O}$ in the 1670-1650 cm^{-1} region, and $\nu_{C=N}$ in the 1610-1550 cm^{-1} region.

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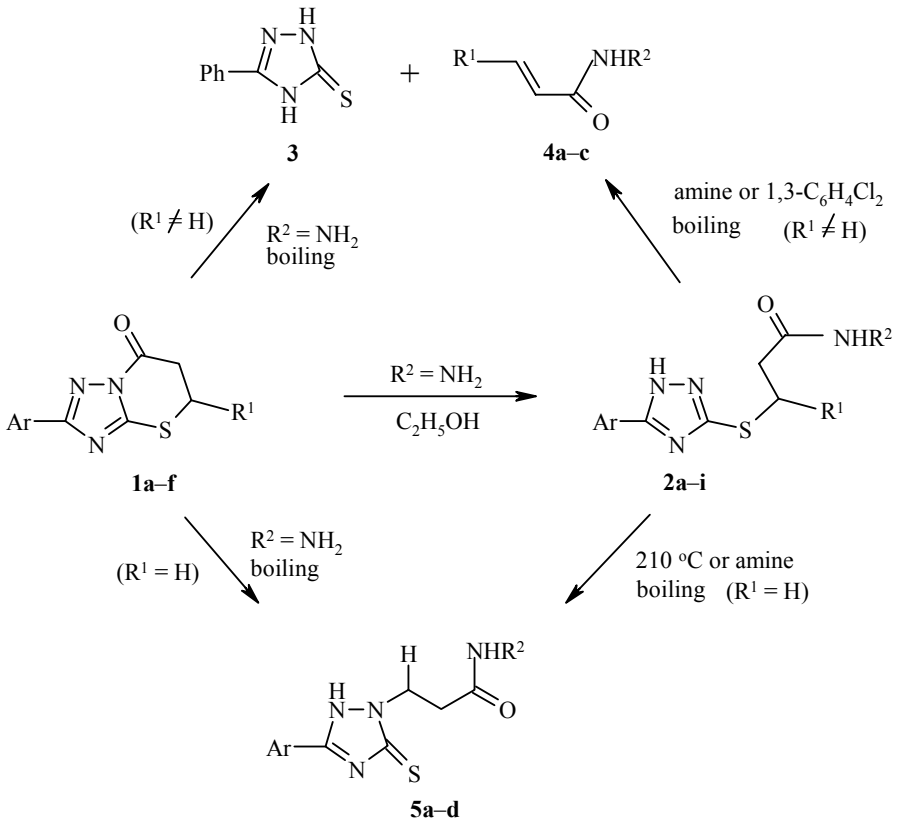

1a–d, **2a–g**, **3**, **5 a**, **b** Ar = Ph; **1e**, **2h**, **5c** Ar = *p*-$MeOC_6H_4$; **1f**, **2i**, **5d** Ar = *p*-ClC_6H_4;
1a, **2a–c, 4a–c** R^1 = Ph; **1b**, **2d** R^1 = *p*-$MeOC_6H_4$; **1c**, **2e** R^1 = *m*-$NO_2C_6H_4$;
1d–f, **2f–i**, **5a–d** R^1 = H; **2a**,**f**, **4a**, **5a** R^2 = Ph; **2b**,**d**,**e**,**g–i**, **4b**, **5b–d** R^2 = $PhCH_2$;
2c, **4c** R^2 = (3-C_5H_4N)CH_2

Aminolysis of monoaryl triazolothiazinones **1d-f** in boiling ethanol also leads to breaking of the N(8)-C(7) bond and formation of amides **2f-i**; and under harsh conditions (when solutions of compounds **1d-f** and **2f-i** are boiled in aniline or benzylamine), the reaction products are 3-(3-aryl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanamides **5a-d**. The same compounds are obtained when amides **2f-i** are heated without solvents at 210°C for 1 h, and also when their solutions are boiled in 1,3-dichlorobenzene or in N,N-dimethylaniline for 2 h.

In the ^{1}H NMR spectra of compounds **1d-f** and **2f-i**, the signal from the S$\underline{CH_2}CH_2CO$ group appears at 3.51-3.55 ppm, while the signal from the N$\underline{CH_2}CH_2CO$ group of the products **5a-d** is observed downfield at 4.34-4.42 ppm. In the IR spectra of compounds **5a-d**, there is no absorption band for the S-H bond (2280-2550 cm^{-1}) and we observe the absorption band for the ν_{N-H} bond (1230-1240 cm^{-1} [4]), indicating the existence of **5a-d** in the thione form, as is preferred for 1,2,4-triazole derivatives [5]. We have reason to believe that the reaction occurs at N(1), since we know that alkylation of 5-alkylthio-3-aryl-1,2,4-triazoles occurs mainly at the N(1) position while there is almost no formation of products of alkylation at N(4) [6, 7]. Apparently the driving force for this isomerization is the thermodynamic factor. The C–N bond is energetically more favorable than the C–S bond (for comparison: the strength of the Alk–SH and Ph–SH bonds are respectively 69 and 86 kcal/mole, while the strengths of the Alk–NH_2 and Ph–NH_2 bonds are respectively 87 and 104 kcal/mol [8]).

TABLE 1 Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
2a	$C_{23}H_{20}N_4OS$	69.27 / 68.98	5.31 / 5.03	13.70 / 13.99	179-181	73
2b	$C_{24}H_{22}N_4OS$	69.63 / 69.54	5.48 / 5.35	13.35 / 13.52	205-206	84
2c	$C_{23}H_{21}N_5OS$	66.42 / 66.49	5.23 / 5.09	16.62 / 16.85	168-170	77
2d	$C_{25}H_{24}N_4O_2S$	67.68 / 67.55	5.68 / 5.44	12.49 / 12.60	201-204	75
2e	$C_{24}H_{21}N_5O_3S$	62.50 / 62.73	4.39 / 4.61	15.50 / 15.24	180-182	79
2f	$C_{17}H_{16}N_4OS$	62.71 / 62.94	5.13 / 4.97	17.41 / 17.27	149-151 (147 [3])	67
2g	$C_{18}H_{18}N_4OS$	63.70 / 63.88	5.19 / 5.36	16.39 / 16.56	133-135	69
2h	$C_{19}H_{20}N_4O_2S$	61.73 / 61.94	5.31 / 5.47	15.49 / 15.21	137-140	72
2i	$C_{18}H_{17}ClN_4OS$	57.76 / 57.98	4.86 / 4.60	15.19 / 15.03	145-148	75
3	$C_8H_7N_3S$	54.01 / 54.22	3.73 / 3.98	23.50 / 23.71	258-260 (256 [9])	69
4a	$C_{15}H_{13}NO$	80.89 / 80.69	5.66 / 5.87	6.36 / 6.27	148-150 (151 [10])	62
4b	$C_{16}H_{15}NO$	80.74 / 80.98	6.51 / 6.37	5.74 / 5.90	107-110 (104 [11])	70
4c	$C_{15}H_{14}N_2O$	75.70 / 75.61	6.01 / 5.92	11.58 / 11.76	81-83	60
5a	$C_{17}H_{16}N_4OS$	63.22 / 62.94	4.73 / 4.97	17.05 / 17.27	265-270	59
5b	$C_{18}H_{18}N_4OS$	64.12 / 63.88	5.07 / 5.36	16.69 / 16.56	237-240	61
5c	$C_{19}H_{20}N_4O_2S$	61.82 / 61.94	5.66 / 5.47	15.43 / 15.21	248-250	55
5d	$C_{18}H_{17}ClN_4OS$	57.73 / 57.98	4.37 / 4.60	14.81 / 15.03	265-270	58

*Compounds **2a,c,e-i, 3, 4a-c** were recrystallized from ethanol; **2b,d, 5a-d** were recrystallized from benzonitrile.

Obviously, conversions of 2-aryl-5-R-5,6-dihydro-7H-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones **1a-f** to form compounds **3, 4a-c**, and **5a-d** occur through a step including formation of 3-propanamides **2a-i**, which when treated with bases or at high temperature apparently eliminate a proton, in this case forming carbanion **6**.

The latter probably is transformed to intermediate **7**, and the subsequent direction of the reaction depends on the presence or absence of a substituent in acrylamides **8**. When R_1 = Ar, the double bond of the 3-arylacrylamide is part of a conjugated system and so is inactive even at high temperatures, and the process stops in the step involving formation of triazolinethione **3** and 3-arylacrylamides **4**. As we know, in unsubstituted (R_1 = H) acrylamides the double bond is quite reactive, and it readily reacts with anion **7** and is converted to the product **5**.

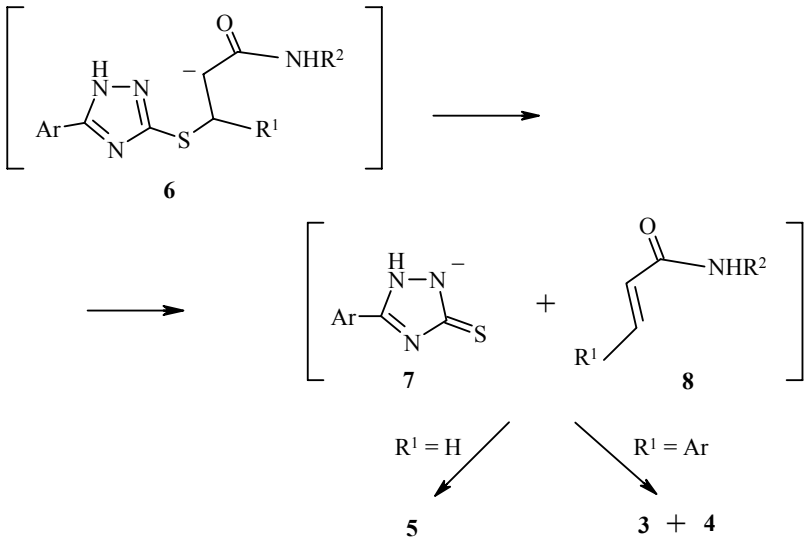

TABLE 2. ^{1}H NMR Spectra of Synthesized Compounds

Com-pound	Chemical shifts, δ, ppm (SSCC, *J*, Hz)
1	2
2a	3.2 (2H, m, H-2); 5.2 (1H, m, H-3); 7.0 (1H, m, H arom.); 7.3-7.6 (12H, m, H arom.); 8.0 (2H, m, H arom.); 10.0 (1H, s, CONH); 14.1 (1H, br. s, NH triazole)
2b	3.0 (2H, m, H-2); 4.1-4.2 (2H, m, NH$\underline{CH_2}$); 5.2 (1H, m, H-3); 6.9 (2H, m, H arom.); 7.2-7.7 (11H, m, H arom.); 8.0 (2H, m, H arom.); 8.5 (1H, br. s, CONH); 14.5 (1H, br. s, NH triazole)
2c	3.0 (2H, m, H-2); 4.1-4.3 (2H, m, NH$\underline{CH_2}$); 5.2 (1H, m, H-3); 7.1-7.6 (10H, m, H arom.); 8.0 (2H, m, H arom.); 8.3 (2H, m, H arom.); 8.5 (1H, br. s, CONH); 14.5 (1H, br. s, NH triazole)
2d	3.0 (2H, m, H-2); 3.7 (3H, s, CH_3O); 4.1-4.3 (2H, m, NH$\underline{CH_2}$); 5.1 (1H, m, H-3); 6.9 (4H, m, H arom.); 7.2 (3H, m, H arom.); 7.3 (2H, d, *J* = 8.1, H arom.); 7.4-7.5 (3H, m, H arom.); 8.0 (2H, m, H arom.); 8.4 (1H, br. s, CONH); 14.4 (1H, br. s, NH triazole)
2e	3.1 (2H, m, H-2); 4.1-4.3 (2H, m, NH$\underline{CH_2}$); 5.3 (1H, m, H-3); 6.9 (2H, m, H arom.); 7.2 (3H, m, H arom.); 7.3-7.7 (4H, m, H arom.); 8.0 (3H, m, H arom.); 8.1 (1H, d, *J* = 7.9, H arom.); 8.3 (1H, m, H arom.); 8.5 (1H, br. s, CONH); 14.3 (1H, br. s, NH triazole)
2g	2.7 (2H, t, *J* = 6.4, H-2); 3.5 (2H, t, *J* = 6.4, H-3); 4.3 (2H, d, *J* = 6.1, NH$\underline{CH_2}$); 7.3 (4H, m, H arom.); 7.5 (4H, m, H arom.); 8.0 (2H, m, H arom.); 8.4 (1H, t, *J* = 6.1, CO$\underline{NH}CH_2$); 14.3 (1H, br. s, NH triazole)
2h	2.6 (2H, t, *J* = 6.3, H-2); 3.5 (2H, t, *J* = 6.3, H-3); 3.8 (3H, s, CH_3O); 4.3 (2H, d, *J* = 6.2, NH$\underline{CH_2}$); 7.0 (2H, d, *J* = 8.2, H arom.); 7.3 (5H, m, H arom.); 7.9 (2H, d, *J* = 8.2, H arom.); 8.4 (1H, t, *J* = 6.2, CO$\underline{NH}CH_2$); 14.2 (1H, br. s, NH triazole)
2i	2.7 (2H, t, *J* = 6.4, H-2); 3.5 (2H, t, *J* = 6.4, H-3); 4.3 (2H, d, *J* = 6.1, NH$\underline{CH_2}$); 7.2 (5H, m, H arom.); 7.6 (2H, d, *J* = 7.9, H arom.); 8.0 (2H, d, *J* = 7.9, H arom.); 8.5 (1H, t, *J* = 6.1, CO$\underline{NH}CH_2$); 14.4 (1H, br. s, NH triazole)
4c	4.4 (2H, d, *J* = 6.0, NH$\underline{CH_2}$); 6.7 (1H, d, *J* = 12.5, H-3); 7.4-7.8 (8H, m, Ar); 8.4 (1H, d, *J* = 3.5, H-6 pyridine); 8.5 (1H, s, H-2 pyridine); 8.7 (1H, t, *J* = 6.0, CO$\underline{NH}CH_2$)

TABLE 2. (continued)

1	2
5a	2.9 (2H, t, *J* = 6.3, H-2); 4.4 (2H, t, *J* = 6.3, H-3); 7.0-7.3 (3H, m, H arom.); 7.4-7.7 (5H, m, H arom.); 7.88 (2H, m, H arom.); 10.1 (1H, s, CONH); 14.0 (1H, br. s, NH triazole)
5c	2.7 (2H, t, *J* = 6.3, H-2); 3.8 (3H, s, CH_3O); 4.3 (2H, d, *J* = 6.0, $NH\underline{CH_2}C_6H_5$); 4.3 (2H, t, *J* = 6.3, H-3); 7.1 (2H, d, *J* = 8.3, H arom.); 7.2 (5H, m, H arom.); 7.8 (2H, d, *J* = 8.3, H arom.); 8.5 (1H, t, *J* = 6.0, $CO\underline{NH}CH_2$); 13.9 (1H, br. s, NH triazole)
5d	2.7 (2H, t, *J* = 6.2, H-2); 4.3 (2H, d, *J* = 6.1, $NH\underline{CH_2}C_6H_5$); 4.3 (2H, t, *J* = 6.2, H-3); 7.1 (5H, H arom.); 7.6 (2H, d, *J* = 7.9, H arom.); 7.9 (2H, d, *J* = 7.9, H arom.); 8.5 (1H, t, *J* = 6.1, $CO\underline{NH}CH_2$); 14.0 (1H, br. s, NH triazole)

EXPERIMENTAL

The 1H NMR spectra were recorded on a Varian 300 (300 MHz) in DMSO-d_6, internal standard TMS. The IR spectra were taken on a UR-20 in KBr disks.

3-R-3-(5-Aryl-4H-1,2,4-triazol-3-ylsulfanyl)propanamides 2a-i. A solution of 10 mmol of 2-aryl-5-R-5,6-dihydro-7H-[1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-one **1a-f** and 12 mmol amine in 10 ml ethanol was boiled for 30 min under reflux and then cooled. The precipitate of propanamide **2a-i** was filtered out, washed with cold ethanol, dried, and recrystallized from an appropriate solvent. The yields and melting points for propanamides **2a-i** are presented in Table 1.

Aminolysis of compounds 1a and 2a-c. A solution of 5 mmol triazolothiazine **1a** or propanamide **2a-c** in 7 ml of the appropriate amine was boiled for 30 min under reflux and then the excess amine was driven off under vacuum. The reaction mass was extracted with hot ethanol (2 × 5 ml) and then triazolinethione **3** was filtered out. Then the filtrate was evaporated down to a volume of 3 ml and cooled. The precipitated 3-arylacrylamide **4a-c** was filtered out and dried.

3-(3-Aryl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)propanamides 5a-d. A solution of 5 mmol triazolothiazinone **1d-f** or propanamide **2f-i** in 5 ml aniline (benzylamine) was boiled under reflux for 2 h. The reaction mass was cooled and 10 ml ether was added. The precipitated propanamide **5a-d** was filtered out and dried.

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