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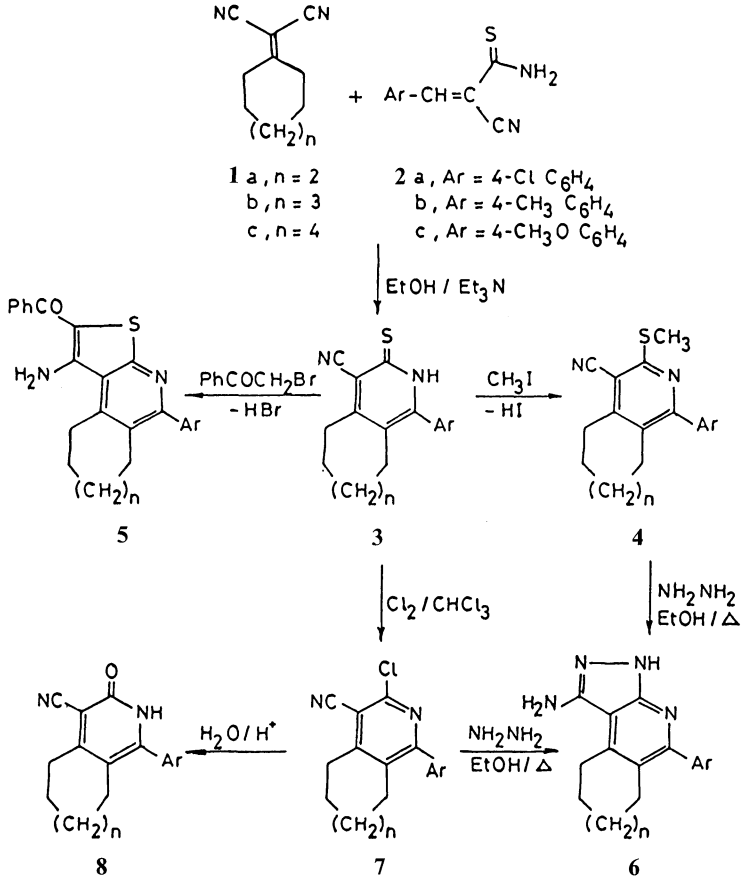
A synthesis of fused 1*H*-pyrazolo[3,4-*b*]pyridines and fused thieno[2,3-*b*]pyridines utilizing fused 2(1*H*)-pyridinethiones as starting components is described. The structures of the products were assigned and confirmed on the basis of their elemental analysis and spectral data.

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 selectivity for a broader range of human tumers.[7] One of these papers[8] 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



3, 4, 5, 6, 7, 8
a, $n=2$; Ar=4-Cl C_6H_4
b, $n=2$; Ar=4-CH_3 C_6H_4
c, $n=2$; Ar=4-CH_3O C_6H_4
d, $n=3$; Ar=4-Cl C_6H_4
e, $n=3$; Ar=4-CH_3 C_6H_4
f, $n=3$; Ar=4-CH_3O C_6H_4
g, $n=4$; Ar=4-Cl C_6H_4
h, $n=4$; Ar=4-CH_3O C_6H_4

Scheme 1.

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

Compound (Color)	Recryst. Solvent	Mp °C	Yield %	Mol. formula	% Found/Required C	H	N	M^+ *m/z*
4a	MeOH	189	66	$C_{16}H_{13}ClN_2S$	64.0	4.5	9.0	300
Yellow					63.9	4.3	9.3	
4b	EtOH	212	55	$C_{17}H_{16}N_2S$	73.1	5.5	9.7	280
Yellow					72.9	5.7	10.0	
4c	EtOH	182	50	$C_{17}H_{16}N_2SO$	68.6	5.5	9.3	
Orange					68.9	5.4	9.5	
4d	Dioxane	230	60	$C_{17}H_{15}ClN_2S$	64.6	4.5	8.6	
Yellow					64.9	4.8	8.9	
4e	MeOH	197	50	$C_{18}H_{18}N_2S$	73.2	5.8	9.2	294
Brown					73.5	6.1	9.5	
4f	EtOH	222	30	$C_{18}H_{18}N_2SO$	69.5	5.5	8.8	
Orange					69.7	5.8	9.0	
4g	MeOH	159	60	$C_{18}H_{17}ClN_2S$	65.5	4.9	8.3	
Orange					65.8	5.2	8.5	
4h	EtOH	178	60	$C_{19}H_{20}N_2SO$	70.1	5.9	8.3	
Yellow					70.4	6.2	8.6	
5a	EtOH–DMF	253	70	$C_{23}H_{17}ClN_2SO$	67.9	4.5	6.6	404
Yellow					68.2	4.2	6.9	
5b	EtOH	230—232	80	$C_{24}H_{20}N_2SO$	74.6	4.8	6.9	384
Brown					75.0	5.2	7.3	
5c	EtOH–DMF	>300	75	$C_{24}H_{20}N_2SO_2$	71.6	4.7	6.8	
Yellow					72.0	5.0	7.0	
5d	DMF	272—274	60	$C_{24}H_{19}ClN_2SO$	68.5	4.4	6.5	
Yellow					68.8	4.5	6.7	
5e	MeOH–DMF	348—350	85	$C_{25}H_{22}N_2SO$	74.2	5.2	6.6	
Brown					75.4	5.5	7.0	
5f	Dioxane	282—284	80	$C_{25}H_{22}N_2SO_2$	72.7	5.5	7.0	
Yellow					72.5	5.3	6.8	
5g	Dioxane	228	70	$C_{25}H_{21}ClN_2SO$	69.0	5.2	6.2	
Yellow					69.4	4.9	6.5	
5h	EtOH	240—242	50	$C_{26}H_{24}N_2SO_2$	73.1	5.5	6.1	428
Yellow					72.9	5.6	6.5	
6a	DMF	>300	90	$C_{15}H_{13}ClN_4$	63.5	5.0	19.3	
Colorless					63.3	4.6	19.7	
6b	Dioxane	284—286	70	$C_{16}H_{16}N_4$	72.5	5.8	21.0	264
White					72.7	6.1	21.2	
6c	EtOH	255	80	$C_{16}H_{16}N_4O$	68.2	5.5	19.7	
White					68.6	5.7	20.0	
6d	Dioxane	212	50	$C_{16}H_{15}ClN_4$	64.5	4.7	18.5	
Buff					64.3	5.0	18.8	
6e	EtOH	198	55	$C_{17}H_{18}N_4$	73.5	6.1	19.8	
Buff					73.4	6.5	20.1	
6f	MeOH	202	60	$C_{17}H_{18}N_4O$	69.0	5.7	18.8	
Yellow					69.4	6.1	19.0	
6g	MeOH	178	40	$C_{17}H_{17}ClN_4$	65.0	5.2	17.5	
White					65.3	5.4	17.9	
6h	MeOH	167	55	$C_{18}H_{20}N_4O$	69.8	6.1	17.9	
White					70.1	6.5	18.2	
7a	MeOH	166	50	$C_{15}H_{10}Cl_2N_2$	62.0	3.8	9.5	
Colorless					62.3	3.5	9.7	
7b	EtOH	180—182	40	$C_{16}H_{13}ClN_2$	71.2	5.0	10.0	
White					71.5	4.8	10.4	
7c	MeOH	201	35	$C_{16}H_{13}ClN_2O$	67.5	4.4	9.5	
White					67.5	4.6	9.8	
7d	MeOH	172	40	$C_{16}H_{12}Cl_2N_2$	63.5	4.2	8.8	
Buff					63.4	4.0	9.2	
7e	EtOH	217	50	$C_{17}H_{15}ClN_2$	72.0	5.0	9.5	
White					72.2	5.3	9.9	
7f	MeOH	171	40	$C_{17}H_{15}ClN_2O$	68.0	5.4	9.0	298
White					68.3	5.0	9.4	
7g	Dioxane	182	50	$C_{17}H_{14}Cl_2N_2$	64.0	4.6	8.5	
Buff					64.4	4.4	8.8	
7h	MeOH	138	60	$C_{18}H_{17}ClN_2O$	68.8	5.5	8.6	
Colorless					69.1	5.4	9.0	

Table 1. (Continued)

Compound (Color)	Recryst. Solvent	Mp °C	Yield %	Mol. formula	% Found/Required C	H	N	M^+ *m/z*
8a	DMF-MeOH	280—282	40	$C_{15}H_{11}ClN_2O$	66.2	4.0	10.0	
Yellow					66.5	4.1	10.4	
8b	DMF	266—268	35	$C_{16}H_{14}N_2O$	76.5	5.5	11.0	
Brown					76.8	5.6	11.2	
8c	Dioxane	290—292	30	$C_{16}H_{14}N_2O_2$	71.8	5.0	10.3	
Yellow					72.2	5.3	10.5	
8d	DMF-EtOH	272—274	50	$C_{16}H_{13}ClN_2O$	67.2	4.3	9.5	
White					67.5	4.6	9.8	
8e	Dioxane	244—246	60	$C_{17}H_{16}N_2O$	77.0	5.8	10.3	
White					77.3	6.1	10.6	
8f	EtOH	258—260	55	$C_{17}H_{16}N_2O_2$	72.5	5.5	10.2	280
Colorless					72.9	5.7	10.0	
8g	MeOH	270—272	45	$C_{17}H_{15}ClN_2O$	68.0	4.8	9.0	
Buff					68.3	5.0	9.4	
8h	EtOH	222—223	50	$C_{18}H_{18}N_2O_2$	73.2	5.8	9.2	
Buff					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 CH_2Cl_2–K_2CO_3 to afford the corresponding *S*-alkyl derivative (**4**). The ^{1}H NMR spectra for **4a** showed a band at δ=2.7 assigned to SCH_3 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 $C_{23}H_{17}ClN_2SO$ (M^+ 404), and ^{1}H 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 ^{1}H 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_6H_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_6H_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_6H_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_6H_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_6H_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_6H_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_6H_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_6H_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_6H_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_6H_4)

Table 2. (Continued)

Compound	IR, ν_{max}/cm^{-1} (selected bands)	^1H NMR, δ	Compound	IR, ν_{max}/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_6H_5 and C_6H_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_6H_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_6H_5 and C_6H_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_6H_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_6H_5 and C_6H_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_6H_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_6H_5 and C_6H_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_6H_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_6H_5 and C_6H_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 δ=5.0 (NH_2) 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 $(CD_3)_2SO$ using $SiMe_4$ 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 literature procedure.[8]

Cycloalkane-Fused 6-Aryl-3-cyano-2-(methylthio)pyridines (4a—h). A mixture of **3** (0.01 mol), K_2CO_3 (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), K_2CO_3 (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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