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SYNTHESIS OF 4-ARYLHYDRAZONO-3-ARYLTHIOMETHYL-4,5-DIHYDRO-1H-1-R-5-PYRAZOLONES

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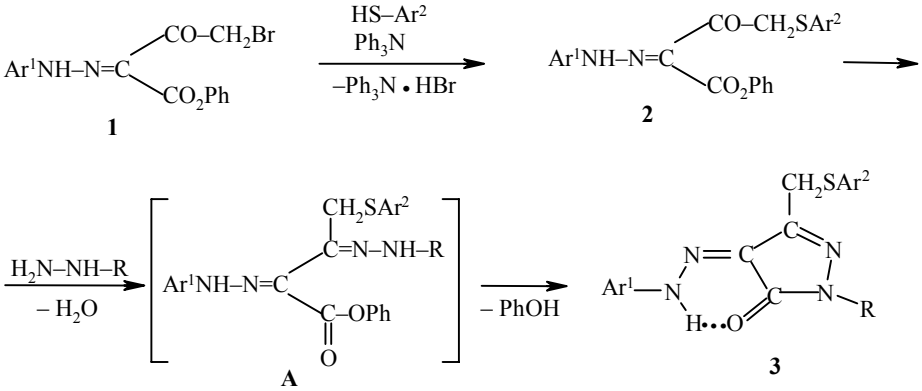
It has been established that interacting ethyl 2-arylhydrazono-4-arylthio-3-oxobutyrates with hydrazine, methylhydrazine, and phenylhydrazine forms 4-arylhydrazono-3-arylthiomethyl-4,5-dihydro-1H-1-R-pyrazolones.

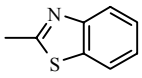
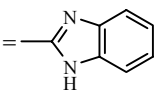
Keywords: 4-arylhydrazono-3-arylthiomethyl-4,5-dihydro-1H-1-R-5-pyrazolones, hydrazine, ethyl 2-arylhydrazono-4-arylthio-3-oxobutyrates, ethyl 2-arylhydrazono-4-bromo-3-oxobutyrates.

The interaction of β-keto esters with hydrazine is the classic method of synthesizing functionalized pyrazolones [1]. Ethyl 2-arylhydrazono-3-oxobutyrate also reacts with hydrazine and its derivatives with the formation of 4-arylhydrazono-3-methyl-5-pyrazolones which possess antimicrobial and fungicidal activity [2,3], and also may be used as dyestuffs [4]. But the use of ethyl 2-arylhydrazono-3-oxobutyrate does not permit the synthesis of 5-pyrazolones modified in position 3 of the pyrazolone ring.

Previously we proposed a convenient method for the synthesis of esters of 2-arylhydrazono-4-bromo-3-oxobutyric acid and showed that they are highly reactive compounds and may be used for the synthesis of nitrogen-containing heterocycles [5-8].



1a–c, **2a–c**, **3a–e** Ar^1 = Ph; **2d**, **3f** Ar^1 = *p*-$MeOC_6H_4$; **2e**, **3g** Ar^1 = *p*-$NO_2C_6H_4$;

2a,**d**,**e**, **3a–c**,**f**,**g** Ar^2 = Ph; **2b**, **3d** Ar^2 =  ; **2c**, **3e** Ar^2 =  ;

3 a R = H, **b** R = Me, **c**, **d**, **e**, **f**, **g** R = Ph

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While continuing these investigations we established that esters of 2-arylhydrazono-4-arylthio-3-oxobutyric acid **2a-e**, synthesized by the interaction of esters of 2-arylhydrazono-4-bromo-3-oxobutyric acid **1a-c** with thiophenol, 2-mercaptobenzothiazole, and 2-mercaptobenzimidazole, are converted by the action of hydrazine and its derivatives (methylhydrazine and phenylhydrazine) in acetic acid into 4-arylhydrazono-3-arylthiomethyl-4,5-dihydro-1H-1-R-5-pyrazolones **3a-g**.

The yields, ^{1}H NMR and IR spectra, data of elemental analysis, and molecular ion peaks $[M]^+$ of the compounds synthesized are given in Tables 1 and 2. In the ^{1}H NMR spectra of thioethers **2a-e** the signals of the CO–CH_2S and NH groups (4.33-4.82 and 11.87-12.16 ppm respectively) are characteristic. In the IR spectra there are absorption bands for the carbonyl group (1610-1710) and the NH group (3000-3100 cm^{-1}). In the ^{1}H NMR spectra of pyrazolones **3a-g** signals were observed for the CH_2S group (4.16-4.74 ppm) and in the IR spectra there were absorption bands for the C=O (1660-1670) and NH (3000-3200 cm^{-1}) groups.

The yields of the heterocyclization products **3a-g** were 40-67%. In our view, the formation of pyrazolones **3a-g** from thioethers **2a-e** proceeds through the intermediate hydrazones **A** [1].

It is known that due to sp^2-hybridization of the imine nitrogen atom and restriction of rotation about the =C–C= bond, the hydrazones of dicarbonyl compounds may exist in *syn* and *anti* forms, each of which may be found in *s-cis* and *s-trans* conformations [9]. But the formation of only one conformation may be asserted for the synthesized compounds from the data of ^{1}H NMR spectroscopy. Consequently there is a basis for supposing that compounds **3a-g** are formed in the *syn-s-cis* form, which is the most stable since it is stabilized by an intramolecular hydrogen bond N–H···O=C [9,10]. Indirect confirmation of the formation of a hydrogen bond is the small reduction of the frequency of the carbonyl group absorption in the IR spectra of compounds **3a-g** in comparison with the initial thioethers **2a-e** (by 10-40 cm^{-1}), and in the ^{1}H NMR spectra of compounds **3a-g** compared with **2a-e** a reduction is observed in the chemical shift of the hydrazone fragment proton of 0.57-0.80 ppm towards low field, which is in agreement with the data of [11,12].

TABLE 1. Characteristics of Compounds **2a-e**, **3a-g**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	$[M]^+$
		C	H	N			
2a	$C_{18}H_{18}N_2O_3S$	63.34 / 63.16	5.11 / 5.26	8.41 / 8.19	97-99	47	342
2b	$C_{19}H_{17}N_3O_3S_2$	57.37 / 57.14	4.41 / 4.26	10.48 / 10.53	112-114	59	399
2c	$C_{19}H_{18}N_4O_3S$	59.35 / 59.69	4.50 / 4.71	14.34 / 14.66	119-121	61	382
2d	$C_{19}H_{20}N_2O_4S$	61.35 / 61.29	5.51 / 5.38	7.30 / 7.53	69-70	69	372
2e	$C_{18}H_{17}N_3O_5S$	55.69 / 55.81	4.22 / 4.39	10.56 / 10.85	117-119	55	387
3a	$C_{16}H_{14}N_4OS$	61.60 / 61.94	4.63 / 4.52	18.31 / 18.06	133-134	44	310
3b	$C_{17}H_{16}N_4OS$	62.71 / 62.96	4.78 / 4.94	17.42 / 17.28	131-132	61	324
3c	$C_{22}H_{18}N_4OS$	68.17 / 68.39	4.39 / 4.66	14.41 / 14.51	126-127	50	386
3d	$C_{23}H_{17}N_5OS_2$	62.51 / 62.30	3.79 / 3.84	15.57 / 15.80	173-175	42	443
3e	$C_{22}H_{18}N_6OS$	65.01 / 64.79	4.13 / 4.23	19.48 / 19.72	219-221	40	426
3f	$C_{23}H_{20}N_4O_2S$	66.55 / 66.35	4.69 / 4.80	13.55 / 13.46	121-123	41	416
3g	$C_{22}H_{17}N_5O_3S$	61.35 / 61.25	3.79 / 3.94	16.45 / 16.24	152-153	67	431

TABLE 2. Spectral Characteristics of Compounds **2a-e**, **3a-g**

Com-pound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)
2a	3000 (NH), 1700 (C=O), 1630, 1600, 1520, 1470	1.28 (3H, t, *J* = 7.5, $\underline{CH_3}CH_2O$); 4.30 (2H, q, *J* = 7.5, $CH_3\underline{CH_2}O$); 4.35 (2H, s, CO–CH_2–S); 7.08-7.42 (10H, m, $2C_6H_5$); 11.95 (1H, s, –NH–N=)
2b	3000 (NH), 1710 (C=O), 1600, 1530, 1470, 1430	1.30 (3H, t, *J* = 7.8, $\underline{CH_3}CH_2O$); 4.29 (2H, q, *J* = 7.8, $CH_3\underline{CH_2}O$); 4.95 (2H, s, CO–CH_2–S); 7.16-7.56 (7H, m, Ar); 7.80 (1H, s, Ar); 8.02 (1H, s, Ar); 12.16 (1H, s, –NH–N=)
2c	3100 (NH), 1670 (C=O), 1600, 1530, 1480, 1400, 1350	1.28 (3H, t, *J* = 7.2, $\underline{CH_3}CH_2O$); 4.30 (2H, q, *J* = 7.2, $CH_3\underline{CH_2}O$); 4.82 (2H, s, CO–CH_2–S); 7.13 (3H, m, Ar); 7.41-7.56 (6H, m, Ar); 12.05 (1H, s, –NH–N=); 12.52 (1H, br. s, NH)
2d	3000 (NH), 1700 (C=O), 1600, 1530, 1480, 1400	1.25 (3H, t, *J* = 7.7, $\underline{CH_3}CH_2O$); 3.79 (3H, s, CH_3O); 4.26 (2H, q, *J* = 7.7, $CH_3\underline{CH_2}O$); 4.33 (2H, s, CO–CH_2–S); 6.97 (2H, d, *J* = 9.1, *p*-C_6H_4); 7.23-7.55 (7H, m, Ar); 12.16 (1H, s, –NH–N=)
2e	3000 (NH), 1700 (C=O), 1600, 1540, 1400, 1350	1.26 (3H, t, *J* = 7.8, $\underline{CH_3}CH_2O$); 4.33 (2H, q, *J* = 7.8, $CH_3\underline{CH_2}O$); 4.41 (2H, s, CO–CH_2–S); 7.20-7.39 (5H, m, C_6H_5); 7.61 (2H, d, *J* = 8.9, *p*-O_2N–C_6H_4); 8.24 (2H, d, *J* = 8.9, *p*-O_2N–C_6H_4); 11.87 (1H, s, –NH–N=)
3a	3100 (NH), 1670 (C=O), 1600, 1550, 1490, 1400	4.16 (2H, s, CH_2–S); 7.21-7.46 (10H, m, $2C_6H_5$); 7.49 (1H, s, CO–NH); 12.44 (1H, br. s, –NH–N=)
3b	3200 (NH), 3050, 1670 (C=O), 1580, 1500,1450	3.28 (3H, s, CH_3); 4.18 (2H, s, CH_2–S); 7.30-7.51 (10H, m, $2C_6H_5$); 12.68 (1H, br. s, –NH–N=)
3c	3100 (NH), 1670 (C=O), 1600, 1560, 1500, 1360	4.29 (2H, s, CH_2–S); 7.16-7.85 (15H, m, $3C_6H_5$); 13.32 (1H, br. s, –NH–N=)
3d	3100 (NH), 1670 (C=O), 1600, 1570, 1500, 1440	4.82 (2H, s, CH_2–S); 7.11-7.35 (4H, m, Ar); 7.40-7.53 (6H, m, Ar); 7.89-8.03 (4H, m, Ar); 13.11 (1H, br. s, –NH–N=)
3e	3050, 1670 (C=O), 1600, 1560, 1500, 1450, 1410	4.74 (2H, s, CH_2–S); 7.16 (6H, m, Ar); 7.45 (6H, m, Ar); 7.86 (2H, d, *J* = 9.1, Ar); 12.03 (1H, br. s, –NH–); 13.19 (1H, br. s, –NH–N=)
3f	3000 (NH), 1660 (C=O), 1600, 1570, 1500, 1450	3.78 (3H, s, CH_3O); 4.28 (2H, s, CH_2–S); 7.03 (2H, d, *J* = 9.6, *p*-C_6H_4); 7.14-7.51 (10H, m, $2C_6H_5$); 7.86 (2H, d, *J* = 9.6, *p*-C_6H_4); 13.18 (1H, br. s, –NH–N=)
3g	3100 (NH), 1670 (C=O), 1600, 1560, 1500, 1350	4.30 (2H, s, CH_2–S); 7.24-7.78 (12H, m, Ar); 8.24 (2H, d, *J* = 9.9, *p*-O_2N–C_6H_4); 13.17 (1H, br. s, –NH–N=)

The given method of synthesis therefore enables the preparation of previously unknown 4-arylhydrazono-4,5-dihydro-1H-1-R-5-pyrazolones containing an arylthiomethyl or hetarylthiomethyl fragment in position 3 of the pyrazolone ring.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Varian-300 (300 MHz) instrument, internal standard was TMS. The IR spectra were recorded on a Specord IR-75 instrument in KBr disks. The mass spectra were taken on a MX-1303 instrument.

Ethyl 2-Arylhydrazono-4-bromo-3-oxobutyrates (1a-c) were synthesized by the procedure of [5].

Ethyl 2-Arylhydrazono-4-arylthio-3-oxobutyrates (2a-e). A solution of thiophenol (10 mmol) and triethylamine (10 mmol) in benzene (50 ml) was added with stirring to a solution of ethyl 2-arylhydrazono-4-bromo-3-oxobutyrate (10 mmol) in benzene (40 ml). The reaction mixture was stirred at 20°C for 30 min, at 50°C for 10 min, and cooled. Triethylamine hydrochloride was filtered off, and the filtrate evaporated to dryness. The residue was recrystallized from alcohol.

4-Arylhydrazono-3-arylthiomethyl-4,5-dihydro-1H-1-R-5-pyrazolones (3a-g). A solution of hydrazine (or methylhydrazine, phenylhydrazine) (10 mmol) in acetic acid (30 ml) was added dropwise with stirring to a solution of 2-arylhydrazono-4-arylthio-3-oxobutyric acid ethyl ester (10 mmol) in acetic acid (30 ml). The reaction mixture was boiled for 8 h, cooled to room temperature, the precipitated solid was filtered off, washed with acetic acid (2 × 10 ml), and recrystallized from acetic acid.

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