Heterocycles Synthesis through Reactions of Nucleophiles with Acrylonitriles. 7. A Novel and Facile One-Step Synthesis of 4*H*-Thiopyrans

Fathy Fahim ABDEL-LATIF
Chemistry Department, Faculty of Science, El-Minia University, El-Minia, A. R. Egypt
(Received February 10, 1989)

Synopsis. Several new 4*H*-thiopyrans were synthesized via a facile one-step method. Structures and reaction mechanisms are also reported and supported by another synthetic routes.

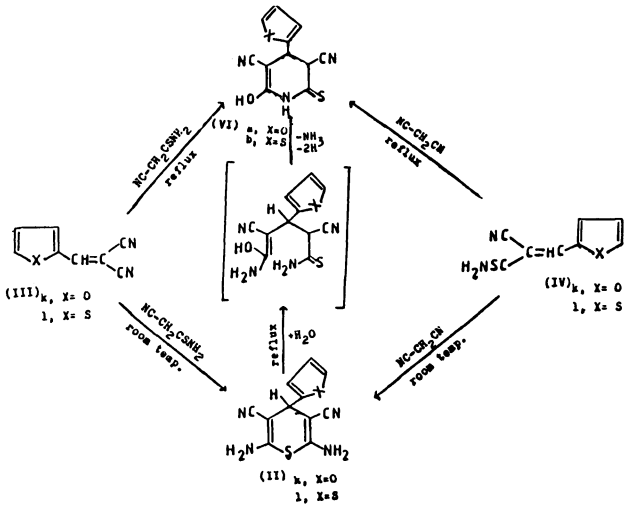
Thiopyrans and pyrans showed considerable biological activities[1-3] and are important as stabilizers for synthetic resins against heat or light.[4] As a continuation of our previous work for the synthesis of heterocyclic compounds of applied value,[5-8] in this work several new 4*H*-thiopyrans were successfully prepared by a facile one-step method from laboratory available chemicals. Stirring cold ethanolic piperidine solution of equimolar amounts of each of substituted benzaldehyde **Ia—j**, malononitrile, and cyanothioacetamide at room temperature afforded 4*H*-thiopyrans **IIa—j**. The structure of **II** was established for the reaction product based on its analytical and various spectral data (c.f. Experimental). For example, **IIb** showed only one cyano absorption band at 2190 cm^{-1} and one singlet due to the two amino groups at 6.5 ppm in the IR and ^1H NMR spectra respectively. This indicates that the molecule has a plane of symmetry and supports the structure of **IIb**.

Formation of **II** is rationalized in terms of the initial condensation of the aldehyde **I** with malononitrile or cyanothioacetamide affording α-cyanocinnamonitrile **III** or 2-cyano-3-phenyl-2-propenthioamide **IV** respectively followed by the Michael addition of the other active methylene compound to the olefinic bond in **III** or **IV** forming the acyclic intermediate **V** which cyclized under the applied conditions to the thiopyran **II** (Scheme 1).

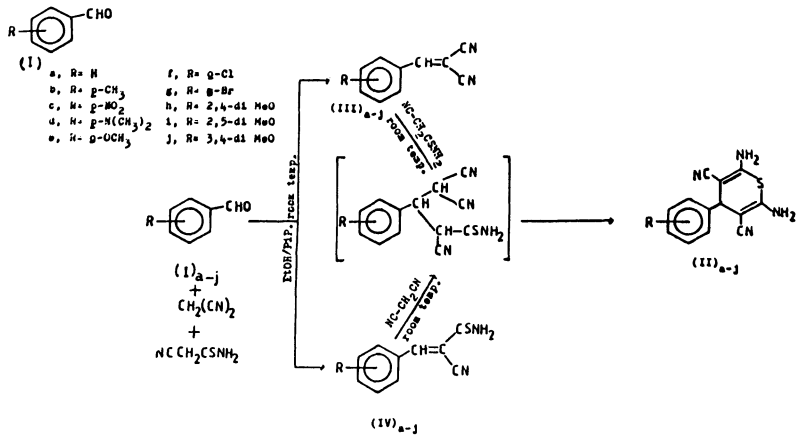
Structural proof was obtained through another route of synthesis by stirring cold ethanolic piperidine solution of an equimolar amount of **III** with cyanothioacetamide at room temperature and also by stirring ethanolic piperidine solution of **IV** with malononitrile at room temperature (c.f. Scheme 1 and Experimental).

On the other hand, synthesis of 2,6-diamino-3,5-dicyano-4-(2-furyl)-4*H*-thiopyran **IIk** was unsuccessful by using furfural instead of substituted benzaldehyde in this one-step method. While preparation of **IIk** was achieved by stirring ethanolic piperidine solution of α-cyano-β-(2-furyl) acrylonitrile **IIIk** and cyanothioacetamide at room temperature.

Compound **IIk** was also synthesized by another route by refluxing cold ethanolic piperidine solution of an equimolar amounts of 2-cyano-3-(2-furyl)-2-propenethioamide **IVk** and malononitrile at room



Scheme 2.



Scheme 1.

temperature (c.f. Scheme 2 and Experimental). In the same mannar, 2,6-diamino-3,5-dicyano-4-(2-thienyl)-4*H*-thiopyrans **III** was synthesized from (**IIII**) and from **IVl** (c.f. Scheme 2 and Experimental).

In contrast to behavior of both **IIIk,l** toward cyanothioacetamide and/or both **IVk,l** toward malononitrile under the previous conditions, refluxing ethanolic piperidine solution of equimolar amounts of **IIIk,l** and cyanothioacetamide afforded the corresponding 2(1*H*)-pyridinethione derivatives **VIa,b**.

Compounds **VIa,b** were also synthesized by refluxing ethanolic piperidine solution of eqimolar amounts of **IVk,l** and malononitrile.

Formation of **VI** is rationalized in terms of the initial formation of **II** which is the kinetically controlled reaction product followed by its rearrangement via ring opening and recyclization under the applied conditions to the final product (c.f. Scheme 2).

Unequivocal support to the previous mechanism was achieved by synthesis of **VIa,b** by refluxing ethanolic piperidine solution of **IIk,l** (c.f. Scheme 2 and Experimental).

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) on Shimadzu 408 spectrophotometer. ^{1}H NMR spectra were recorded in DMSO-d_6 on a 90 MHz on a Varian EM-390 spectrometer with Me_4Si as an internal standard and chemical shifts are expressed as δ values. Analytical data were obtained from the microanalytical data unit at Cairo university.

Synthesis of 4*H*-Thiopyrans (II) (General Procedure). Method A: A suspension of equimolar amounts (0.01 mol) of eacn of aromatic aldehyde **Ia—j**, malononitrile, and cyanothioacetamide in ethanol (100 ml) and a catalytic amount of piperidine was stirred at room temperature for 5—6 h. The solid obtained or formed after trituration with water was collected by filtration and crystalized from a proper solvent.

Method B: A suspension of equimolar amounts (0.01 mol) of **IIIa—l** or **IVa—l** was treated with 0.01 mol of cyanothioacetamide or malononitrile and a catalytic amount of piperidine was stirred at room temperature for 3—4 h. The solid product was collected as in method A.

2,6-Diamino-3,5-dicyano-4-phenyl-4*H*-thiopyran (IIa). Colorless crystals (from ethanol), mp 183—184 °C, yield 65%; IR 3460, 3420, 3350, 3210 (NH_2), 2920 (CH stretches), 2200 (CN), and 1635, 1600 cm^{-1} (C=C, δ_{NH_2}). ^{1}H NMR δ=4.2 (s, 1H, thiopyran H-4), 6.5 (s, 4H, 2NH_2), and 7.5 (m, 5H, aromatic protons). Found: C, 61.70; H, 3.80; N, 22.30; S, 12.50%. Calcd for $C_{13}H_{10}N_4S$: C, 61.41; H, 3.93; N, 22.04; S, 12.59%.

2,6-Diamino-3,5-dicyano-4(*p*-tolyl)-4*H*-thiopyran (IIb). Pale yellow crystals (from dil. ethanol), mp 147—149 °C, yield 60%; IR 3470, 3410, 3350, 3210 (NH_2), 2910, 2850 (CH, CH_3 stretches), 2190 (CN), and 1620, 1600 cm^{-1} (C=C, δ_{NH_2}). ^{1}H NMR δ=2.2 (s, 3H, CH_3), 4.1 (s, 1H, thiopyran H-4), 6.5 (s, 4H, 2NH_2), and 7.5 (m, 4H, aromatic protons). Found: C, 62.70; H, 4.40; N, 21.10; S, 11.70%. Calcd for $C_{14}H_{12}N_4S$: C, 62.68; H, 4.47; N, 20.89; S, 11.94%.

2,6-Diamino-3,5-dicyano-4-(*p*-nitrophenyl)-4*H*-thiopyran (IIc). Straw yellow crystals (from dioxane), mp 189 °C, yield 62%; IR 3450, 3410, 3360, 3230 (NH_2), 2920 (CH stretch), 2200 (CN), and 1635, 1610 cm^{-1} (C=C, δ_{NH_2}). ^{1}H NMR δ=4.3 (s, 1H, thiopyran H-4), 6.6 (s, 4H, 2NH_2), and 7.7 (m, 4H, aromatic protons). Found: C, 52.00; H, 2.90; N, 23.40; S, 10.80%. Calcd for $C_{13}H_9N_5O_2S$: C, 52.17; H, 3.01; N, 23.41; S, 10.70%.

2,6-Diamino-3,5-dicyano-4-(*p*-dimethylaminophenyl)-4*H*-thiopyran (IId). Orange crystals (from dioxane), mp 163 °C, yield 85%; IR 3480, 3430, 3320 (NH_2), 2910, 2870 (CH, CH_3 stretches), 2190 (CN), and 1630, 1610 cm^{-1} (C=C, δ_{NH_2}). Found: C, 60.60; H, 5.20; N, 23.70; S, 11.00%. Calcd for $C_{15}H_{15}N_5S$: C, 60.60; H, 5.05; N, 23.57; S, 10.77%.

2,6-Diamino-3,5-dicyano-4-(*o*-methoxyphenyl)-4*H*-thiopyran (IIe). Colorless crystals (from ethanol), mp 180 °C, yield 60%; IR 3400, 3330, 3290 (NH_2), 2950, 2900 (CH, CH_3 stretches), 2210, 2200 (CN), and 1650, 1610 cm^{-1} (C=C, δ_{NH_2}). Found: C, 59.00; H, 4.20; N, 20.00; S, 10.90%. Calcd for $C_{14}H_{12}N_4SO$: C, 59.15; H, 4.22; N, 19.72; S, 11.26%.

2,6-Diamino-3,5-dicyano-4-(*o*-chlorophenyl)-4*H*-thiopyran (IIf). Colorless crystals (from dil. methanol), mp 145—147 °C, yield 50%; IR 3450, 3350, 3250, 3200 (NH_2), 2910, 2800 (CH, stretch), 2200 (CN) and 1625, 1590 cm^{-1} (C=C, δ_{NH_2}). Found: C, 54.10; H, 3.30; N, 19.50; Cl, 12.60; S, 11.10%. Calcd for $C_{13}H_9N_4ClS$: C, 54.07; H, 3.12; N, 19.41; Cl, 12.30; S, 11.09%.

2,6-Diamino-3,5-dicyano-4-(*m*-bromophenyl)-4*H*-thiopyran (IIg). Colorless crystals (from ethanol), mp 189—191 °C, yield 78%; IR 3450, 3350, 3250 (NH_2), 2890, 2850 (CH, stretch), 2200, 2195 (CN) and 1630, 1620, 1600 cm^{-1} (C=C, δ_{NH_2}). Found: C, 47.00; H, 3.00; N, 16.80; Br, 23.70; S, 9.50%. Calcd for $C_{13}H_9N_4BrS$: C, 46.85; H, 2.70; N, 16.81; Br, 24.02; S, 9.61%.

2,6-Diamino-3,5-dicyano-4-(2,4-dimethoxyphenyl)-4*H*-thiopyran (IIh). Pale yellow crystals (from ethanol), mp 159 °C, yield 70%; IR 3450, 3320, 3200 (NH_2), 2910, 2850 (CH, CH_3 stretches), 2200 (CN) and 1635—1620, 1600 cm^{-1} (C=C, δ_{NH_2}). Found: C, 57.10; H, 4.60; N, 18.00; S, 10.30%. Calcd for $C_{15}H_{14}N_4SO_2$: C, 57.32; H, 4.46; N, 17.83; S, 10.19%.

2,6-Diamino-3,5-dicyano-4-(2,5-dimethoxyphenyl)-4*H*-thiopyran (IIi). Colorless crystals (from dil. methanol), mp 152 °C, yield 60%; IR 3450, 3420, 3350, 3200 (NH_2), 2950, 2890, 2850 (CH, CH_3 stretches), 2200, 2192 (CN), and 1630, 1600 cm^{-1} (C=C, δ_{NH_2}). Found: C, 57.20; H, 4.50; N, 17.80; S, 10.10%. Calcd for $C_{15}H_{14}N_4SO_2$: C, 57.32; H, 4.46; N, 17.83; S, 10.19%.

2,6-Diamino-3,5-dicyano-4-(3,4-dimethoxyphenyl)-4*H*-thiopyran (IIj). Yellow crystals (from dil. methanol), mp 140 °C, yield 50%. Found: C, 57.00; H, 4.70; N, 17.60; S, 10.30%. Calcd for $C_{15}H_{14}N_4SO_2$: C, 57.32; H, 4.45; N, 17.83; S, 10.19%.

2,6-Diamino-3,5-dicyano-4-(2-furyl)-4*H*-thiopyran (IIk). Colorless crystals (turns to yellow on standing in light) (from dil. ethanol), mp 170 °C, yield 70% (method B); IR 3400, 3330, 3200 (NH_2), 2900, 2850 (CH stretch), 2185 (CN), and 635—1620 (br), 1605 cm^{-1} (C=C, δ_{NH_2}). ^{1}H NMR δ=3.3 (s, 2H, NH_2), 4.3 (s, 1H, thiopyran H-4), 6.0 (*d*1H, furan H-3), 6.3 (q, 1H, furan H-4), 6.9 (s, 2H, NH_2), and 7.5 (d, 1H, furan H-5). Found: C, 54.40; H, 3.80; N, 23.10; S, 13.30%. Calcd for $C_{11}H_8N_4OS$: C, 64.09; H, 27.00; N, 22.95; S, 13.11%.

2,6-Diamino-3,5-dicyano-4-(2-thienyl)-4*H*-thiopyran (III). Gray crystals (from methanol), mp 140 °C, yield 75% (method B), IR 3420, 3320, 3200 (NH_2), 2900, 2850 (CH, stretches), 2190 (CN) and 1635, 1620, 1600 cm^{-1} (C=C, δ_{NH_2}). Found: C, 51.10; H, 2.90; N, 21.40; S, 24.50%. Calcd for $C_{11}H_8N_4S_2$: C, 50.77; H, 3.07; N, 21.53; S, 24.61%.

Synthesis of 2(1*H*)-Pyridinethione (VI) (General Procedure). Method A: To a suspension of an equimolar amount 0.01 mol of **IIIk,l** and/or **IVk,l** in ethanol (50 ml) was added 0.01 mol of cyanothioacetamide and/or malononitrile and catalytic amount of piperidine. The reaction mixture was refluxed for 3 h and then evaporated in vacuo. The residue was triturated with water and acidified with acetic acid. The solid obtained was collected by filtration and recrystallized

from the propar solvent.

Method B: To a solution of **IIk,l** (1.0 g) in ethanol (30 ml) was added 3 drops of piperidine and the reaction mixture was refluxed for 6 h, then left to cool, and then treated as in method A.

3,5-Dicyano-3,4-dihydro-4-(2-furyl)-6-hydroxy-2(1*H*)-pyridinethione (VIa). Red crystals (from ethanol), mp 140 °C, yield 80%, IR, 3450—3100 (br NH, OH), 2900 (CH) 2200 (CN) and br 1670—1630 cm^{-1} (br CO, C=N). ^1H NMR δ=3.1 (s, br, 2H, OH and NH) and 6.5—7.5 (m, 3H, furan 3H). Found: C, 54.50; H, 1.90; N, 17.00; S, 13.40%. Calcd for $C_{11}H_5N_3O_2S$: C, 54.32; H, 2.06; N, 17.28; S, 13.17%.

3,5-Dicyano-3,4-dihydro-4-(2-thienyl)-6-hydroxy-2(1*H*)-pyridinethione (VIb). Yellow crystals (from dil. methanol), mp 190 °C, yield 60%, IR, 3350, 3200 (NH, OH), 2900, 2850 (CH), 2200 (CN) and 11670—1640 (br), 1600 cm^{-1} (CO, C=C). Found: C, 50.80; H; 1.70; N, 16.00; S, 24.40%. Calcd for $C_{11}H_5N_3OS_2$: C, 50.96; H, 1.93, N, 16.22; S 24.71%.

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