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SYNTHESIS OF 2-ARYL-5H-[1,3,4]-THIADIAZOLO[2,3-*b*]QUINAZOLIN-5-ONES

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3-Amino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-ones were converted into 2-aryl-5H-[1,3,4]thiadiazolo[2,3-b]quinazolin-5-ones on treatment with carboxylic acids and $POCl_3$. 3-Arylmethylidenamino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-ones also cyclized to 2-aryl-5H-[1,3,4]thiadiazolo[2,3-b]quinazolin-5-ones when oxidized with potassium chlorate in acetic acid, but on heating they were deaminated to give 2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one and aryl nitriles.

Keywords: 3-amino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one, 3-arylmethylidenamino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-ones, aryl nitriles, 2-aryl-5H-[1,3,4]thiadiazolo[2,3-*b*]quinazolin-5-ones, 2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one, potassium chlorate, deamination, cyclization.

3-Amino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one (**1**) contains two reactive centers – thioxo and amino groups – and can be used for the synthesis of condensed heterocycles [1-5], including some with antihypertonic, antibacterial, and fungicidal properties [4, 5]. Hence it is a timely synthetic problem to prepare new heterocycles containing the quinazolin-4-one unit.

The aim of the present study was the synthesis of 2-aryl-5H-[1,3,4]thiadiazolo[2,3-*b*]quinazolin-5-ones, which, using the general methods for the synthesis of condensed systems containing 1,3,4-thiadiazole [6], may be obtained by the condensation of compound **1** with carboxylic acids in the presence of dehydrating agents, and also by the oxidative cyclization of 3-arylmethylidenamino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-ones.

We have established that 2-aryl-5H-[1,3,4]thiadiazolo[2,3-*b*]quinazolin-5-ones **3a-e** are formed when compound **1** was heated with aromatic carboxylic acids **2a-e** in $POCl_3$ for 2 h. The yields of **3a-e** were 66-73%.

In the ^{1}H NMR spectra of compounds **3a-e** there are characteristic signals of the protons of the quinazoline and aromatic rings (7.11-8.41 ppm), while absorption bands for the C=O and C=N groups (1690-1710 and 1580-1610 cm^{-1} respectively) were observed in their IR spectra.

3-Arylmethylidenamino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-ones **5a-d** were obtained in 67-79% yields by the reaction of compound **1** with the aromatic aldehydes **4a-d** in acetic acid. The characteristic signals of the protons of the azomethine (N=CH) and thioamide groups (NH–C=S) at 8.51- 8.91 and 13.00-13.21 ppm respectively were observed in the ^{1}H NMR spectra of the azomethine **5a-d**.

In attempting to carry out the oxidative cyclization of the azomethines **5a**,**b**,**d** into the [1,3,4]thiadiazolo[2,3-*b*]quinazolin-5-ones **3** by heating in nitrobenzene (as was suggested for the preparation of [1,2,4]thiazolo[3,4-*b*][1,3,4]thiadiazole from 5-thioxo-4-phenylmethylidenamino-4H-1,2,4-thiazole [7]), we established that cyclization did not occur under these conditions but instead the azomethines **5a**,**b**,**d** underwent deamination to give 2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one **6** and the aryl nitriles **7a-c**. The same conversion occurred on heating azomethines **5a**,**b**,**d** at 200°C without a solvent.

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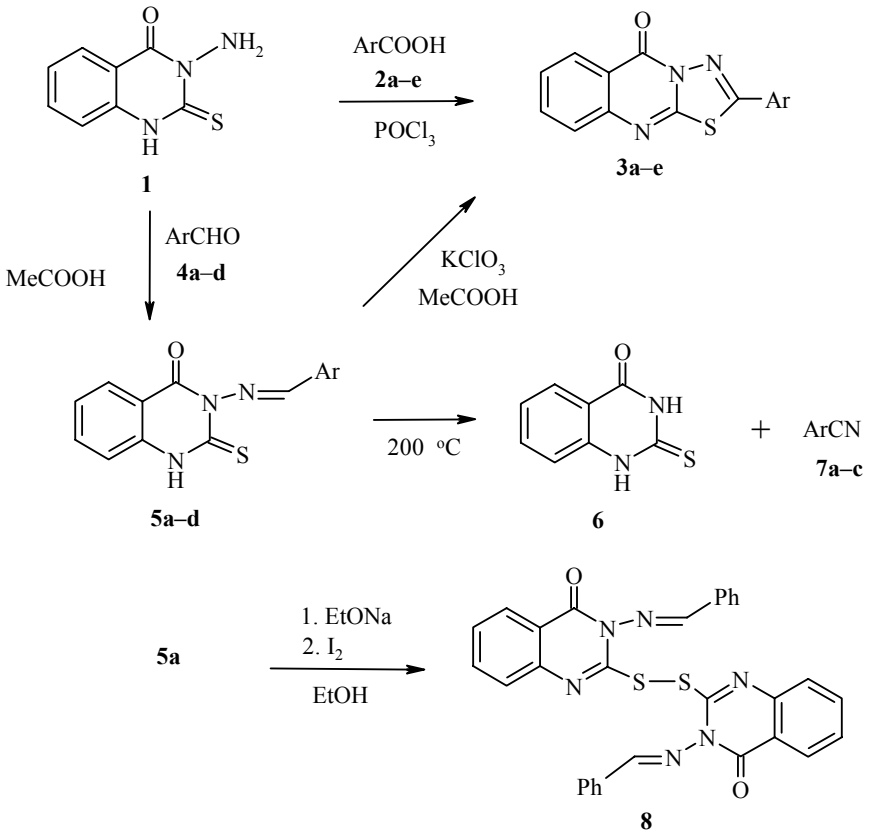

2-7 a Ar = Ph, **b** Ar = 4-$MeOC_6H_4$; **2c**–**5c** Ar = 3,4-$(MeO)_2C_6H_3$; **2d**, **3d** Ar = 4- $O_2NC_6H_4$; **4d**, **5d**, **7c** Ar = 3-$O_2NC_6H_4$; **2e**, **3e** Ar = 3-thienyl

In all probability, the deamination of the azomethines **5a**,**b**,**d** is explained by the fact that the electron density of atom $N_{(3)}$ of the 1,3-diazine ring of the azomethines **5a-d** is partly shifted towards the C=O and C=S acceptor groups and this, in turn, makes the $N_{(3)}$–N bond unstable and makes possible its easy rupture at high temperatures.

In an attempt to oxidatively cyclize azomethine **5a** it was found that di(3-phenylmethylidenamino-3,4-dihydro-4-oxoquinazolin-2-yl) disulfide **8** was formed from its reaction with iodine in the presence of sodium ethoxide.

We have developed a new method for the oxidative cyclization of the azomethines **5** into [1,3,4]thiadiazolo[2,3-b]quinazolin-5-ones **3** by reacting the azomethines **5** with potassium chlorate in boiling acetic acid. However the reaction works only with the azomethines **5b,c** which contain donor substituents in the phenyl ring, and the yields of compounds **3b,c** were only 32-38% as a result of side reactions. It is very likely that this reaction has a free radical mechanism as in the case of the oxidative cyclization of 1-(R-methylidenamino)-2-amino(hydroxy)benzenes into 2-R-benzimidazole (2-R-benzoxazole) with lead tetraacetate [8,9] and copper(II) acetate [10] in acetic acid.

So we have developed two methods for the synthesis of 2-aryl-5H-[1,3,4]thiadiazolo[2,3-*b*]quinazolin-5-ones, one of which (heating 3-amino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one with aromatic carboxylic acids in $POCl_3$) has preparative value.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a*	$C_{15}H_9N_3OS$	64.72 / 64.50	3.41 / 3.25	15.29 / 15.04	227-230	73
3b	$C_{16}H_{11}N_3O_2S$	61.85 / 62.12	3.81 / 3.58	13.33 / 13.58	225-227	68
3c	$C_{17}H_{13}N_3O_3S$	59.89 / 60.17	4.02 / 3.86	12.60 / 12.38	262-265	69
3d	$C_{15}H_8N_4O_3S$	55.82 / 55.55	2.20 / 2.49	17.01 / 17.28	308-310	70
3e	$C_{13}H_7N_3OS_2$	55.01 / 54.72	2.24 / 2.47	14.97 / 14.73	262-264	66
5a	$C_{15}H_{11}N_3OS$	63.82 / 64.04	4.21 / 3.94	15.17 / 14.94	272-274	75
5b	$C_{16}H_{13}N_3O_2S$	62.00 / 61.72	4.04 / 4.21	13.22 / 13.50	282-284	73
5c	$C_{17}H_{15}N_3O_3S$	60.07 / 59.81	4.19 / 4.43	12.52 / 12.31	278-280	67
5d	$C_{15}H_{10}N_4O_3S$	55.50 / 55.21	2.80 / 3.09	16.92 / 17.17	273-275	79
6	$C_8H_6N_2OS$	54.15 / 53.92	3.20 / 3.39	16.00 / 15.72	299-302 (304-305 [11])	64
7a	C_7H_5N	81.76 / 81.53	5.16 / 4.89	13.40 / 13.58	—*[2]	59
7b	C_8H_7NO	71.96 / 72.17	5.42 / 5.30	10.35 / 10.52	53-55 (57-59 [13])	52
7c	$C_7H_4N_2O_2$	56.48 / 56.76	3.01 / 2.72	19.20 / 18.91	112-115 (115-117 [14]) 111-117	49
8	$C_{30}H_{20}N_6O_2S_2$	63.98 / 64.27	3.50 / 3.60	15.21 / 14.99	299-301	69

* Found, %: S 11.22. Calculated %: S 11.48.

*[2] Bp 185-188°C (760 mmHg); bp 191°C [12].

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

Compound	IR spectrum, ν, cm^{-1}	^{1}H NMR, δ, ppm (*J*, Hz)
1	2	3
3a	3100, 1700 (C=O), 1590 (C=N), 1565, 1555, 1505, 1475	7.54 (2H, m, H_{Ar}); 7.64 (3H, m, H_{Ar}); 7.87 (1H, m, H_{Ar}); 8.00 (2H, m, H_{Ar}); 8.29 (1H, d, *J* = 7.5, H_{Ar})
3b	3000, 1700 (C=O), 1610 (C=N), 1580, 1550, 1505, 1460	3.84 (3H, s, CH_3O); 7.11 (2H, d, *J* = 8.1, *p*-C_6H_4); 7.53 (1H, m, H_{Ar}); 7.65 (1H, d, *J* = 8.4, H_{Ar}); 7.88 (3H, m, H_{Ar}); 8.25 (1H, d, *J* = 8.4, H_{Ar})
3c	3100, 3000, 1690 (C=O), 1600 (C=N), 1580, 1560, 1520, 1470	3.86 (3H, s, CH_3O); 3.90 (3H, s, CH_3O); 7.14 (1H, d, *J* = 7.8, H_{Ar}); 7.46-7.57 (3H, m, H_{Ar}); 7.67 (1H, d, *J* = 7.8, H_{Ar}); 7.88 (1H, m, H_{Ar}); 8.26 (1H, d, *J* = 8.7, H_{Ar})
3d	3100, 1710 (C=O), 1600 (C=N), 1580, 1560, 1470, 1410	7.58 (1H, m, H_{Ar}); 7.70 (1H, d, *J* = 7.8, H_{Ar}); 7.91 (1H, m, H_{Ar}); 8.25-8.31 (3H, m, H_{Ar}); 8.41 (2H, d, *J* = 8.7, *p*-C_6H_4)
3e	3100, 1700 (C=O), 1610 (C=N), 1580, 1560, 1505, 1465	7.31 (1H, d. d, J_1 = 5.1, J_2 = 2.8, H_{Het}-4); 7.55 (1H, m, H_{Ar}); 7.68 (1H, d, *J* = 7.8, H_{Ar}); 7.86-7.93 (2H, m, H_{Ar}); 8.03 (1H, d, *J* = 5.1, H_{Het}-3); 8.27 (1H, d, *J* = 8.4, H_{Ar})

TABLE 2 (continued)

1	2	3
5a	3250, 1680 (C=O), 1620 (C=N), 1540, 1490, 1410	7.32-7.40 (2H, m, H_{Ar}); 7.59 (3H, m, H_{Ar}); 7.74 (1H, m, H_{Ar}); 7.95-8.01 (4H, m, H_{Ar}); 8.67 (1H, s, N=CH); 13.09 (1H, s, NH)
5b	3250, 3000, 1660 (C=O), 1630 (C=N), 1610, 1570, 1540, 1490	3.87 (3H, s, CH_3O); 7.12 (2H, d, J = 8.5, *p*-C_6H_4); 7.36 (1H, m, H_{Ar}); 7.44 (1H, d, J = 8.1, H_{Ar}); 7.76 (1H, m, H_{Ar}); 7.88 (2H, d, J = 8.5, *p*-C_6H_4); 8.01 (1H, d, J = 8.1, H_{Ar}); 8.53 (1H, s, N=CH); 13.00 (1H, s, NH)
5c	3200, 3000, 1710 (C=O), 1620 (C=N), 1600, 1580, 1540, 1520	3.85 (3H, s, CH_3O); 3.87 (3H, s, CH_3O); 7.14 (1H, d, J = 8.4, H_{Ar}); 7.37 (1H, m, H_{Ar}); 7.45 (2H, m, H_{Ar}); 7.55 (1H, d, J = 1.2, H_{Ar}); 7.78 (1H, m, H_{Ar}); 8.00 (1H, d, J = 7.2, H_{Ar}); 8.51 (1H, s, N=CH); 13.08 (1H, s, NH)
5d	3200, 3100, 3000, 1690 (C=O), 1620 (C=N), 1540, 1490	7.39 (1H, m, H_{Ar}); 7.47 (1H, d, J = 8.4, H_{Ar}); 7.81 (1H, m, H_{Ar}); 7.90 (1H, m, H_{Ar}); 8.02 (1H, d, J = 7.5, H_{Ar}); 8.39 (1H, d, J = 7.8, H_{Ar}); 8.50 (1H, d, J = 8.4, H_{Ar}); 8.76 (1H, c, H_{Ar}); 8.91 (1H, s, N=CH); 13.21 (1H, s, NH)
8	3100, 1680 (C=O), 1600 (C=N), 1580, 1550, 1470	7.52-7.70 (4H, m, H_{Ar}); 8.02 (2H, m, H_{Ar}); 8.15 (2H, d, J = 7.5, H_{Ar}); 9.68 (2H, s, N=CH)

EXPERIMENTAL

^{1}H NMR spectra were recorded with a Varian 300 (300 MHz) in DMSO-d_6 with TMS as internal standard. IR spectra of KBr disks were recorded on a UR-20 machine. The physico-chemical and spectroscopic characteristics of the compounds synthesized are cited in Tables 1 and 2.

Synthesis of 2-Aryl-5H-[1,3,4]thiadiazolo[2,3-*b*]quinazolin-5-ones 3a-e. A. A solution of the acids **2a-e** (2.1 mmol) and 3-amino-2-thioxo-1,2,3,4-tetrahydroquinazoline-4-one (0.386 g, 2 mmol) in $POCl_3$ (2.30 g, 15 mmol) was refluxed for 2h. The mixture was cooled, poured into cold water (10 ml), the products **3a-e** were filtered off, washed with 5% NaOH solution (5 ml), water (10 ml), dried and recrystallized from acetic acid.

B. A solution of azomethine **5b,c** (10 mmol) and potassium chlorate (0.49 g, 4 mmol) in acetic acid (10 ml) was boiled for 30 min, cooled, and diluted with water (30 ml). The precipitate of **3b,c** was filtered off, dried, and recrystallized from acetic acid. Yields: **3b** 38%, **3c** 32%.

Synthesis of 3-Arylmethylidenamino-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-ones 5a-d. A solution of an aldehyde **4a-d** (10 mmol) and compound **1** (10 mmol) in acetic acid (15 ml) was boiled for 7 h, then cooled and the azomethine **5a-d** was filtered off, washed with diethyl ether (2 x 5 ml), and dried.

Deamination of Compounds 5a,b,d. The azomethines **5a,b,d** (10 mmol) were heated at 200°C for 30 min, then cooled and treated with diethyl ether (10 ml). The precipitate of 2-thioxo-1,2,3,4-tetrahydroquinazolin-4-one **6** was filtered off and dried. The ether solution was evaporated and compound **7a** was purified by distillation while compounds **7b,c** were recrystallized from 2-propanol.

Synthesis of Di(3-phenylmethylidenamino-3,4-dihydro-4-oxoquinazolin-2-yl) Disulfide (8). A solution of iodine (0,635 g, 2.5 mmol) in ethanol (10 ml) was added drop-wise to a solution of azomethine **5a** (1.405 g, 5 mmol) and sodium ethoxide (5 mmol) in anhydrous ethanol (10 ml). The precipitate of compound **8** was filtered off, dried and recrystallized from benzonitrile.

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