Chemistry of Heterocyclic Compounds, Vol. 46, No. 8, 2010

SYNTHESIS OF NOVEL CONDENSED PYRIDINES AND PYRIDO[2,3-*d*]PYRIMIDINES

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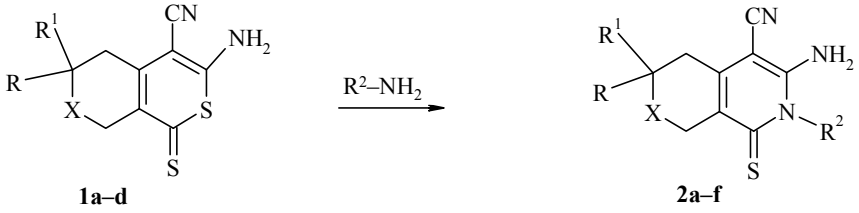
Methods have been developed for the synthesis of novel derivatives of pyrano[3,4-c]pyridines, 2,7-naphthyridines, and condensed pyrido[2,3-d]pyrimidines by condensation of thiopyranthiones.

Keywords: 2,7-naphthyridines, pyrano[3,4-*c*]pyridines, pyrido[2,3-*d*]pyrimidines, thiopyranthione, cyclization.

Derivatives of pyranopyridines and isoquinolines show antibacterial activity [1] whereas 2,7-naphthyridines are phosphodiesterase inhibitors [2]. With the aim of searching for biologically active compounds we have carried out in this study the synthesis of novel condensed pyridine derivatives (pyranopyridines, 2,7-naphthyridines, isoquinolines, and pyrido[2,3-*d*]pyrimidines). In order to prepare these compounds we have broadened the area of use of a previously reported recyclization of pyrano(pyrido)[3,4-*c*]thiopyran-1-thiones to pyrano[3,4-*c*]pyridines and 2,7-naphthyridines [3]. Hence the reaction of the known condensed thiopyranthiones **1a-d** [4, 5] with hydrazine hydrate or methylamine gave the corresponding pyridinethiones **2a-f**.



1a–d **2a–f**

1a, **2a**,**b** X = O, R = Me, R^1 = Et; **1b**, **2c**,**d** X = NMe, R = R^1 = H; **1c**, **2e** X = O, R = Pr-*i*, R^1 = H; **1d**, **2f** X = NCH_2Ph, R = R^1 = H; **2 a**,**c** R^2 = NH_2; **b**,**d–f** R^2 = Me

The reaction of the compound **2b** prepared and also the previously reported pyridinethiones **2g**,**h** [3, 6] with triethyl orthoformate gave the ethoxymethylideneamino derivatives of tetrahydro-1H-pyrano-[3,4-*c*]pyridine **3a**,**c** and hexahydroisoquinoline **3b**. Compounds **3a-c** can be treated with ammonia to give the corresponding amino derivatives **4a-c** and compound **3c** with methylamine gave the methylamino derivative **4d**. Cyclization of the derivatives **4a-d** using sodium ethylate gave the condensed 1-amino(aminomethyl)pyrido-[2,3-*d*]pyrimidines **5a-d**. It should be noted that compound **3c** and hydrazine hydrate gave the 1-hydrazino derivative **5e** immediately and the corresponding intermediate compound **4e** was not separated.

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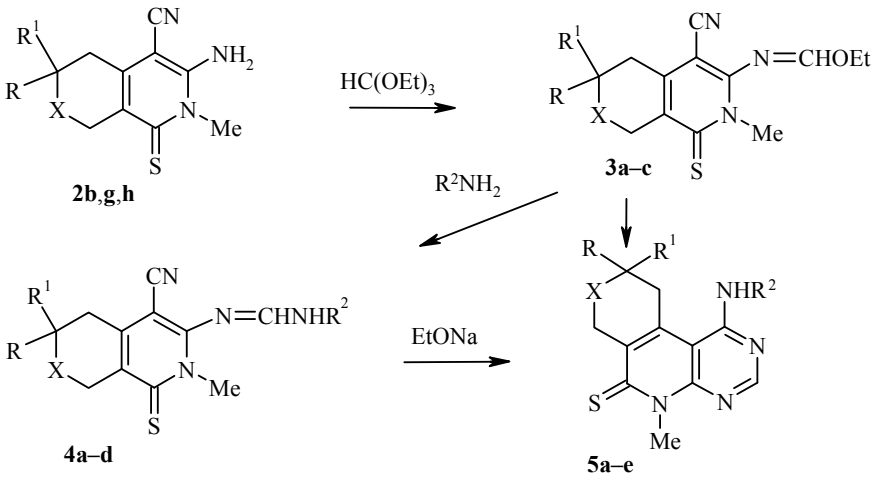
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1222-1226, August, 2010. Original article submitted August 25, 2009; revision submitted March 31, 2010.



2b, **3a**–**5a** X = O, R = Me, R^1 = Et; **2g**, **3b**–**5b** X = CH_2, R = R^1 = H;
2h, **3c**, **4c**,**d**, **5c**,**d**,**e** X = O, R = R^1 = Me; **4**, **5 a–c** R^2 = H, **d** R^2= Me; **5e** R^2= NH_2

The composition and structure of the compounds prepared were confirmed by the results of elemental analysis (see Table 1) as well as from IR and ^{1}H NMR spectroscopic data (see Experimental).

TABLE 1. Physicochemical Characteristics of Compounds **2-5**

Compound	Empirical formula	Found, % / Calculated, %				mp,°C	Yield, %
		C	H	N	S		
2a	$C_{12}H_{16}N_4OS$	54.39 / 54.52	6.21 / 6.10	21.28 / 21.19	12.21 / 12.13	232-234	56.8
2b	$C_{13}H_{17}N_3OS$	59.42 / 59.29	6.22 / 6.51	15.84 / 15.95	12.23 / 12.18	220-222	63.5
2c	$C_{10}H_{13}N_5S$	51.24 / 51.04	5.43 / 5.57	29.92 / 29.76	13.51 / 13.63	240-243	64.1
2d	$C_{11}H_{14}N_4S$	56.21 / 56.38	6.18 / 6.02	24.02 / 23.91	13.60 / 13.69	221-224	66.7
2e	$C_{13}H_{17}N_3OS$	59.04 / 59.29	6.70 / 6.51	16.08 / 15.95	12.07 / 12.18	208-210	67.6
2f	$C_{17}H_{18}N_4S$	65.92 / 65.78	5.70 / 5.84	18.19 / 18.05	10.26 / 10.33	228-229	60.3
3a	$C_{16}H_{21}N_3O_2S$	60.31 / 60.16	6.84 / 6.63	13.03 / 13.15	10.24 / 10.04	105-107	69.4
3b	$C_{14}H_{17}N_3OS$	61.25 / 61.06	6.07 / 6.22	15.38 / 15.26	11.41 / 11.64	109-110	70.4
3c	$C_{15}H_{19}N_3O_2S$	58.72 / 58.99	6.42 / 6.27	13.54 / 13.76	10.61 / 10.50	127-128	71.2
4a	$C_{14}H_{18}N_4OS$	58.11 / 57.91	6.02 / 6.25	19.41 / 19.29	11.19 / 11.04	237-239	72.1
4b	$C_{12}H_{14}N_4S$	58.74 / 58.51	5.58 / 5.73	22.88 / 22.74	12.89 / 13.02	256-257	65.1
4c	$C_{13}H_{16}N_4OS$	56.69 / 56.50	6.03 / 5.84	20.12 / 20.27	11.69 / 11.60	240-241	69.1
4d	$C_{14}H_{18}N_4OS$	57.81 / 57.91	6.37 / 6.25	19.08 / 19.29	10.95 / 11.04	242-244	65.7
5a	$C_{14}H_{18}N_4OS$	58.05 / 57.91	6.01 / 6.25	19.36 / 19.29	11.19 / 11.04	251-253	70.1
5b	$C_{12}H_{14}N_4S$	58.78 / 58.51	5.85 / 5.73	22.94 / 22.74	13.11 / 13.02	292-294	72.4
5c	$C_{13}H_{16}N_4OS$	56.63 / 56.50	6.05 / 5.84	20.02 / 20.27	11.47 / 11.60	270-272	74.1
5d	$C_{14}H_{18}N_4OS$	57.72 / 57.91	6.14 / 6.25	19.12 / 19.29	10.88 / 11.04	259-262	70.2
5e	$C_{13}H_{17}N_5OS$	53.43 / 53.59	6.01 / 5.88	24.21 / 24.04	11.18 / 11.00	254-256	71.3

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer for a suspension in vaseline oil. ^{1}H NMR spectra for the compounds synthesized were recorded on a Varian Mercury 300 VX instrument (300 MHz) using DMSO-d_6 solvent and with TMS as internal standard. Mass spectra were taken on an MX-1320 instrument with direct introduction of the sample into the ion source and an electron ionization energy of 70 eV. The purity of the compounds was monitored by TLC on Silufol UV-254 plates using the systems: ethanol–chloroform, 1:2 (**2a**,**c**), ethanol–chloroform, 1:1 (**2b**,**d-f**), acetone–hexane, 1: 1 (**3a-c**), or butanol–acetic acid–water, 4:2:5 (**4a-d**, **5a-e**).

The characteristics for the compounds prepared are given in Table 1.

6,7-Diamino-3-ethyl-3-methyl-8-thioxo-3,4,7,8-tetrahydro-1H-pyrano[3,4-*c*]pyridine-5-carbonitrile (2a) and 2,3-Diamino-7-methyl-1-thioxo-1,2,5,6,7,8-hexahydro-2,7-naphthyridine-4-carbonitrile (2c) (General Method). A mixture of compound **1a** or **1b** (5 mmol) and an 80% aqueous solution of hydrazine hydrate (10 ml) was held on a boiling water bath for 4 h. The cooled reaction mixture was treated with water (50 ml) and the crystals of the corresponding product formed were filtered off, washed with water, dried, and recrystallized from dioxane.

IR spectrum of compound **2a** or **2c** (basic spectroscopic data identical), ν, cm^{-1}: 3150-3460 (NH_2), 2220 (CN), 1580-1590 (C=C Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): compound **2a** – 0.96 (3H, t, J = 7.4, $CH_2C\underline{H}_3$); 1.18 (3H, s, CH_3); 1.50 (1H, dq, $^2J_1$ = 14.0, $^3J_2$ = 7.4, $C\underline{H}_2CH_3$); 1.62 (1H, dq, $^2J_1$ = 14.0, $^3J_2$ = 7.4, $CH_2C\underline{H}_3$); 2.42 (1H, d, ^2J = 17.2, CH_2); 2.52 (1H, d, ^2J = 17.2, CH_2); 4.35 (1H, d, ^2J = 16.2, OCH_2); 4.40 (1H, d, ^2J = 16.2, OCH_2); 6.45 (2H, s, NNH_2); 7.45 (2H, br. s, NH_2); compound **2c** – 2.44 (3H, s, CH_3); 2.61 (2H, t, ^3J = 5.8, CH_2); 2.75 (2H, t, ^3J = 5.8, $NC\underline{H}_2CH_2$); 3.36 (2H, s, NCH_2); 6.50 (2H, s, NNH_2); 7.36 (2H, br. s, NH_2).

6-Amino-3-ethyl-3,7-dimethyl-8-thioxo- (2b) and 6-Amino-3-isopropyl-7-methyl-8-thioxo-1,2,7,8-tetrahydro-1H-pyrano[3,4-*c*]pyridine-5-carbonitrile (2e), 3-Amino-2,7-dimethyl- (2d) and 3-Amino-7-benzyl-2-methyl-1-thioxo-1,2,5,6,7,8-hexahydro-2,7-naphthyridine-4-carbonitrile (2f) (General Method). A mixture of compound **1a**,**c**,**d** or **1f** (5 mmol) and a 25% aqueous solution of methylamine (20 ml) was held for 5 h at 70-80ºC. The cooled mixture was treated with water (50 ml), and the crystals of the products **2b**,**d**,**e** or **2f** formed respectively were filtered off, washed with water, and recrystallized from ethanol. IR spectrum of compounds **2b**,**d-f**, ν, cm^{-1}: 3190-3450 (NH_2), 2220 (CN), 1600 (C=C Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): compound **2b** – 0.96 (3H, t, ^3J = 7.4, $CH_2C\underline{H}_3$); 1.17 (3H, s, CH_3); 1.50 (1H, m) and 1.59 (1H, m, $C\underline{H}_2CH_3$); 2.39 (1H, d, ^2J = 17.3, CH_2); 2.49 (1H, d, ^2J = 17.3, CH_2); 3.94 (3H, s, NCH_3); 4.32 (1H, d, ^2J = 16.4, OCH_2); 4.38 (1H, d, ^2J = 16.4, OCH_2); 7.43 (2H, br. s, NH_2); compound **2d** – 2.40 (3H, s, NCH_3); 2.54 (2H, t, ^3J = 5.8, CH_2); 2.70 (2H, t, ^3J = 5.8, $NC\underline{H}_2CH_2$); 3.30 (2H, s, NCH_2); 3.95 (3H, s, NCH_3); 7.36 (2H, br. s, NH_2); compound **2e** – 1.00 (3H, d, ^3J = 6.1, CH_3); 1.02 (3H, d, ^3J = 6.1, CH_3); 1.78 (1H, m, CH); 2.43 (1H, dd, $^2J_1$ = 17.0, $^2J_2$ = 10.1, CH_2); 2.52 (1H, m, CH_2); 3.19 (1H, m, OCH); 3.93 (3H, s, NCH_3); 4.18 (1H, d, ^2J = 15.7, OCH_2); 4.71 (1H, d, ^2J = 15.7, OCH_2); 7.43 (2H, br. s, NH_2); compound **2f** – 2.58 (2H, t, ^3J = 5.6, $C\underline{H}_2CH_2N$); 2.69 (2H, t, ^3J = 5.6, $CH_2C\underline{H}_2N$); 3.45 (2H, s, NCH_2); 3.68 (2H, s, NCH_2); 3.95 (3H, s, NCH_3); 7.17-7.33 (5H, m, Ph); 7.36 (2H, br. s, NH_2).

3-Ethyl-3,7-dimethyl-8-thioxo- (3a) and 6-[(*E*)-(Ethoxymethylidene)amino]-3,3,7-trimethyl-8-thioxo-3,4,7,8-tetrahydro-1H-pyrano[3,4-*c*]pyridine-5-carbonitrile (3c), 3-[(*E*)-(Ethoxymethylidene)amino]-2-methyl-1-thioxo-1,2,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (3b) (General Method). A mixture of compound **2b**,**g** or **2h** (5 mmol) and triethyl orthoformate (25 ml) was refluxed using a reflux condenser for 3 h. The excess ester was distilled off and the residue was treated with hexane (10 ml). The crystalline products **3a-c** were filtered off, washed with hexane, dried, and recrystallized from hexane. IR spectrum of compounds **3a-c**, ν, cm^{-1}: 2230 (CN), 1650 (C=N), 1600 (C=C Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): compound **3b** – 1.46 (3H, t, ^3J = 7.1, $CH_2C\underline{H}_3$); 1.79 (4H, m, CH_2CH_2); 2.67 (2H, m, CH_2); 2.71 (2H, m, CH_2); 3.86 (3H, s, NCH_3); 4.48 (2H, q, ^3J = 7.1, $C\underline{H}_2CH_3$); 8.20 (1H, s, CH); compound **3c** – 1.29 (6H, s, $2CH_3$); 1.47 (3H, t, ^3J = 7.5, $CH_2C\underline{H}_3$); 2.61 (2H, s, CH_2); 3.83 (3H, s, NCH_3); 4.40-4.60 (4H, m, CH_2O, $C\underline{H}_2CH_3$); 8.22 (1H, s, CHO).

6-[(*E*)-(Aminomethylidene)amino]-3-ethyl-3,7-dimethyl-8-thioxo- (4a), 6-[(*E*)-(Aminomethylidene)-amino]-3,3,7-trimethyl-8-thioxo- (4c) and 3,3,7-Trimethyl-6-[(*E*)-(methylaminomethylidene)amino]-8-thioxo-3,4,7,8-tetrahydro-1H-pyrano[3,4-*c*]pyridine-5-carbonitrile (4d), 3-[(*E*)-(Aminomethylidene)-amino]-2-methyl-1-thioxo-1,2,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (4b) (General Method). A mixture of compound **3a**,**b** or **3c** (5 mmol) and a 20% ethanol solution of methylamine (20 ml) was held at 20-22ºC for 48 h. The crystals formed were filtered off, washed with water, dried, and recrystallized from ethanol. IR spectrum of compounds **4a-d**, ν, cm^{-1}: 3120-3440 (NH, NH_2), 2220 (CN), 1670 (C=N), 1580 (C=C Ar).

1-Amino-9-ethyl-5,9-dimethyl- (5a), 1-Amino-5,9,9-trimethyl- (5c), 5,9,9-Trimethyl-1-methyl-amino- (5d) and 1-Hydrazino-5,9,9-trimethyl-5,6,9,10-tetrahydro-7H-pyrano[4',3':4,5]pyrido[2,3-*d*]pyrimidine-6-thione (5e), and 1-Amino-5-methyl-7,8,9,10-tetrahydropyrimido[4,5-*c*]isoquinoline-6-thione (5b) (General Method). Compound **4a-d** (5 mmol) was added to a solution of sodium ethylate prepared from sodium (1.12 g, 5.2 mmol) and absolute ethanol (20 ml). The mixture was refluxed using a reflux condenser for 20 min. After cooling, the crystals of the corresponding product formed were filtered off, washed with water, dried, and recrystallized from DMSO. IR spectrum of compounds **5a-d**, ν, cm^{-1}: 3320-3500 (NH, NH_2); 1600-1610 (C=C Ar). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): compound **5a** – 0.96 (3H, t, ^3J = 7.4, $CH_2C\underline{H}_3$); 1.16 (3H, s, CH_3); 1.50 and 1.63 (1H, m and 1H, m, $C\underline{H}_2CH_3$); 2.86 (1H, d, ^2J = 17.3, CH_2); 3.03 (1H, d, ^2J = 17.3, CH_2); 4.17 (3H, s, NCH_3); 4.53 (1H, d, ^2J = 17.5, OCH_2); 4.61 (1H, d, ^2J = 17.5, OCH_2); 7.24 (2H, br. s, NH_2); 8.26 (1H, s, NCH); compound **5b** – 1.69-1.85 (4H, m, CH_2CH_2); 2.80 (2H, t, ^3J = 6.2, CH_2); 3.05 (2H, t, ^3J = 6.2, CH_2); 4.19 (3H, s, NCH_3); 7.16 (2H, br. s, NH_2); 8.23 (1H, s, NCH); compound **5d** – 1.25 (6H, s, $2CH_3$); 3.02 (3H, s, NCH_3); 3.04 (2H, s, CH_2); 4.18 (3H, s, NCH_3); 4.60 (2H, s, OCH_2); 7.06 (1H, br. s, NH); 8.36 (1H, s, NCH). Mass spectrum of compound **5c**, *m/z* (I_{rel}, %): 277 (15), 276 $[M]^+$ (74), 261 (37), 260 (91), 243 (50).

1-Hydrazino-5,9,9-trimethyl-5,7,9,10-tetrahydro-6H-pyrano[4',3':4,5]pyrido[2,3-d]pyrimidine-6-thione (5e). A mixture of compound **3c** (1.53 g, 5 mmol), hydrazine hydrate (3 ml), and ethanol (15 ml) was refluxed using a reflux condenser for 2 h. After cooling, the crystals of product **5e** were filtered off, washed with water, dried, and recrystallized from DMSO. Mass spectrum, *m/z* (I_{rel}, %): 292 (4), 291 $[M]^+$ (30), 276 (38), 275 (47), 260 (62), 249 (100).

REFERENCES

1. E. G. Paronikyan, G. V. Mirzoyan, A. S. Noravyan, D. A. Avakimyan, and Yu. Z. Ter-Zakharyan, *Khim.-Farm. Zh.*, **24**, No. 11, 29 (1993).
2. T. Ukita, Y. Nakamura, A. Kubo, Y. Yamamoto, Y. Moritani, K. Saruta, T. Higashijima, J. Kotera, K. Fujishige, M. Takagi, K. Kikkawa, and K. Omori, *Bioorg. Med. Chem. Lett.*, **13**, 2341 (2003).
3. E. G. Paronikyan, G. V. Mirzoyan, and A. S. Noravyan, *Khim. Zh. Armenii*, **48**, No. 3, 132 (1995).
4. E. G. Paronikyan and A. S. Noravyan, *Khim. Geterotsikl. Soedin.*, 914 (1999). [*Chem. Heterocycl. Comp.*, **35**, 799 (1999)].
5. K. Gewald, *J. Prakt. Chem.*, **31**, 209 (1966).
6. K. Gewald, M. Buchwalder, and M. Peukert, *J. Prakt. Chem.*, **315**, 679 (1973).