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CYCLOACYLATION OF 3-OXO-3-R^1-N-R^2-PROPANETHIOAMIDES BY 3-ARYL-2-PROPENOYL CHLORIDES

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The products of cyclocondensation of 3-oxo-3-R^1-N-R^2-propanethioamides with 3-aryl-2-propenoyl chlorides in acetone in the presence of potassium carbonate are 5-acyl-1-aryl(alkyl)-4-aryl-6-thioxopiperidin-2-ones, 5-acyl-2-aryl-6-aryl(alkyl)amino-2,3-dihydro-4H-thiopyran-4-ones, and 2-acetonylidene-3,6-diaryl-5,6-dihydro-4H-1,3-thiazin-4-ones, the structure of which is proven by both spectral methods and chemical conversions.

Keywords: 3-aryl-2-propenoyl chlorides, aryl bromomethyl ketones, 5,6-dihydro-4H-1,3-thiazin-4-ones, 2,3-dihydro-4H-thiopyran-4-ones, 3-oxopropanethioamides, cycloacylation.

Earlier we developed a general method for obtaining condensed heterocycles containing a 1,3-triazine ring, based on the reaction of nitrogen-containing thiones with 3-aryl-2-propenoyl chlorides in pyridine [1-4]. In this work, we have studied the reaction of 3-oxo-3-R^1-N-R^2-propanethioamides **1a-c** with 3-aryl-2-propenoyl chlorides **2a-c**. Since 3-oxo-3-R^1-N-R^2-propanethioamides **1a-c** have several reaction centers [5, 6], the products of this reaction can be 3,4-dihydro-2H-pyran-2-ones, 4H-pyran-4-ones, 4H-1,3-thiazin-4-ones, 6H-1,3-thiazin-6-ones, 4H-thiopyran-4-ones, 2H-thiopyran-2-ones, 4H-piperidin-4-ones, and 6-thioxopiperidin-2-ones, which complicates isolation and identification of the compounds formed.

The optimal conditions for carrying out the reaction involve stirring a solution of 3-oxo-3-R^1-N-R^2-propanethioamides **1a-c** and 3-aryl-2-propenoyl chlorides **2a-c** in acetone in the presence of K_2CO_3 at 20-50°C for 2.5 h. The products of each reaction, according to TLC and ^{1}H NMR spectroscopy, are a mixture of two compounds which have the same elemental composition and were separated by treatment of the reaction mixture with a 5% aqueous NaOH solution. Detailed analysis of the ^{1}H NMR, ^{13}C NMR, and IR spectra of the reaction products, and also comparison of this information with the spectral data for 4H-thiopyran-4-ones and 4H-piperidin-4-ones given in [7], showed that as a result of the reaction, 4-aryl-1-aryl(alkyl)-5-acyl-6-thioxopiperidin-2-ones **3a-d**, 2-aryl-6-aryl(alkyl)amino-5-acyl-2,3-dihydro-4H-thiopyran-4-ones **4a-d**, and 2-acetonylidene-6-(4-nitrophenyl)-3-phenyl-5,6-dihydro-4H-1,3-thiazin-4-one (**5**) were formed.

The type of heterocycles, their ratio and yield depend on the nature of the substituents R^1, R^2, and Ar^1 in the starting 3-oxo-3-R^1-N-R^2-propanethioamides **1a-c** and 3-aryl-2-propenoyl chlorides **2a-c**. Acylation of 3-oxo-N-phenylbutanethioamide **1a** by 3-phenyl-2-propenoyl chloride (**2a**) and 3-(4-chlorophenyl)-2-propenoyl chloride (**2b**) leads to formation of 6-thioxopiperidin-2-ones **3a,b** and 4H-thiopyran-4-ones **4a,b** in 1:1 ratio, the products of condensation of thioamide **1a** with 3-(4-nitrophenyl)-2-propenoyl chloride **2c** are 6-thioxopiperidin-2-one **3c** and 4H-1,3-thiazin-4-one **5**, also in an equimolar ratio.

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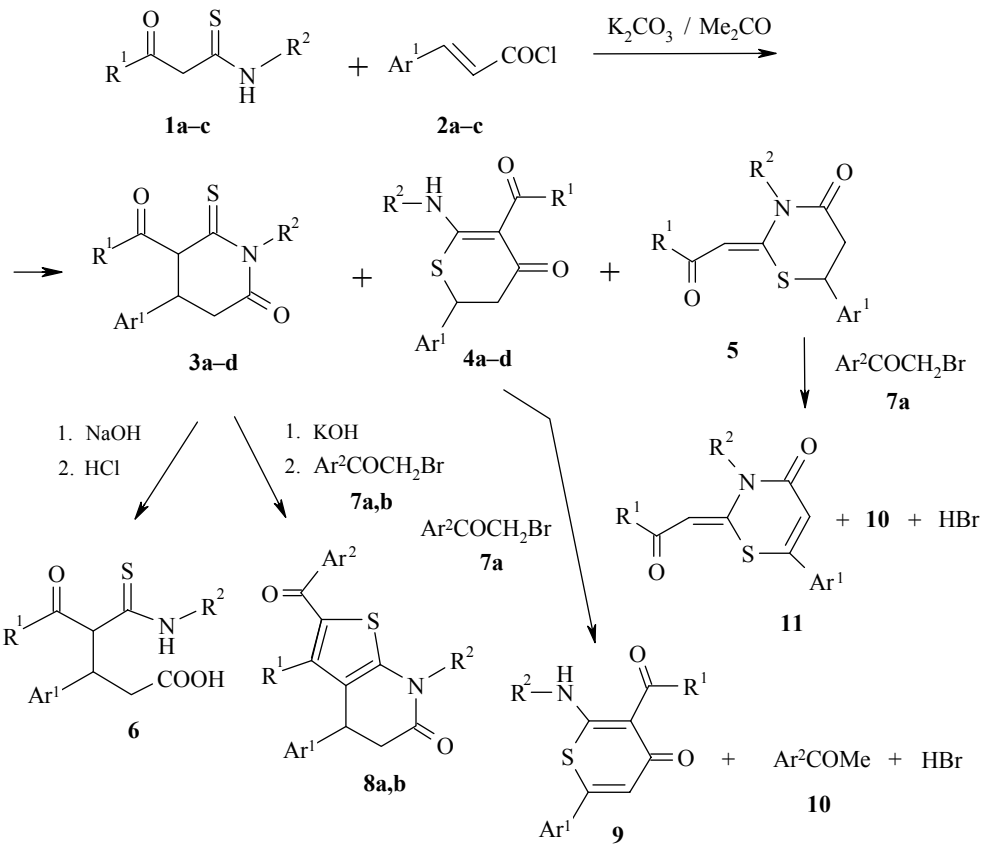

1a, **3a-c**, **4a**,**b**, **5**, **8a**,**b**, **9**, **11** R^1 = Me; **1b**,**c**, **3d**, **4c**,**d**, **6** R^1 = Ph; **1a**,**c**, **3a-c**, **4a**,**b**,**d**, **5**, **8a**,**b**, **9-11** R^2 = Ph; **1b**, **3d**, **4c**, **6** R^2 = Me; **2a**, **3a**,**d**, **4a**,**c**,**d**, **6**, **8a**, **9** Ar^1 = Ph; **2b – 4b** Ar^1 = *p*-ClC_6H_4; **2c**, **3c**, **5**, **8b**, **11** Ar^1 = *p*-$O_2NC_6H_4$; **7b**, **8a** Ar^2 = *p*-FC_6H_4; **7a**, **8b**, **10** Ar^2 = Ph

In reaction of compound **2a** with 3-oxo-3-phenyl-N-methylpropanethioamide (**1b**), we obtain 6-thioxopiperidin-2-one **3d** and 4H-thiopyran-4-one **4c** in 1.8:1 ratio, and when **2a** reacts with 3-oxo-3-N-diphenylpropanethioamide (**1c**), only 4H-thiopyran-4-one **4d** is formed. We should note that the amide bond of 6-thioxopiperidin-2-ones **3a-d** (for the example of compound **3d**) in an aqueous NaOH solution is readily hydrolyzed at elevated temperature. In this case, the sodium salt of the corresponding carboxylic acid is formed, from which by treatment with HCl we isolated 4-benzoyl-5-methylamino-5-thioxo-3-phenylpentanoic acid (**6**) in pure form (Tables 1 and 2).

In the ^{1}H NMR spectra, characteristic features are signals from protons of the OH(SH) groups of 6-thioxopiperidin-2-ones **3a-d** (δ 15.79-16.14 ppm), the protons of the NH groups of 4H-thiopyran-4-ones **4a-d** (δ 12.1-14.26 ppm), the proton of the O=C–CH= group of 1,3-thiazin-4-one **5** (δ 5.38 ppm). Characteristic features of the IR spectra are absorption bands for the carbonyl group O=C–N of 6-thioxopiperidin-2-ones **3a-d** (ν 1720 cm^{-1}), bands for the O=C–C group of 4H-thiopyran-4-ones **4a-d** (ν 1640-1650 cm^{-1}), bands for the O=C–CH= (ν 1600 cm^{-1}) and O=C–N (ν 1730 cm^{-1}) groups of 1,3-thiazin-4-one **5**. The downfield shift of the signals for the protons of the NH groups of 4H-thiopyran-4-ones **4a-d** (δ 12.15-14.26 ppm) is explained by the existence of an intramolecular hydrogen bond NH···O=C [7]. Since 6-thioxopiperidin-2-ones **3a-d** are β-thioxocarbonyl compounds, as we know [8] they can exist in ketone, enol, and enethiol forms, where the latter two forms apparently are stabilized by an intramolecular hydrogen bond. In solution, there is probably a dynamic equilibrium between these tautomeric forms, and the singlet signals far downfield (δ 15.79-16.14 ppm) are averaged signals for the protons of the chelated OH groups of the enol forms and SH groups of the enethiol forms of **3a-d**.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
3a	$C_{19}H_{17}NO_2S$	70.35 / 70.56	5.28 / 5.30	4.49 / 4.33	153-154	44
3b	$C_{19}H_{16}ClNO_2S$	63.52 / 63.77	4.27 / 4.51	4.20 / 3.91	158-160	39
3c	$C_{19}H_{16}N_2O_4S$	61.73 / 61.95	4.49 / 4.38	7.39 / 7.60	182-184	43
3d	$C_{19}H_{17}NO_2S$	70.70 / 70.56	5.09 / 5.30	4.49 / 4.33	147-149	50
4a	$C_{19}H_{17}NO_2S$	70.68 / 70.56	5.11 / 5.30	4.52 / 4.33	140-142 (145-146 [7])	40
4b	$C_{19}H_{16}ClNO_2S$	63.59 / 63.77	4.30 / 4.51	4.09 / 3.91	157-159	41
4c	$C_{19}H_{17}NO_2S$	70.74 / 70.56	5.42 / 5.30	4.46 / 4.33	136-138	28
4d	$C_{24}H_{19}NO_2S$	75.03 / 74.78	4.98 / 4.97	3.74 / 3.63	180-183	72
5	$C_{19}H_{16}N_2O_4S$	62.13 / 61.95	4.62 / 4.38	7.84 / 7.60	185-187	46
6	$C_{19}H_{19}NO_3S$	66.99 / 66.84	5.70 / 5.61	4.35 / 4.10	240-243	72
8a	$C_{27}H_{20}FNO_2S$	73.62 / 73.45	4.61 / 4.57	3.03 / 3.17	229-231	80
8b	$C_{27}H_{20}N_2O_4S$	68.93 / 69.22	4.21 / 4.30	6.13 / 5.98	237-239	76
9	$C_{19}H_{15}NO_2S$	70.82 / 71.01	4.58 / 4.70	4.21 / 4.36	225-227	51
10	C_8H_8O	80.24 / 79.97	6.93 / 6.71	—	15-17 (20-20.5 [11])	42
11	$C_{19}H_{14}N_2O_4S$	62.55 / 62.29	3.72 / 3.85	7.86 / 7.65	245-247	45

With the aim of confirming the structure of heterocycles **3a-d, 4a-d**, and **5**, we chemically studied their reaction with aryl bromomethyl ketones. The products of reaction of 6-thioxopiperidin-2-ones **3a,c** with aryl bromomethyl ketones **7a,b** are 2-aroyl-4,7-diaryl-3-methyl-4,5-dihydro-6H-thieno[2,3-*b*]pyridin-6-ones **8a,b**, where these compounds were obtained in preparative yields (76-80%). We also planned to carry out recyclization of the thiopyran and thiazine ring to form a thiazole ring by treatment with bromomethyl phenyl ketone, as we were able to do in [9]. However, we found that when 4H-thiopyran-4-one **4a** and compound **5** were melted at 150°C with phenacyl bromide **7a**, recyclization did not occur but rather we saw dehydrogenation of compounds **4a** and **5** with formation of more stable aromatic heterocycles: respectively 3-acetyl-6-phenyl-2-phenylamino-4H-thiopyran-4-one (**9**) and 2-acetonylidene-6-(4-nitrophenyl)-3-phenyl-2H-1,3-thiazin-4-one (**11**).

Since there are different substituents near the CH=(C-2) double bond of 1,3-thiazin-4-ones **5** and **11**, these compounds can exist in *E*- and *Z*-forms. Earlier we carried out an X-ray diffraction study of 2-acetonylidene-3,4-diphenyl-2,3-dihydrothiazole, which is similar in structure to compounds **5** and **11**, and we established that this compound is the *Z*-isomer due to steric conditions [10]. Therefore with high percentage probability, we can say that 1,3-thiazin-4-ones **5** and **11** are also *Z*-isomers.

The results obtained for cycloacylation of 3-oxo-3-R^1-N-R^2-propanethioamides **1a-c** are probably explained by the fact that thioamides **1a-c** in the presence of K_2CO_3 can be acylated by 3-aryl-2-propenoyl chlorides **2a-c** both at the NH group and at the site of highest nucleophilicity: the active methylene group. In the first case, probably an intermediate amide is formed, which may be converted (depending on the nature of the

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

Com-pound	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (*J*, Hz)
3a*	3400, 3000, 1720 (C=O), 1560, 1500, 1460, 1420, 1330	2.17 (3H, s, CH_3C=O); 2.96 (1H, m, H-3); 3.34 (1H, m, H-3); 4.42 (1H, m, H-4); 6.83 (1H, br. s, H_{Ar}); 7.15-7.41 (9H, m, H_{Ar}); 16.09 (1H, s, OH)
3b	3400, 3000, 1720 (C=O), 1600, 1570, 1500, 1420	2.16 (3H, s, CH_3C=O); 2.90 (1H, m, H-3); 3.30 (1H, m, H-3); 4.43 (1H, m, H-4); 6.86 (1H, br. s, H_{Ar}); 7.15 (1H, br. s, H_{Ar}); 7.30 (2H, d, *J* = 9.0, H_{Ar}); 7.40-7.45 (5H, m, H_{Ar}); 16.10 (1H, s, OH)
3c	3400, 3000, 1720 (C=O), 1610, 1580, 1530, 1470, 1420	2.17 (3H, s, CH_3C=O); 3.00 (1H, m, H-3); 3.45 (1H, m, H-3); 4.63 (1H, m, H-4); 6.93 (1H, br. s, H_{Ar}); 7.16 (1H, br. s, H_{Ar}); 7.39 (3H, m, H_{Ar}); 7.57 (2H, d, *J* = 7.3, H_{Ar}); 8.27 (2H, d, *J* = 7.3, H_{Ar}); 16.14 (1H, s, OH)
3d	3400, 3000, 1720 (C=O), 1610, 1570, 1500, 1460	2.98 (2H, m, H-3); 3.59 (3H, s, CH_3N); 4.07 (1H, m, H-4); 7.05-7.57 (10H, m, H_{Ar}); 15.79 (1H, s, OH)
4a*[2]	—	2.50 (3H, s, CH_3C=O); 2.86 (1H, m, H-3); 3.27 (1H, m, H-3); 4.84 (1H, m, H-2); 7.30-7.52 (10H, m, H_{Ar}); 14.13 (1H, s, NH)
4b	3000, 1650, 1590, 1530, 1500, 1470, 1420, 1390	2.51 (3H, s, CH_3C=O); 2.82 (1H, m, H-3); 3.21 (1H, m, H-3); 4.86 (1H, m, H-2); 7.05-7.58 (9H, m, H_{Ar}); 14.26 (1H, s, NH)
4c	3100, 1645, 1560, 1440, 1380	2.79 (1H, m, H-3); 3.09 (3H, d, *J* = 3.4, $C\underline{H_3}NH$); 3.25 (1H, m, H-3); 4.48 (1H, m, H-2); 7.25-7.61 (10H, m, H_{Ar}); 13.90 (1H, br. s, NH)
4d	3050, 1650, 1610, 1540, 1470	2.82 (1H, m, H-3); 3.04 (1H, m, H-3); 5.12 (1H, m, H-2); 7.03-7.60 (15H, m, H_{Ar}); 12.15 (1H, br. s, NH)
5	3100, 1730, 1660, 1610, 1530, 1470, 1360	1.94 (3H, s, CH_3C=O); 3.35 (1H, m, H-5); 3.58 (1H, m, H-5); 4.65 (1H, m, H-6); 5.38 (1H, s, CH=); 7.43-7.62 (7H, m, H_{Ar}); 8.20 (2H, d, *J* = 8.4, H_{Ar})
6	3000, 1720, 1680, 1610, 1560, 1470, 1430	3.03 (3H, d, *J* = 4.0, $C\underline{H_3}NH$); 3.60 (2H, m, H-2); 4.01 (1H, m, H-3); 5.31 (1H, d, *J* = 11.2, H-4); 7.06-7.51 (8H, m, H_{Ar}); 7.80 (2H, m, H_{Ar}); 10.62 (1H, q, *J* = 4.0, $CH_3N\underline{H}$); 12.01 (1H, br. s, COOH)
8a	3000, 1700, 1630, 1610, 1570, 1410	2.16 (3H, s, 3-CH_3); 2.84 (1H, m, H-5); 3.49 (1H, m, H-5); 4.47 (1H, m, H-4); 7.24-7.68 (14H, m, H_{Ar})
8b	3000, 1710, 1630, 1610, 1540, 1500	2.15 (3H, s, 3-CH_3); 2.87 (1H, m, H-5); 3.54 (1H, m, H-5); 4.70 (1H, m, H-4); 7.31-7.63 (12H, m, H_{Ar}); 8.24 (2H, d, *J* = 8.6, H_{Ar})
9	3100, 1680, 1630, 1580, 1430, 1200	2.52 (3H, s, CH_3C=O); 7.32-7.54 (10H, m, H_{Ar}); 7.71 (1H, s, H-5); 12.56 (1H, s, NH)
11	3000, 1720, 1670, 1600, 1550, 1500	2.10 (3H, s, CH_3C=O); 5.70 (1H, s, CH=); 7.40 (2H, m, H_{Ar}); 7.61 (3H, m, H_{Ar}); 7.81 (1H, s, H-5); 7.93 (2H, d, *J* = 8.4, H_{Ar}); 8.41 (2H, d, *J* = 8.4, H_{Ar})

* ^{13}C NMR spectrum of compound **3a** (75 MHz, $CDCl_3$), δ, ppm: 22.1 (CH_3), 38.1 (C-4), 39.6 (C-3), 109.8 (C-6), 126.6, 127.7, 128.5, 128.8, 129.1, 129.8, 138.5, 139.8 (CAr), 167.8 (C-2), 180.5 (C-5), 194.3 (C=O).

*[2] The ^{1}H and ^{13}C NMR spectra of compound **4a** in $CDCl_3$ and also the IR spectrum match those described in [7].

substituent on the phenyl ring and the electron density on the C-3 atom of the 3-aryl-2-propenoyl substituent) either to 6-thioxopiperidin-2-ones **3a-d** or to 4H-1,3-thiazin-4-one **5**. In the second case, probably the C-acylation product is obtained, intramolecular cyclization of which leads to 4H-thiopyran-4-ones **4a-d**.

EXPERIMENTAL

The ^{1}H 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.

5-Acyl-4-aryl-1-aryl(alkyl)-6-thioxopiperidin-2-ones 3a-d, 5-Acyl-2-aryl-6-aryl(alkyl)amino-2,3-dihydro-4H-thiopyran-4-ones 4a-d, and 2-Acetonylidene-6-(4-nitrophenyl)-3-phenyl-5,6-dihydro-4H-1,3-thiazin-4-one (5). A solution of 3-aryl-2-propenoyl chloride **2a-c** (10 mmol) in acetone (3 ml) was added with vigorous stirring at 20°C to a solution of 3-oxo-3-R^1-N-R^2-propanethioamide **1a-c** (10 mmol) in anhydrous acetone (5 ml) containing suspended dry K_2CO_3 (15 mmol). The mixture was stirred for 2 h at 20°C and then for 0.5 h at 50°C, and then cooled down. The suspension of potassium hydrogen carbonate and potassium chloride was filtered out from the reaction mixture. The filtrate was evaporated down and the crystalline residue was ground with a 5% aqueous NaOH solution (10 ml) at 20°C. The 4H-thiopyran-4-one **4a-d** (1,3-thiazin-4-one **5**) insoluble in alkaline solution was filtered out, dried in air, and recrystallized from ethanol. The alkaline filtrate, containing the sodium salt of 6-thioxopiperidin-2-one, was acidified with a 20% aqueous HCl solution; the precipitated reaction product **3a-d** was filtered out, dried, and recrystallized from ethanol.

4-Benzoyl-5-methylamino-3-phenyl-5-thioxopentanoic Acid (6). A solution of 5-benzoyl-1-methyl-4-phenyl-6-thioxopiperidin-2-one (**3d**) (5 mmol) and NaOH (15 mmol) in water (5 ml) was held for 10 min at 60°C, cooled down, and acidified with 10% aqueous HCl. The precipitated product **6** was filtered out, dried, and recrystallized from acetic acid.

2-Aroyl-4,7-diaryl-3-methyl-4,5-dihydro-6H-thieno[2,3-*b*]pyridin-6-ones 8a,b. Aryl bromomethyl ketone **7a,b** (5 mmol) was added at 20°C to a solution of 5-acyl-1,4-diaryl-6-thioxopiperidin-2-one **3a,c** (5 mmol) and KOH (5 mmol) in ethanol (3 ml). The reaction mixture was diluted with cold water (10 ml), and the precipitated reaction product **8a,b** was filtered out, dried, and recrystallized from acetic acid.

3-Acetyl-6-phenyl-2-phenylamino-4H-thiopyran-4-one (9) and **2-acetonylidene-6-(4-nitrophenyl)-3-phenyl-2H-1,3-thiazin-4-one (11).** A mixture of 4H-thiopyran-4-one (**4a**) (5 mmol) (4H-1,3-thiazin-4-one **5**) and bromomethyl phenyl ketone (**7a**) (5 mmol) was held for 5 min at a temperature of 150°C, cooled down, and ground with ethanol (3 ml), then boiled for 5 min, and cooled. Then 4H-thiopyran-4-one (**9**) (2H-1,3-thiazin-4-one **11**) was filtered out, dried, and recrystallized from acetic acid. The ethanol solution was evaporated down, and the oil obtained was extracted with hot hexane (3 × 5 mL). The hexane was evaporated off and the acetophenone **10** was distilled under a water-jet vacuum.

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