

Studies on Fused 2(1*H*)-Pyridinethiones: New Routes for the Synthesis of Fused 1*H*-Pyrazolo[3,4-*b*]pyridines and Fused Thieno[2,3-*b*]pyridines

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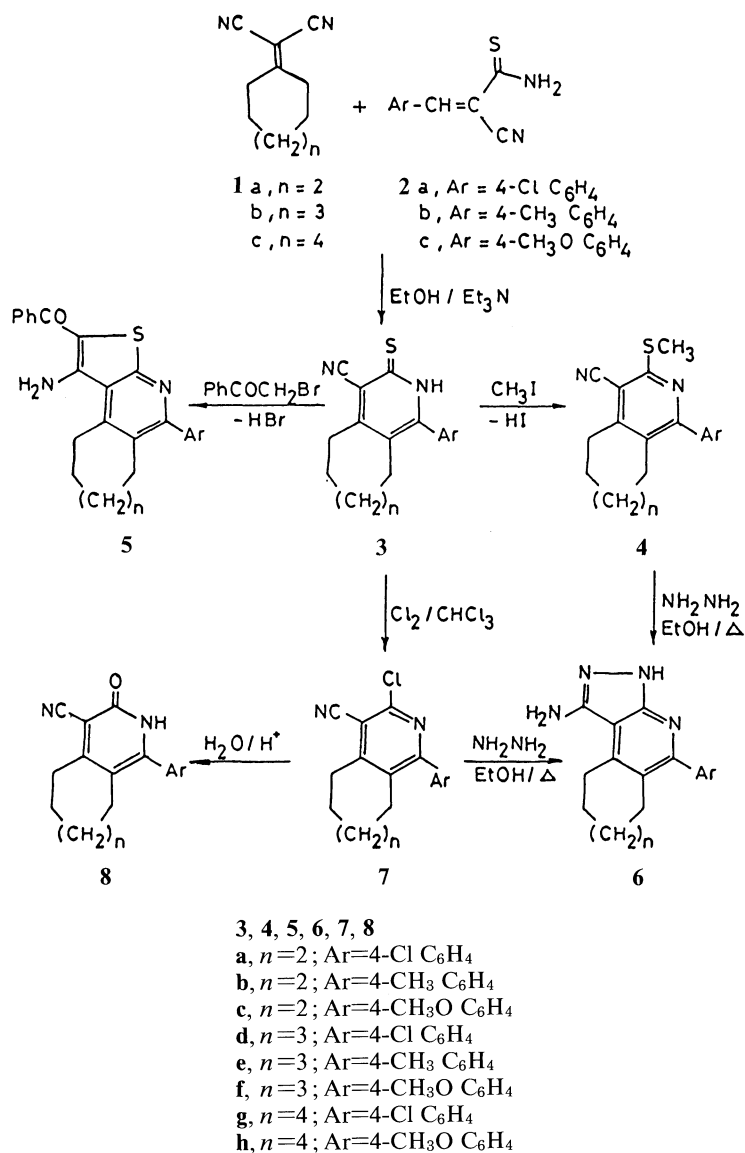
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A synthesis of fused 1*H*-pyrazolo[3,4-*b*]pyridines and fused thieno[2,3-*b*]pyridines utilizing fused 2(1*H*)-pyridinethiones as starting components is described. The structures of the products were assigned and confirmed on the basis of their elemental analysis and spectral data.

We have described several novel syntheses of 2(1*H*)-pyridinethiones.^{1–4} These compounds, as well as a number of 2(1*H*)-pyridinone derivatives, are considered important as intermediates for the synthesis of various pyrido[2,3-*b*]pyrazine analogs of the pteridine and folic acid ring systems.^{5,6} The latter have a greater selectiv-

ity for a broader range of human tumors.⁷ One of these papers⁸) has described the novel reaction of cycloalkylidenemalononitriles (**1**) with 2-arylmethylene-2-cyanothioacetamides (**2**) producing the fused 2(1*H*)-pyridinethiones (**3**) of the unexpected structure. We have explained the formation of **3** by a reaction



Scheme 1.

Table 1. Characterization Data for **4a—h**, **5a—h**, **6a—h**, **7a—h**, and **8a—h**

Compound (Color)	Recryst. Solvent	Mp	Yield	Mol. formula	% Found/ Required			M ⁺
		°C	%		C	H	N	<i>m/z</i>
4a Yellow	MeOH	189	66	C ₁₆ H ₁₃ ClN ₂ S	64.0 63.9	4.5 4.3	9.0 9.3	300
4b Yellow	EtOH	212	55	C ₁₇ H ₁₆ N ₂ S	73.1 72.9	5.5 5.7	9.7 10.0	280
4c Orange	EtOH	182	50	C ₁₇ H ₁₆ N ₂ SO	68.6 68.9	5.5 5.4	9.3 9.5	
4d Yellow	Dioxane	230	60	C ₁₇ H ₁₅ ClN ₂ S	64.6 64.9	4.5 4.8	8.6 8.9	
4e Brown	MeOH	197	50	C ₁₈ H ₁₈ N ₂ S	73.2 73.5	5.8 6.1	9.2 9.5	294
4f Orange	EtOH	222	30	C ₁₈ H ₁₈ N ₂ SO	69.5 69.7	5.5 5.8	8.8 9.0	
4g Orange	MeOH	159	60	C ₁₈ H ₁₇ ClN ₂ S	65.5 65.8	4.9 5.2	8.3 8.5	
4h Yellow	EtOH	178	60	C ₁₉ H ₂₀ N ₂ SO	70.1 70.4	5.9 6.2	8.3 8.6	
5a Yellow	EtOH–DMF	253	70	C ₂₃ H ₁₇ ClN ₂ SO	67.9 68.2	4.5 4.2	6.6 6.9	404
5b Brown	EtOH	230—232	80	C ₂₄ H ₂₀ N ₂ SO	74.6 75.0	4.8 5.2	6.9 7.3	384
5c Yellow	EtOH–DMF	>300	75	C ₂₄ H ₂₀ N ₂ SO ₂	71.6 72.0	4.7 5.0	6.8 7.0	
5d Yellow	DMF	272—274	60	C ₂₄ H ₁₉ ClN ₂ SO	68.5 68.8	4.4 4.5	6.5 6.7	
5e Brown	MeOH–DMF	348—350	85	C ₂₅ H ₂₂ N ₂ SO	74.2 75.4	5.2 5.5	6.6 7.0	
5f Yellow	Dioxane	282—284	80	C ₂₅ H ₂₂ N ₂ SO ₂	72.7 72.5	5.5 5.3	7.0 6.8	
5g Yellow	Dioxane	228	70	C ₂₅ H ₂₁ ClN ₂ SO	69.0 69.4	5.2 4.9	6.2 6.5	
5h Yellow	EtOH	240—242	50	C ₂₆ H ₂₄ N ₂ SO ₂	73.1 72.9	5.5 5.6	6.1 6.5	428
6a Colorless	DMF	>300	90	C ₁₅ H ₁₃ ClN ₄	63.5 63.3	5.0 4.6	19.3 19.7	
6b White	Dioxane	284—286	70	C ₁₆ H ₁₆ N ₄	72.5 72.7	5.8 6.1	21.0 21.2	264
6c White	EtOH	255	80	C ₁₆ H ₁₆ N ₄ O	68.2 68.6	5.5 5.7	19.7 20.0	
6d Buff	Dioxane	212	50	C ₁₆ H ₁₅ ClN ₄	64.5 64.3	4.7 5.0	18.5 18.8	
6e Buff	EtOH	198	55	C ₁₇ H ₁₈ N ₄	73.5 73.4	6.1 6.5	19.8 20.1	
6f Yellow	MeOH	202	60	C ₁₇ H ₁₈ N ₄ O	69.0 69.4	5.7 6.1	18.8 19.0	
6g White	MeOH	178	40	C ₁₇ H ₁₇ ClN ₄	65.0 65.3	5.2 5.4	17.5 17.9	
6h White	MeOH	167	55	C ₁₈ H ₂₀ N ₄ O	69.8 70.1	6.1 6.5	17.9 18.2	
7a Colorless	MeOH	166	50	C ₁₅ H ₁₀ Cl ₂ N ₂	62.0 62.3	3.8 3.5	9.5 9.7	
7b White	EtOH	180—182	40	C ₁₆ H ₁₃ ClN ₂	71.2 71.5	5.0 4.8	10.0 10.4	
7c White	MeOH	201	35	C ₁₆ H ₁₃ ClN ₂ O	67.5 67.5	4.4 4.6	9.5 9.8	
7d Buff	MeOH	172	40	C ₁₆ H ₁₂ Cl ₂ N ₂	63.5 63.4	4.2 4.0	8.8 9.2	
7e White	EtOH	217	50	C ₁₇ H ₁₅ ClN ₂	72.0 72.2	5.0 5.3	9.5 9.9	
7f White	MeOH	171	40	C ₁₇ H ₁₅ ClN ₂ O	68.0 68.3	5.4 5.0	9.0 9.4	298
7g Buff	Dioxane	182	50	C ₁₇ H ₁₄ Cl ₂ N ₂	64.0 64.4	4.6 4.4	8.5 8.8	
7h Colorless	MeOH	138	60	C ₁₈ H ₁₇ ClN ₂ O	68.8 69.1	5.5 5.4	8.6 9.0	

Table 1. (Continued)

Compound (Color)	Recryst. Solvent	Mp	Yield	Mol. formula	% Found/Required			M ⁺
		°C	%		C	H	N	<i>m/z</i>
8a Yellow	DMF-MeOH	280—282	40	C ₁₅ H ₁₁ ClN ₂ O	66.2	4.0	10.0	
8b Brown	DMF	266—268	35	C ₁₆ H ₁₄ N ₂ O	66.5	4.1	10.4	
8c Yellow	Dioxane	290—292	30	C ₁₆ H ₁₄ N ₂ O ₂	76.5	5.5	11.0	
8d White	DMF-EtOH	272—274	50	C ₁₆ H ₁₃ ClN ₂ O	76.8	5.6	11.2	
8e White	Dioxane	244—246	60	C ₁₇ H ₁₆ N ₂ O	71.8	5.0	10.3	
8f Colorless	EtOH	258—260	55	C ₁₇ H ₁₆ N ₂ O ₂	72.2	5.3	10.5	
8g Buff	MeOH	270—272	45	C ₁₇ H ₁₅ ClN ₂ O	67.2	4.3	9.5	
8h Buff	EtOH	222—223	50	C ₁₈ H ₁₈ N ₂ O ₂	67.5	4.6	9.8	
					77.0	5.8	10.3	
					77.3	6.1	10.6	
					72.5	5.5	10.2	280
					72.9	5.7	10.0	
					68.0	4.8	9.0	
					68.3	5.0	9.4	
					73.2	5.8	9.2	
					73.5	6.1	9.5	

sequence initiated by the exchange reaction between the cycloalkylidene group of **1** and the arylmethylene group of **2**. In conjunction with this work we report a novel synthesis of fused 1*H*-pyrazolo[3,4-*b*]pyridines and fused thieno[2,3-*b*]pyridines utilizing the fused 2(1*H*)-pyridinethiones (**3**) as starting material. Moreover, the results of our work aimed to define the scope and limitation of our procedures for the synthesis of fused pyridine derivatives. Thus, it has been found that **3**⁸ reacted with methyl iodide in CH₂Cl₂-K₂CO₃ to afford the corresponding *S*-alkyl derivative (**4**). The ¹H NMR spectra for **4a** showed a band at δ=2.7 assigned to SCH₃

group. When **3** were subjected to the reaction of phenacyl bromide as alkylating agent, the *S*-alkylated derivatives could not be isolated, but cyclize to the fused thieno[2,3-*b*]pyridine derivatives (**5**). The structure of compounds **5** was established on the bases of elemental analysis and spectral data. Thus, the IR spectrum of **5a** revealed the absence of a CN band, the mass was compatible with the molecular formula C₂₃H₁₇ClN₂SO (M⁺ 404), and ¹H NMR contained a broad band at δ=6.7 assignable to an amino function and a multiplet at δ=7.3—7.8 assigned to the aromatic protons (cf. Tables 1 and 2).

Table 2. IR and ¹H NMR Data for Compounds Listed in Table 1

Compound	IR, ν _{max} /cm ⁻¹ (selected bands)	¹ H NMR, δ	Compound	IR, ν _{max} /cm ⁻¹ (selected bands)	¹ H NMR, δ
4a	2225 (CN)	2.21 (m, 2H, CH ₂), 2.50 (m, 2H, CH ₂), 2.72 (s, 3H, CH ₃), 3.2 (m, 2H, CH ₂), 7.13—7.65 (m, 4H, C ₆ H ₄)	6a	3435, 3297 (NH ₂ and NH)	1.90 (m, 2H, CH ₂), 2.72—3.17 (m, 4H, 2CH ₂), 5.00 (s, br, 2H, NH ₂), 6.88—7.55 (m, 4H, C ₆ H ₄), 11.62 (s, br, 1H, NH)
4c	2220 (CN)	2.20 (m, 2H, CH ₂), 2.60 (m, 2H, CH ₂), 2.82 (s, 3H, CH ₃), 2.95 (m, 2H, CH ₂), 3.92 (s, 3H, OCH ₃), 7.12—7.63 (m, 4H, C ₆ H ₄)	6c	3450, 3300 (NH ₂ and NH)	2.18 (m, 2H, CH ₂), 2.77—3.24 (m, 4H, 2CH ₂), 3.92 (s, 3H, OCH ₃), 5.28 (s, br, 2H, NH ₂), 7.00—7.64 (m, 4H, C ₆ H ₄), 11.82 (s, br, 1H, NH)
4d	2220 (CN)	1.68 (m, 4H, 2CH ₂), 2.60 (m, 2H, CH ₂), 2.72 (s, 3H, CH ₃), 2.93 (m, 2H, CH ₂), 7.00—7.65 (m, 4H, C ₆ H ₄)	6d	3480, 3350 (NH ₂ and NH)	1.68 (m, 4H, 2CH ₂), 2.58 (m, 2H, CH ₂), 2.90 (m, 2H, CH ₂), 5.11 (s, br, 2H, NH ₂), 6.95—7.70 (m, 4H, C ₆ H ₄), 11.72 (s, br, 1H, NH)
4g	2225 (CN)	1.15—1.73 (m, 6H, 3CH ₂), 2.14—2.44 (m, 2H, CH ₂), 2.77 (s, 3H, CH ₃), 3.08 (m, 2H, CH ₂), 7.18—7.58 (m, 4H, C ₆ H ₄)	6g	3420, 3300 (NH ₂ and NH)	1.3—1.95 (m, 6H, 3CH ₂), 2.40 (m, 2H, CH ₂), 3.12 (m, 2H, CH ₂), 5.28 (s, br, 2H, NH ₂), 7.00—7.50 (m, 4H, C ₆ H ₄), 11.55 (s, br, 1H, NH)
4h	2220 (CN)	1.17—1.84 (m, 6H, 3CH ₂), 2.15—2.55 (m, 2H, CH ₂), 2.80 (s, 3H, CH ₃), 2.98 (m, 2H, CH ₂), 3.88 (s, 3H, OCH ₃), 6.98—7.44 (m, 4H, C ₆ H ₄)	7a	2220 (CN)	2.22 (m, 2H, CH ₂), 2.66 (m, 2H, CH ₂), 2.94 (m, 2H, CH ₂), 7.0—7.62 (m, 4H, C ₆ H ₄)

Table 2. (Continued)

Compound	IR, $\nu_{\max}/\text{cm}^{-1}$ (selected bands)	^1H NMR, δ	Compound	IR, $\nu_{\max}/\text{cm}^{-1}$ (selected bands)	^1H NMR, δ
5a	3480, 3300 (NH ₂), 1685 (CO)	2.18 (m, 2H, CH ₂), 2.48 (m, 2H, CH ₂), 2.69 (s, 2H, CH ₂), 6.72 (s, br, 2H, NH ₂), 7.35— 7.80 (m, 9H, C ₆ H ₅ and C ₆ H ₄)	7d	2230 (CN)	1.78 (m, 4H, 2CH ₂), 2.50 (m, 2H, CH ₂), 2.88 (m, 2H, CH ₂), 6.98—7.62 (m, 4H, C ₆ H ₄)
5b	3400, 3320 (NH ₂), 1680 (CO)	2.25 (m, 2H, CH ₂), 2.55 (m, 2H, CH ₂), 2.66 (s, 3H, CH ₃), 2.88, (m, 2H, CH ₂), 6.71 (s, br, 2H, NH ₂), 7.35—7.85 (m, 9H, C ₆ H ₅ and C ₆ H ₄)	8d	3439, 3309 (NH), 2218 (CN), 1650 (CO)	1.60 (m, 2H, CH ₂), 1.68 (m, 2H, CH ₂), 2.22 (m, 2H, CH ₂), 2.64 (m, 2H, CH ₂), 7.1—7.78 (m, 4H, C ₆ H ₄), 12.68 (s, br, 1H, NH)
5d	3450, 3330 (NH ₂), 1670 (CO)	1.58 (m, 4H, 2CH ₂), 2.65 (m, 2H, CH ₂), 2.84 (m, 2H, CH ₂), 6.81 (s, br, 2H, NH ₂), 7.22—7.72 (m, 9H, C ₆ H ₅ and C ₆ H ₄)	8g	3400, 3330 (NH), 2220 (CN), 1645 (CO)	1.45 (m, 2H, CH ₂), 1.63 (m, 2H, CH ₂), 1.78 (m, 2H, CH ₂), 2.46 (m, 2H, CH ₂), 2.86 (m, 2H, CH ₂), 6.96— 7.80 (m, 4H, C ₆ H ₄), 12.48 (s, br, 1H, NH)
5f	3400, 3300 (NH ₂), 1685 (CO)	1.75 (m, 4H, 2CH ₂), 2.58 (m, 2H, CH ₂), 2.80 (m, 2H, CH ₂), 3.92 (s, 3H, OCH ₃), 6.72 (s, br, 2H, NH ₂), 7.27— 7.66 (m, 9H, C ₆ H ₅ and C ₆ H ₄)	8h	3500, 3330 (NH), 2218 (CN), 1655 (CO)	1.46 (m, 2H, CH ₂), 1.67 (m, 2H, CH ₂), 1.78 (m, 2H, CH ₂), 2.24 (m, 2H, CH ₂), 2.88 (m, 2H, CH ₂), 3.94 (s, 3H, OCH ₃), 7.00—7.72 (m, 4H, C ₆ H ₄), 12.48 (s, br, 1H, NH)
5g	3420, 3300 (NH ₂), 1680 (CO)	1.28—1.92 (m, 6H, 3CH ₂), 2.40 (m, 2H, CH ₂), 2.95 (m, 2H, CH ₂), 6.74 (s, br, 2H, NH ₂), 7.08—8.02 (m, 9H, C ₆ H ₅ and C ₆ H ₄)			

A 2-chloro derivative corresponding to the compound **3** can be prepared by treating the 2(1*H*)-pyridinethiones (**3**) with chlorine gas in chloroform at room temperature. Structure **7** was established based on elemental analysis and spectral data (MS, IR, ^1H NMR). The IR spectra of compound **7a** showed absence of a NH band. Compounds **7** reacted with hydrazine hydrate in refluxing ethanol containing catalytic amounts of triethylamine for 3 h to give the 1*H*-pyrazolo[3,4-*b*]pyridine derivatives (**6**). Compounds **6** could also be prepared by the reaction of **4** with hydrazine hydrate under the same conditions. The structure of **6** was established by mass spectroscopy, IR and ^1H NMR data. The IR spectra of compound **6a** showed absence of a CN band and its ^1H NMR spectra a band at $\delta=5.0$ (NH₂) and 11.6 (NH). Hydrolysis of **7** with HCl in ethanol led to the fused 1,2-dihydro-2-oxo-3-pyridinecarbonitriles (**8**). The results indicate that the fused 2(1*H*)-pyridinethiones (**3**) can be utilized as an excellent starting material for the preparation of other heterocyclic compounds which are not readily accessible.

Experimental

All melting points are uncorrected. IR spectra were obtained (KBr disc) on a Pye Unicam Spectra-1000 or on a Shimadzu IR 200 instrument. ^1H NMR spectra were measured on a Wilmad 270 MHz spectrometer for solutions in (CD₃)₂SO using SiMe₄ as an internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Centre at Cairo University.

Compounds **3a—h** were prepared according to our litera-

ture procedure.⁸⁾

Cycloalkane-Fused 6-Aryl-3-cyano-2-(methylthio)pyridines (4a—h). A mixture of **3** (0.01 mol), K₂CO₃ (0.02 mol), and MeI (0.015 mol) in dry dichloromethane (50 ml) was stirred at room temperature for 24 h and then diluted with cold water (100 ml). The dichloromethane layer was washed several times with water, dried and then evaporated. The resulting solid product was collected by filtration and crystallized from the appropriate solvent.

Cycloalkane-Fused 3-Amino-6-aryl-2-benzoylthieno[2,3-*b*]pyridines (5a—h). A mixture of **3** (0.01 mol), K₂CO₃ (0.02 mol), and phenacyl bromide (0.01 mol) in dry DMF (50 ml) was stirred at 50—60 °C for 3 h and then diluted with cold water (50 ml). The resulting solid product was collected by filtration and crystallized from the appropriate solvent.

Cycloalkane-Fused 3-Amino-6-aryl-1*H*-pyrazolo[3,4-*b*]pyridines (6a—h). To a mixture of **4** or **7** (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (50 ml), triethylamine (0.5 ml) was added. The mixture was heated under reflux for 3 h, and then allowed to stand overnight. The resultant precipitate was isolated by suction and crystallized from the appropriate solvent.

Cycloalkane-Fused 6-Aryl-2-chloro-3-cyanopyridines (7a—h). A solution of **3** (0.01 mol) in chloroform (50 ml) was stirred under a stream of dry chlorine gas for 2 h, and then set aside overnight. The resultant precipitate was filtered off and crystallized from the appropriate solvent.

Cycloalkane-Fused 6-Aryl-3-cyano-2(1*H*)-pyridinones (8a—h). Concentrated hydrochloric acid (3 ml, 37.5%) was added to a solution of **7** (0.01 mol) in ethanol (50 ml). The mixture was heated under reflux for 2 h and then evaporated under reduced pressure. The remaining product was triturated with water and neutralized by addition of aqueous ammonia. The solid product was filtered off and crystallized from the appropriate solvent.

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References

- 1) G. E. H. Elgemeie, H. A. Elfahham, and H. A. Nabey, *Bull. Chem. Soc. Jpn.*, **61**, 4431 (1988).
 - 2) G. E. H. Elgemeie, H. A. Elfahham, and R. Mekhamer, *Sulfur Lett.*, **8**, 187 (1988).
 - 3) G. E. H. Elgemeie, H. A. Elfahham, and H. Nabey, *Sulfur Lett.*, **9**, 47 (1989).
 - 4) G. E. H. Elgemeie and M. M. M. Ramiz, *Phosphorus Sulfur*, **46**, 95 (1989).
 - 5) C. Temple, R. D. Elliot, and J. A. Montgomery, *J. Org. Chem.*, **47**, 761 (1982).
 - 6) E. C. Taylor, D. C. Palmer, T. J. George, S. R. Fletcher, C. P. Tseng, P. J. Harrington, and G. P. Beardsley, *J. Org. Chem.*, **48**, 4852 (1983).
 - 7) W. D. Ensminger, G. B. Grindey, and J. A. Hoglind, "Advances in Cancer Chemotherapy," ed by A. Rosowsky, Marcel Dekker, New York (1979), Vol. 1, pp. 61—109.
 - 8) G. E. H. Elgemeie, H. A. Regaila, and N. Shehata, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1267.
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