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SYNTHESIS OF AZINYLTHIOUREAS AND THEIR HETEROCYCLIZATION USING α-CHLOROACETOACETIC ESTER

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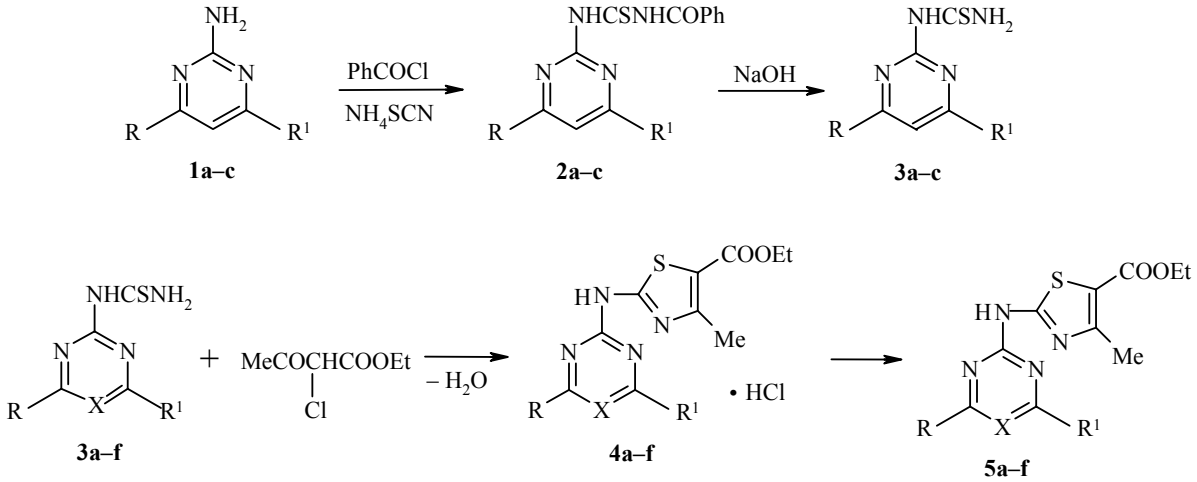
Treatment of aminopyrimidines with a mixture of PhCOCl and NH_4SCN and subsequent debenzoylation of the N-benzoyl-N'-(4,6-substituted pyrimidin-2-yl)thioureas obtained gave pyrimidinyl-2-thioureas. The heterocyclization of the azinyl-2-thioureas with α-chloroacetoacetic ester gave ethyl 2-(4,6-substituted azin-2-yl)aminothiazole-5-carboxylates.

Keywords: azinylthioureas, thiazole-5-carboxylic acid, heterocyclization.

Treatment of thioureas and related compounds with halo-β-dicarbonyl compounds gives thiazole derivatives [1-4]. It might be expected that, in similar conditions, azinyl(pyrimidinyl, *sym*-triazinyl)thioureas would give azinylaminothiazoles which, having a multinuclear heterocyclic system, would be of interest as potential pesticides and medicinal compounds.



1–5 a R = R¹ = Me, **b** R = Me, R¹ = OMe, **c** R = R¹ = OMe; **3–5 d** R = R¹ = NHEt, **e** R = NHEt, R¹ = NHPr-*i*, **f** R = R¹ = NHPr-*i*; **3–5 a–c** X = CH, **d–f** X = N

With this objective treatment of the 2-aminopyrimidines **1a-c** with a mixture of benzoyl chloride and ammonium thiocyanate gave the N-benzoyl-N'-(pyrimidin-2-yl)thioureas **2a-c**, debenzoylation of which in basic medium gave the pyrimidin-2-yl thioureas **3a-c**.

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TABLE 1. Characteristics of Compounds **2, 3** and **5**

Compound	Empirical formula	Found, % / Calculated, %		mp,°C	Yield, %
		N	S		
2a	$C_{14}H_{14}N_4OS$	19.76 / 19.58	12.11 / 11.89	181-183	87
2b	$C_{14}H_{14}N_4O_2S$	18.81 / 18.54	10.91 / 10.60	176-177	63
2c	$C_{14}H_{14}N_4O_3S$	17.40 / 17.61	10.35 / 10.06	171-173	76
3a	$C_7H_{10}N_4S$	30.49 / 30.77	17.16 / 17.58	264-265	95
3b	$C_7H_{10}N_4OS$	28.59 / 28.28	15.81 / 16.16	222-223	60
3c	$C_7H_{10}N_4O_2S$	25.79 / 26.17	15.36 / 14.95	275-277	70
5a	$C_{13}H_{16}N_4O_2S$	19.40 / 19.18	11.31 / 10.96	157-158	75
5b	$C_{13}H_{16}N_4O_3S$	17.85 / 18.18	10.64 / 10.39	169-170	70
5c	$C_{13}H_{16}N_4O_4S$	17.56 / 17.28	10.29 / 9.88	152-154	79
5d	$C_{14}H_{21}N_7O_2S$	27.54 / 27.92	8.87 / 9.12	264-266	81
5e	$C_{15}H_{23}N_7O_2S$	27.22 / 26.85	8.45 / 8.77	197-199	79
5f	$C_{16}H_{25}N_7O_2S$	26.27 / 25.86	8.72 / 8.44	182-184	80

TABLE 2. ^{1}H NMR Spectra of Compounds **2, 3,** and **5**

Compound	Chemical shifts, δ, ppm. (SSCC, *J*, Hz)
2a	2.42 (6H, s, $(CH_3)_2$); 6.75 (1H, s, CH); 7.50-8.05 (5H, m, C_6H_5); 11.50 (1H, br. s, NH); 12.75 (1H, br. s, NH)
2b	2.40 (3H, s, CH_3); 3.96 (3H, s, OCH_3); 6.42 (1H, s, CH); 7.50-8.08 (5H, m, C_6H_5); 11.35 (1H, br. s, NH); 13.70 (1H, br. s, NH)
2c	3.95 (6H, s, $(OCH_3)_2$); 5.83 (1H, s, CH); 7.42-8.08 (5H, m, C_6H_5); 11.90 (1H, br. s, NH); 12.50 (1H, br. s, NH)
3a	2.40 (6H, s, $(CH_3)_2$); 6.72 (1H, s, CH); 8.20 (2H, v. br. s , NH_2); 11.20 (1H, br. s, NH)
3b	2.42 (3H, s, CH_3); 3.95 (3H, s, OCH_3); 6.45 (1H, s, CH); 8.25 (2H, v. br. s , NH_2); 10.90 (1H, br. s, NH)
3c	3.95 (6H, s, $(OCH_3)_2$; 5.92 (1H, s, CH); 8.10 (2H, v. br. s , NH_2); 10.95 (1H, br. s, NH)
5a	1.35 (3H, t, *J* = 6.5, $\underline{CH_3}$–CH_2); 2.42 (6H, s, $(CH_3)_2$); 2.56 (3H, s, CH_3 thiazole); 4.25 (2H, q, *J* = 6.5, OCH_2); 6.72 (1H, s, CH); 11.20 (1H, br. s, NH)
5b	1.35 (3H, t, *J* = 6.25, $\underline{CH_3}$–CH_2); 2.40 (3H, s, CH_3); 2.56 (3H, s, CH_3 thiazole); 4.03 (3H, s, OCH_3); 4.27 (2H, q, *J* = 6.25, OCH_2); 6.20 (1H, s, CH); 11.40 (1H, br. s, NH)
5c	1.35 (3H, t, *J* = 6.4, $\underline{CH_3}$–CH_2); 2.56 (3H, s, CH_3 thiazole); 4.00 (6H, s, $(OCH_3)_2$); 4.25 (2H, q, *J* = 6.4, OCH_2); 5.63 (1H, s, CH); 11.42 (1H, br. s, NH)
5d	1.18 (6H, br. t, $\underline{CH_3}$–CH_2N); 1.33 (3H, t, *J* = 6.2, $\underline{CH_3}$–CH_2O); 2.53 (3H, s, CH_3 thiazole); 3.38 (4H, br. m, NCH_2); 4.22 (2H, q, *J* = 6.2, OCH_2); 7.10 (2H, br. s, NH(Et)); 11.00 (1H, br. s, NH)
5e	1.15-1.25 (9H, br. m, CH_3(Et and Pr-*i*)); 1.30 (3H, t, *J* = 6.4, $\underline{CH_3}$–CH_2O); 2.55 (3H, s, CH_3 thiazole); 3.40 (4H, br. m, NCH_2); 4.23 (2H, q, *J* = 6.4, OCH_2); 4.10-4.30 (1H, br. m, CH(Pr-*i*)); 6.75 and 8.00 (2H, br. s, NH(Alk)); 11.50 (1H, br. s, NH)
5f	1.12-1.28 (12H, br. m, CH_3(Pr-*i*)); 1.35 (3H, t, *J* = 6.4, $\underline{CH_3}$–CH_2O); 2.57 (3H, s, CH_3 thiazole); 4.22 (2H, q, *J* = 6.4, OCH_2); 4.10-4.25 (2H, br. m, CH(Pr-*i*)); 6.50-6.70 (2H, br. s, NH(Alk)); 11.17 (1H, br. s, NH)

Refluxing compounds **3a-f** (compounds **3d-f** had been prepared earlier [5]) with α-chloroacetoacetic ester in absolute ethanol gave the ethyl 2-(4,6-substituted azin-2-yl)aminothiazole-5-carboxylate hydrochlorides **4a-f**, neutralization of which was carried out to give the bases **5a-f**. The structure of the latter was confirmed by ^{1}H NMR spectroscopic data.

EXPERIMENTAL

Monitoring of the reaction course and the purity of the compounds synthesized was performed chromatographically of Silufol UV-254 plates using acetone–hexane (2:1) as eluent. IR spectra were obtained on a UR-20 instrument for KBr tablets. ^{1}H NMR spectra were obtained on a Mercury-300 (300 MHz) spectrometer using DMSO-d_6 with TMS as internal standard.

N-Benzoyl-N'-(4-R-6-R^1-pyrimidin-2-yl)thioureas 2a-c. PhCOCl (2.4 ml, 20 mmol) was added with stirring to a solution of NH_4SCN (1.7 g, 20 mmol) in acetone (10 ml) and the reaction mixture was refluxed for 5 min. Compound **1a-c** (20 mmol) was added in small portions at a rate such that the mixture refluxed gently. After 30 min the mixture was poured into iced water (150 ml), filtered, and the precipitated compound **2a-c** was filtered off and washed on the filter with EtOH.

N-4,6-Substituted Pyrimidin-2-ylthioureas 3a-c. Compound **2a-c** (11 mmol) was added to a solution of NaOH (1.7 g, 38 mmol) in water (20 ml) and the mixture was refluxed for 30 min. The precipitated compound **3a-c** was separated and washed on the filter with water.

Ethyl 2-(4,6-Substituted azin-2-yl)aminothiazole-5-carboxylates 5a-f. A suspension of α-chloro-acetoacetic ester (1.4 ml, 10 mmol) and azinylthiourea **3a-f** (10 mmol) in absolute EtOH (15 ml) was refluxed for 5 h. The product was filtered, the filtrate evaporated, and the residue was triturated with petroleum ether to give the ethyl ester hydrochlorides **4a-f**. A suspension of the compound **4a-f** (10 mmol) in $CHCl_3$ (25 ml) was then neutralized with Na_2CO_3 (0.58 g, 5.5 mmol) (finely ground powder). After 2 h the product was filtered, the filtrate was evaporated, and the residue was recrystallized from a mixture of heptane and toluene (2:1).

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