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ACYLATION OF 2-AZAHETARYLACETONITRILES WITH (ACETYLTHIO)ACETYL AND α-(ACETYLTHIO)-PROPIONYL CHLORIDES. PRODUCTION OF 5-AMINO-4-HETARYLTHIOPHEN-3(2H)-ONES

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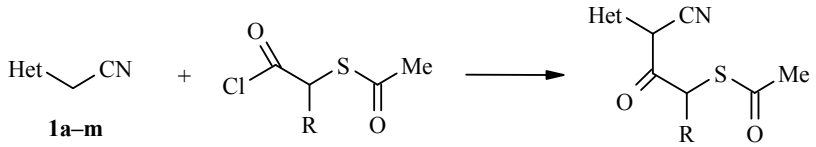
3-Cyano-3-hetaryl-2-oxopropyl- and 3-cyano-3-hetaryl-1-methyl-2-oxopropyl ethanethioates were obtained by the acylation of 2-azahetarylacetonitriles with (acetylthio)acetyl and α-(acetylthio)propionyl chlorides respectively. They are deacetylated by the action of amines and undergo cyclization with the formation of 5-amino-4-hetarylthiophen-2(2H)-ones.

Keywords: 2-azahetarylacetonitriles, 5-amino-4-hetarylthiophen-3(2H)-ones, (acetylthio)acetyl and α-(acetylthio)propionyl chlorides, acylation.

Earlier [1, 2] we showed that the reaction of hetarylacetonitriles with (acetylthio)acetyl chloride (like the reactions with the anhydrides [3] and acid chlorides [4-7] of carboxylic acids) leads to C-acylated hetarylacetonitriles, which are deacetylated in the presence of bases and undergo spontaneous cyclization to 5-amino-4-hetarylthiophen-3(2H)-ones.

In the present work we continued these investigations and extended them to the quinazoline-, benzimidazolyl-, and benzothiazolylacetonitriles **1a-m** and (acetylthio)acetyl and α-(acetylthio)propionyl chlorides **2a**,**b**. The reaction takes place in DMF at room temperature and leads to high yields of the corresponding C-acyl derivatives (**3a-n**) (Table 1).



2a, 3a-i R = H, **2b**, **3j-n** R = Me; **1a-i, 3a-j** Het = R^1-4-oxo-3,4-dihydroquinazol-2-yl, **1j-l**, **3k-m** Het = R^2-(1H-benzimidazol-2-yl), **1m, 3n** Het = benzothiazol-2-yl; **a** R^1 = H, **b**,**j** R^1 = 6-Me, **c** R^1 = 6,8-Me_2, **d** R^1 = 6,7-$(OMe)_2$, **e** R^1 = 6-F, **f** R^1 = 6-Cl, **g** R^1 = 6-Br, **h** R^1 = 7-Cl, **i** R^1 = 6-I, **k** R^2 = H, **l** R^2 = Me, **m** R^2 = Br

Compounds **3a-n** can exist in one of three tautomeric forms: **A**, **B**, or **C**.

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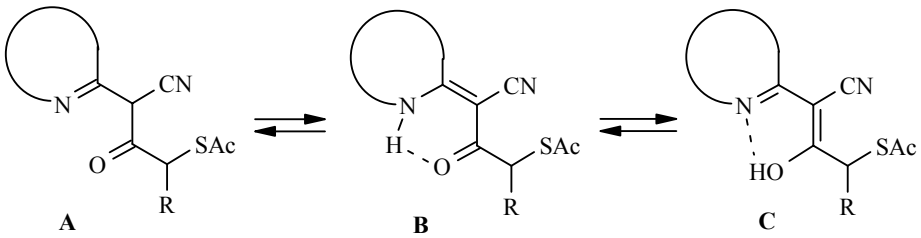


The proposed structure of the C-acyl derivatives **3a-n** is confirmed in the IR spectra by the presence of absorption bands for the carbonyl group of the quinazolone ring at 1700-1680 cm^{-1} (compounds **3a-j**) and bands for the conjugated carbonyl group C=O of the acyl fragment at 1650 cm^{-1} (compounds **3a-n**) participating in the formation of an intramolecular hydrogen bond. The strong absorption band of the conjugated nitrile group is observed at 2200-2180 cm^{-1}. The absorption in the region of 3180-3150 cm^{-1} is due to the NH bonds of the quinazoline ring (compounds **3a-j**). The ^1H NMR spectra of compounds **3a-i**, recorded in DMSO-d_6, contain signals for the aromatic protons of the quinazoline ring in the region of 7.34-8.23, a three-proton singlet for the S-acetyl group in the region of 2.39-2.40 ppm, and a two-proton singlet for the methylene group in the region of 4.11-4.14 ppm. In the downfield region there signals for two protons exchanging with D_2O, i.e., at 12.33-12.39 ppm for the NH proton at position 3 of quinazolone and at 13.32-14.12 ppm for the chelated proton at the nitrogen atom at position 1 of the molecule. The chelated NH proton is subject to the strong screening action of the carbonyl group and heterocyclic ring, and its signal is therefore observed in the most downfield region. Notable features in the ^1H NMR spectra of compounds **3j-n** are: A three-proton singlet for the S-acetyl group at 2.32-2.35 ppm; a doublet for the methyl group attached to the methine proton at 1.45-1.48 ppm; a quartet for the methine proton at 4.71-4.74 ppm; a signal for the chelated NH proton in the region of 12.85-13.55 ppm. On the basis of the foregoing we consider that the compounds exist in solution in form **B** with an intramolecular hydrogen bond. This conclusion agrees with published data for such compounds [7].

TABLE 1. The Characteristics of Compounds **3a-n** and **4a-k**

Compound	Name of compound	Empirical formula	Found, % / Calculated, %		mp, °C*	Yield, %
			N	S		
1	2	3	4	5	6	7
3a	3-Cyano-2-oxo-3-(4-oxo-3,4-dihydro-2-quinazolyl)propyl ethanethioate	$C_{14}H_{11}N_3OS$	14.02 / 13.95	10.61 / 10.64	>300	85
3b	3-Cyano-3-(6-methyl-4-oxo-3,4-dihydro-2-quinazolyl)-2-oxopropyl ethanethioate	$C_{15}H_{13}N_3O_3S$	13.37 / 13.33	9.99 / 10.17	293	83
3c	3-Cyano-3-(6,8-dimethyl-4-oxo-3,4-dihydro-2-quinazolyl)-2-oxopropyl ethanethioate	$C_{16}H_{15}N_3O_3S$	12.83 / 12.76	10.01 / 9.74	>300	85
3d	3-Cyano-3-(6,7-dimethoxy-4-oxo-3,4-dihydro-2-quinazolyl)-2-oxopropyl ethanethioate	$C_{16}H_{15}N_3O_5S$	11.59 / 11.63	8.90 / 8.87	298	81
3e	3-Cyano-3-(6-fluoro-4-oxo-3,4-dihydro-2-quinazolyl)-2-oxopropyl ethanethioate	$C_{14}H_{10}FN_3O_3S$	13.18 / 13.16	10.10 / 10.04	286	78
3f	3-(6-Chloro-4-oxo-3,4-dihydro-2-quinazolyl)-3-cyano-2-oxopropyl ethanethioate	$C_{14}H_{10}ClN_3O_3S$	12.54 / 12.51	9.52 / 9.55	273	83

TABLE 1 (continued)

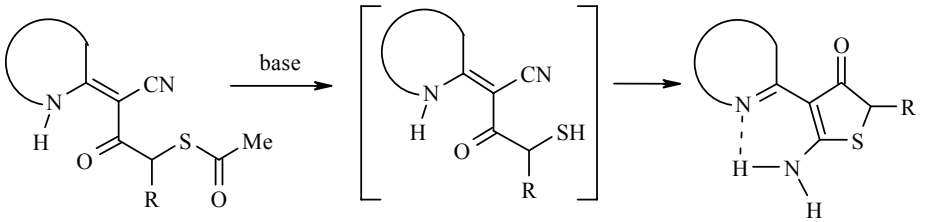
1	2	3	4	5	6	7
3g	3-(6-Bromo-4-oxo-3,4-dihydro-2-quinazolyl)-3-cyano-2-oxopropyl ethanethioate	$C_{14}H_{10}BrN_3O_3S$	11.10 / 11.05	8.44 / 8.43	286	81
3h	3-(7-Chloro-4-oxo-3,4-dihydro-2-quinazolyl)-3-cyano-2-oxopropyl ethanethioate	$C_{14}H_{10}ClN_3O_3S$	12.52 / 12.51	9.55 / 9.55	284	78
3i	3-Cyano-2-(6-iodo-4-oxo-3,4-dihydro-2-quinazolyl)-2-oxopropyl ethanethioate	$C_{14}H_{10}IN_3O_3S$	10.01 / 9.84	7.55 / 7.51	294	79
3j	3-Cyano-1-methyl-3-(6-methyl-4-oxo-3,4-dihydro-2-quinazolyl)-2-oxopropyl ethanethioate	$C_{16}H_{15}N_3O_3S$	12.82 / 12.76	9.77 / 9.73	146	80
3k	3-Cyano-1-methyl-3-(1H-benzo[*d*]imidazol-2-yl)-2-oxopropyl ethanethioate	$C_{14}H_{13}N_3O_2S$	14.67 / 14.62	11.18 / 11.16	224	75
3l	3-Cyano-1-methyl-3-(1-methyl-1H-benzo[*d*]imidazol-2-yl)-2-oxopropyl ethanethioate	$C_{15}H_{15}N_3O_2S$	14.00 / 13.94	10.70 / 10.64	202	85
3m	3-(1-Benzyl-1H-benzo[*d*]-imidazol-2-yl)-3-cyano-1-methyl-2-oxopropyl ethanethioate	$C_{21}H_{19}N_3O_2S$	11.22 / 11.13	8.51 / 8.49	152	82
3n	3-(1,3-Benzothiazol-2-yl)-3-cyano-1-methyl-2-oxopropyl ethanethioate	$C_{14}H_{12}N_2O_2S$	9.22 / 9.20	21.10 / 21.07	222	84
4a	2-(2-Amino-4-oxo-4,5-dihydro-3-thienyl)-4(3H)-quinazolinone	$C_{12}H_9N_3O_2S$	16.24 / 16.21	12.37 / 12.37	>300	82
4b	2-(2-Amino-4-oxo-4,5-dihydro-3-thienyl)-6-methyl-4(3H)-quinazolinone	$C_{13}H_{11}N_3O_2S$	15.41 / 15.37	11.76 / 11.73	>300	85
4c	2-(2-Amino-4-oxo-4,5-dihydro-3-thienyl)-6,8-dimethyl-4(3H)-quinazolinone	$C_{14}H_{13}N_3OS_2$	14.65 / 14.62	11.09 / 11.16	>300	79
4d	2-(2-Amino-4-oxo-4,5-dihydro-3-thienyl)-6,7-dimethoxy-4(3H)-quinazolinone	$C_{14}H_{13}N_3O_4S$	13.19 / 13.16	10.07 / 10.04	>300	75
4e	2-(2-Amino-4-oxo-4,5-dihydro-3-thienyl)-6-fluoro-4(3H)-quinazolinone	$C_{12}H_8FN_3O_2S$	15.34 / 15.50	11.55 / 11.56	>300	80
4f	2-(2-Amino-4-oxo-4,5-dihydro-3-thienyl)-6-chloro-4(3H)-quinazolinone	$C_{12}H_8ClN_3O_2S$	14.45 / 14.31	10.97 / 10.92	>300	78
4g	2-(2-Amino-4-oxo-4,5-dihydro-3-thienyl)-6-bromo-4(3H)-quinazolinone	$C_{12}H_8BrN_3O_2S$	12.46 / 12.43	9.51 / 9.48	>300	67
4h	2-(2-Amino-4-oxo-4,5-dihydro-3-thienyl)-7-chloro-4(3H)-quinazolinone	$C_{12}H_8ClN_3O_2S$	14.29 / 14.31	10.91 / 10.92	>300	82
4i	2-(2-Amino-4-oxo-4,5-dihydro-3-thienyl)-6-iodo-4(3H)-quinazolinone	$C_{12}H_8IN_3O_2S$	10.93 / 10.91	8.33 / 8.32	>300	78
4j	2-(2-Amino-5-methyl-4-oxo-4,5-dihydro-3-thienyl)benzimidazole	$C_{12}H_{11}N_3OS$	17.22 / 17.13	13.15 / 13.07	215	75
4k	2-(2-Amino-5-methyl-4-oxo-4,5-dihydro-3-thienyl)-1-methylbenzimidazole	$C_{13}H_{13}N_3OS$	16.19 / 16.20	12.37 / 12.36	>300	80

* Solvents for crystallization: DMF (compounds **3a-i** and **4a-i**), *n*-BuOH (compounds **3j** and **4j**,**k**), and 2-PrOH (compounds **3k-n**).

TABLE 2. The ^{1}H NMR Spectra of Compounds **3a**-**n** and **4a**-**k**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
3a	2.39 (3H, s, $SCOCH_3$); 4.13 (2H, s, CH_2); 7.45 (1H, m, H-6); 7.83 (2H, m, H-7,8); 8.03 (1H, d, *J* = 7.6, H-5); 12.49 (1H, s, NH); 13.33 (1H, s, NH)
3b	2.39 (3H, s, $SCOCH_3$); 2.42 (3H, s, CH_3); 4.12 (2H, s, CH_2); 7.66 (1H, d, *J* = 8.0, H-7); 7.73 (1H, d, *J* = 8.8, H-8); 7.82 (1H, s, H-5); 12.42 (1H, s, NH); 13.31 (1H, s, NH)
3c	2.37 (3H, s, CH_3); 2.38 (3H, s, CH_3); 2.40 (3H, s, $SCOCH_3$); 4.14 (2H, s, CH_2); 7.55 (1H, s, H-7); 7.68 (1H, s, H-5); 12.33 (1H, s, NH); 14.11 (1H, s, NH)
3d	2.39 (3H, s, $SCOCH_3$); 3.85 (3H, s, CH_3O); 3.89 (3H, s, CH_3O); 4.11 (2H, s, CH_2); 7.35 (1H, s, H-8); 7.47 (1H, s, H-5); 12.38 (1H, s, NH); 13.22 (1H, s, NH)
3e	2.39 (3H, s, $SCOCH_3$); 4.12 (2H, s, CH_2); 7.74 (2H, m, H-7,8); 7.90 (1H, s, H-5); 13.22 (1H, s, NH); NH – exchange with water
3f	2.39 (3H, s, $SCOCH_3$); 4.13 (2H, s, CH_2); 7.85 (2H, m, H-7,8); 7.94 (1H, s, H-5); 13.48 (1H, s, NH); NH – exchange with water
3g	2.39 (3H, s, $SCOCH_3$); 4.12 (2H, s, CH_2); 7.78 (1H, m, H-8); 7.97 (1H, m, H-7); 8.06 (1H, s, H-5); 13.45 (1H, s, NH); NH – exchange with water
3h	2.39 (3H, s, $SCOCH_3$); 4.12 (2H, s, CH_2); 7.47 (1H, d, *J* = 8, H-5); 7.90 (1H, s, H-8); 8.01 (1H, d, *J* = 6.8, H-6); 13.40 (1H, s, NH); NH – exchange with water
3i	2.39 (3H, s, $SCOCH_3$); 4.12 (2H, s, CH_2); 7.62 (1H, d, *J* = 8.8, H-8); 8.09 (1H, d, *J* = 8.4, H-7); 8.23 (1H, s, H-5); 13.42 (1H, s, NH); NH – exchange with water
3j	1.46 (3H, d, *J* = 6.8, CH_3); 2.35 (3H, s, $SCOCH_3$); 2.43 (3H, s, CH_3); 4.73 (1H, q, *J* = 6.8, CH); 7.58 (1H, d, *J* = 8.4, H-7); 7.74 (1H, d, *J* = 8.4, H-8); 7.82 (1H, s, H-5); 12.33 (1H, s, NH); 13.48 (1H, s, NH)
3k	1.47 (3H, d, *J* = 6.8, CH_3); 2.34 (3H, s, $SCOCH_3$); 4.71 (1H, q, *J* = 6.8, CH); 7.21 (2H, t, *J* = 7.2, H-5,6); 7.50 (2H, d, *J* = 6.8, H-4,7); 12.85 (2H, s, 1-NH, 3-NH)
3l	1.47 (3H, d, *J* = 6.8, CH_3); 2.35 (3H, s, $SCOCH_3$); 3.96 (3H, s, NCH_3); 4.85 (1H, q, *J* = 6.8, CH); 7.33 (2H, t, *J* = 7.2, H-5,6); 7.63 (2H, d, *J* = 7.6, H-4,7); 13.34 (1H, s, NH)
3m	1.47 (3H, d, *J* = 6.8, CH_3); 2.32 (3H, s, $SCOCH_3$); 4.79 (1H, q, *J* = 6.8, CH); 5.83 (2H, s, CH_2Ph); 7.47 (1H, d, *J* = 7.6, H-4(7)); 7.71 (1H, d, *J* = 7.6, H-7(4)); 7.20-7.35 (7H, m, $CH_2C_6H_5$, 5,6-Het)
3n	1.47 (3H, d, *J* = 6.8, CH_3); 2.35 (3H, s, $SCOCH_3$); 4.75 (1H, q, *J* = 6.8, CH); 7.31 (1H, t, *J* = 7.2, H-5); 7.45 (1H, t, *J* = 7.6, H-6); 7.67 (1H, d, *J* = 6.0, H-4); 7.89 (1H, d, *J* = 7.6, H-7); 13.55 (1H, s, NH)
4a	3.93 (2H, s, CH_2); 7.36 (1H, t, *J* = 6.8, H-6); 7.71-7.72 (2H, m, H-7,8); 8.02 (1H, d, *J* = 7.6, H-5); 9.99 (1H, s, NH_2); 10.55 (1H, s, NH_2); 12.30 (1H, s, NH)
4b	2.41 (3H, s, CH_3); 3.97 (2H, s, CH_2); 7.59 (1H, d, *J* = 8, H-7); 7.67 (1H, d, *J* = 8.8, H-8); 7.85 (1H, s, H-5); 9.99 (1H, s, NH_2); 10.57 (1H, s, NH_2); 12.31 (1H, s, NH)
4c	2.36 (3H, s, CH_3); 2.39 (3H, s, CH_3); 3.96 (2H, s, CH_2); 7.44 (1H, s, H-7); 7.68 (1H, s, H-5); 10.11 (1H, s, NH_2); 10.48 (1H, s, NH_2); 12.21 (1H, s, NH)
4d	3.85 (3H, s, OCH_3); 3.90 (3H, s, OCH_3); 3.95 (2H, s, CH_2); 7.35 (1H, s, H-8); 7.37 (1H, s, H-5); 9.93 (1H, s, NH_2); 10.55 (1H, s, NH_2); 12.20 (1H, s, NH)
4e	3.96 (2H, s, CH_2); 7.66 (1H, d, *J* = 9.2, H-8); 7.71 (1H, d, *J* = 7.6, H-7); 9.99 (1H, s, NH_2); 10.46 (1H, s, NH_2); 12.41 (1H, s, NH)
4f	3.97 (2H, s, CH_2); 7.78 (2H, m, H-7,8); 7.94 (1H, s, H-5); 9.95 (1H, s, NH_2); 10.46 (1H, s, NH_2); 12.43 (1H, s, NH)
4g	3.98 (2H, s, CH_2); 7.77 (2H, m, H-7,8); 7.91 (1H, s, H-5); 9.98 (1H, s, NH_2); 10.43 (1H, s, NH_2); 12.47 (1H, s, NH)
4h	3.99 (2H, s, CH_2); 7.41 (1H, d, *J* = 8.4, H-6); 7.98 (1H, s, H-8); 8.01 (1H, d, *J* = 8.4, H-5); 10.05 (1H, s, NH_2); 10.50 (1H, s, NH_2); 12.39 (1H, s, NH)
4i	3.98 (2H, s, CH_2); 7.84 (2H, m, H-7,8); 7.97 (1H, s, H-5); 9.99 (1H, s, NH_2); 10.56 (1H, s, NH_2); 12.49 (1H, s, NH)
4j	1.53 (3H, d, *J* = 6.8, 5-CH_3 thioph.); 4.08 (1H, m, H-5 thioph.); 7.12 (2H, t, *J* = 6.8, H-5,6); 7.52-7.59 (2H, d, *J* = 6.8, H-4,7); 9.55 (1H, s, NH_2); 10.07 (1H, s, NH_2); 12.02 (1H, s, NH)
4k	1.52 (3H, d, *J* = 7.2, 5-CH_3 thioph.); 3.69 (3H, s, CH_3-benzimid.); 4.01 (1H, m, H-5 thioph.); 7.21 (2H, t, *J* = 7.0, H-5,6); 7.51 (1H, d, *J* = 6.8, H-7); 7.57 (1H, d, *J* = 7.2, H-4); 8.70 (1H, s, NH_2); 9.05 (1H, s, NH_2)

The S-acetyl derivatives **3a-i**,**k**,**l** are readily deacetylated by the action of a base (ammonia, dimethylamine, or piperidine) with the formation of reactive γ-mercaptonitriles, which cannot be isolated since intramolecular addition of the mercapto group to the nitrile group occurs, and the 5-aminothiophen-3(2H)-ones **4a-k** are formed.



In the ^{1}H NMR spectra of compounds **4a-k** the signals for the protons of the amino group are observed in the form of two one-proton singlets in the region of 8.70-10.11 and 9.06-10.57 ppm, due to the nonequivalence of the protons of the amino group on account of the presence of the intramolecular hydrogen bond. These signals disappear when D_2O is added. The protons of the methylene group give a two-proton singlet in the region of 3.94-3.98 ppm (for compounds **4a-i**), while compounds **4j**,**k** give a doublet for the methyl group at 1.53 ppm (J = 6.8 and J = 7.2 Hz) and a quartet for the methine proton at 4.08 ppm. The N–H proton of the quinazolone ring (compounds **4a-i**) absorbs in the most downfield region at 12.20-12.43 ppm. The IR spectra of the obtained compounds do not contain the absorption of the nitrile group in the region of 2200-2180 cm^{-1}, but there are two absorption bands due to the stretching vibrations of the primary amino group in the regions of 3340-3330 (asymmetric vibrations) and 3260-3250 cm^{-1} (symmetric vibrations). The absorption of the carbonyl group is not observed in the IR spectra of the compounds, which is typical of compounds with a β-enaminoketone fragment [2, 8]. According to the spectral data, compounds **4a-k** exist entirely in the form of amino ketones.

EXPERIMENTAL

The reactions and the purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates in the 9:1 chloroform–methanol system. The ^{1}H NMR spectra were recorded on a Varian Mercury 400 spectrometer (400 MHz) in DMSO-d_6 with TMS as internal standard. The IR spectra were recorded on Pye-Unicam SP 3-300 instrument. The melting points were measured on a small-scale Boetius heater bench with a VEB Analytik PHMK 05 observation device.

Synthesis of 3-Cyano-3-hetaryl-1-R-2-oxopropyl Ethanethioate (3a-n) (General Procedure). To a solution of the 2-azahetarylacetonitrile **1a-m** (5 mmol) in DMF (5 ml) at room temperature (25°C) we added (acetylthio)acetyl chloride **2a** or α-(acetylthio)propionyl chloride **2b** respectively (5.5 mmol). The reaction mixture was left for 24 h, and the precipitate was filtered off, washed with water, dried, and recrystallized.

Synthesis of 5-Amino-4-hetarylthiophen-3(2H)-ones (4a-k) (General Procedure). To a solution of the respective compound **3a-i**,**k**,**l** (5 mmol) in DMF (5 ml) we added the base (ammonia, diethylamine, or piperidine) (10 mmol), and we left the mixture at 30-40°C for 24 h. The precipitate was filtered off, washed with water, dried, and recrystallized.

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