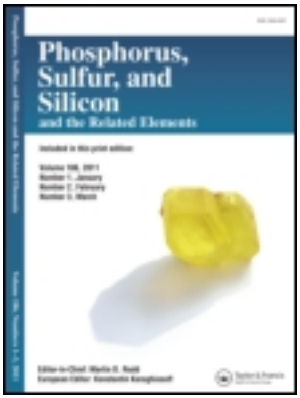

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A NOVEL SYNTHESIS OF THIENO[2,3-b]PYRIDINE, PYRIDOTHIENOTRIAZINE AND PYRIDOTHIENOPYRIMIDINE DERIVATIVES

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A NOVEL SYNTHESIS OF THIENO[2,3-b]PYRIDINE, PYRIDOTHIENOTRIAZINE AND PYRIDOTHIENOPYRIMIDINE DERIVATIVES

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Pyridinethiones **1a,b** prepared according to literature procedures[1] were reacted with chloroacetamide (**2**), p-chlorophenacylbromide (**8**), α-chloroacetylacetone (**11**), ethylchloroacetate (**15**) to give 2-S-acetamidopyridines **3a,b**, 2-S-aroylmethylpyridine **9[a]**†, **b**, thieno[2,3-b]pyridines **14a,b** and 2-S-ethoxycarbonylmethylpyridines **16a,b** respectively. Cyclization reactions on **3a,b, 9b**, and **16a,b** to synthesize **4a,b, 10a,b** and **17a,b** respectively. Nitrous acid, acetic anhydride and formic acid had been used to build a new additional ring in **5a,b, 6a,b** and **7a,b** through their reactions with **4a,b**. Hydrazidic acid derivatives **18a,b** used as a synthons for the preparation of 2-pyrazoloylthieno[2,3-b]pyridines **21a,b**, pyridothienopyrimidines **22a,b**, and 2-hydrazonothieno[2,3-b]pyridines **25a-d** through their reactions with acetylacetone (**20**), formic acid and either aromatic aldehyde **23a,b** or cinnamonitriles **24a,b** respectively.

Keywords: cyanothioacetamide; chloroacetyl derivatives; pyridines; annelated pyridines; Schiff's base

INTRODUCTION

During the last few years our research group has been interested in the chemistry of pyridinethione derivatives.[2–11] The expected biological activities of pyridines as antioipmic[12], antimycotic[13], antidepressant[14] and thienopyridines as inhibitors of clopidogrel, vapiprast and argatroban on the middle cerebral artery thrombosis in rate[15] as well as triazines as herbicides[16] stimulated our interest in the synthesis of several new deriva-

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† Square brackets means that the labeled compound was nonisolable

tives of these ring systems which are required for a medicinal chemistry program.

RESULTS AND DISSCUTION

It has been found that pyridinethione derivative **1a** reacted with chloroacetamide (**2**) in methanolic sodium methoxide to afford a product of molecular formula $C_{18}H_{16}ClN_3O_3S$ which corresponded to simple addition of equimolecular amounts of each of **1a** and **2** followed by loss of hydrogen chloride. The IR spectrum of this reaction product showed the bands corresponded to CN, amidic-CO and NH_2 groups. Its ^{1}H-NMR spectrum revealed the signals corresponding to CH_3-, CH_3CH_2-and NH protons. Moreover, its mass spectrum gave m/z=389 and m/z=391 which is the same molecular weight required for a compound with molecular formula $C_{18}H_{16}ClN_3O_3S$ (cf. Chart 1). By considering all the above mentioned data in addition to elemental analysis (Table I), this reaction product could be formulated as the 2-S-acetamidopyridine derivative **3a**.

Analogously, **1b** reacted with **2** to give the corresponding 2-S-acetamidopyridine derivative **3b**. The structure of **3b** was also established based on elemental and spectral data studies (cf. Table I and II).

On the other hand, the structure of **3a,b** was further confirmed via their cyclization into the corresponding thieno[2,3-b]pyridine derivatives **4a,b** respectively by the action of boiling KOH solution. The presence and the position of both NH_2 and $CONH_2$ groups in **4a,b** were confirmed by the reaction of **4a,b** with nitrous acid, acetic anhydride and formic acid. Thus, nitrous acid reacted with each of **4a,b** to give the corresponding pyrido[2′,3′:5,4]thieno[3,2-d]-1,2,3-triazin-4-ones **5a,b** respectively. The formation of **5a,b** in this reaction proceeded via initial diazotization of the amino group followed by dehydrochlorination to give the corresponding **5a,b**

An interesting reaction with acetic anhydride also took place. Thus, treatment of each of **4a,b** with acetic anhydride caused acetylative cyclization to give products also free from bands of NH_2 groups in their IR spectra and instead, the signals of the newly born CH_3 group was revealed in the ^{1}H-NMR spectra of these reaction products. Based on the above data, these reaction products could be form-ulated as pyrido[3′,2′:4,5]thieno

[3,2-d]pyrimidinone derivatives **6a,b** respectively. The formation of **6a,b** in this reaction is assumed to proceed via initial acetylation of the NH_2 group of the thiophene ring in **4a,b** followed by cyclization via loss of water to afford the final products **6a,b** respectively.

On the other hand, formic acid reacted with each of **4a,b** to give a reaction only one NH proton was also exchanged when these products were treated with D_2O during performing their ^{1}H-NMR spectra. Based on these data, these reaction products were formulated as the pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidinone derivatives **7a,b**. Compounds **5–7** were found to exist in the keto form rather than the enol one because each did not develop any colour with a dilute ferric chloride solution

Furthermore, compound **1a** reacted also with ω-bromo-p-chloroacetophenone **8** to afford a reaction products corresponded to equimolecular addition of **1a** to **8** followed by loss of hydrogen bromide. The IR spectrum of the product was entirely free from the bands of the nitrile function, instead, the bands of the newly formed amino group were detected and this was also revealed in ^{1}H-NMR spectrum.

Based on the above facts, this product was formulated as thieno[2,3-b]pyridine derivative **10a**. The formation of **10a** in this reaction most likely proceeded via the first formation of the 2-S-aroylmethylpyridine intermediate derivative which underwent cyclization via addition to the nitrile function to afford the final isolable product **10a**. Trials to obtain the corresponding **9a** were unsuccessful under a variety of reaction conditions.

In contrast to the behaviour of **1a** towards the action of **8**, compound **1b** reacted with the same reagent under the same reaction conditions to give a product corresponding to equimolecular addition of **1b** to **8** followed by loss of hydrogen bromide. Surprisingly, the IR spectrum of this product showed the presence of the band characteristic of the nitrile function. This reaction product could then be formulated as the 2-S-aroylmethylpyridine derivative **9b** (cf. Experimental Section and Chart 1). On the other hand, the structure of **9b** was further confirmed via its cyclization into the corresponding thieno[2,3-b]pyridine derivative **10b** by the action of boiling KOH solution. The structures of **10a,b** had been established based on the data given from the elemental analyses, IR and ^{1}H-NMR spectra. (cf. Tables I and II). Furthermore, the structure of **10b** elucidated based on the ^{13}C-NMR spectrum which revealed the signals corresponding to (C=O ester) at 6 =167.7 and (C=O ketonic) at δ = 189.1.

TABLE I Characterization data of the newly synthesized compounds

Colour	Solvent of cryst.	M.P (°C)	Yield (%)	Mol. Formula	% Analysis, Calcd/Found			
					C	H	N	S
	EtOH	162	70	$C_{18}H_{16}ClN_3O_3S$	55.46	4.11	10.78	8.22
					55.6	4.1	10.9	8.3
	EtOH	152	65	$C_{16}H_{15}N_3O_4S$	55.65	4.35	12.17	9.28
					55.5	4.3	12.0	9.1
	EtOH	236–8	68	$C_{18}H_{16}ClN_3O_3S$	55.46	4.11	10.78	8.22
					55.4	4.0	10.5	8.1
	EtOH	200–2	60	$C_{16}H_{15}N_3O_4S$	55.65	4.35	12.17	9.28
					55.6	4.3	12.0	9.2
	EtOH	>300	73	$C_{18}H_{13}ClN_4O_3S$	53.93	3.25	13.98	7.99
					54.0	3.2	13.8	7.9
	EtOH	176	75	$C_{16}H_{12}N_4O_4S$	53.93	3.37	15.73	8.38
		dec.			54.0	3.4	15.5	8.3
	EtOH	280	71	$C_{20}H_{16}ClN_3O_3S$	58.04	3.87	10.16	7.74
					57.9	3.8	10.0	7.6
	EtOH	230	80	$C_{18}H_{15}N_3O_4S$	58.54	4.07	11.38	8.67
					58.5	4.1	11.2	8.5
	EtOH	>300	68	$C_{19}H_{14}ClN_3O_3S$	57.07	3.50	10.51	8.01
					57.0	3.4	10.5	8.0
	EtOH	248	75	$C_{17}H_{13}N_3O_4S$	57.46	3.66	11.83	9.01
					57.5	3.5	11.7	9.0

lour	Solvent of cryst.	M.P (°C)	Yield (%)	Mol. Formula	% Analysis, Calcd/Found			
					C	H	N	S
	EtOH	142	72	$C_{22}H_{17}N_2O_4S$	65.19	4.20	6.91	7.90
					65.0	4.1	6.7	7.8
	EtOH	186	60	$C_{24}H_{18}ClN_2O_3S$	59.38	3.70	5.77	6.59
					59.4	3.6	5.6	6.5
yellow	EtOH	120	64	$C_{22}H_{17}N_2O_4S$	65.19	4.20	6.90	7.90
					65.2	4.2	6.7	7.9
	EtOH	156	80	$C_{19}H_{17}ClN_2O_3S$	58.69	4.38	7.21	8.24
					58.6	4.3	7.0	8.2
	EtOH	106	75	$C_{17}H_{16}N_2O_4S$	59.30	4.65	8.14	9.30
					59.2	4.5	8.0	9.2
	EtOH	110	60	$C_{20}H_{19}ClN_2O_4S$	57.35	4.54	6.69	7.65
					57.3	4.5	6.5	7.7
	EtOH	95	80	$C_{18}H_{18}N_2O_5S$	57.75	4.81	7.49	8.56
					57.8	4.7	7.3	8.5
ee	EtOH	165	65	$C_{20}H_{19}ClN_2O_4S$	57.35	4.54	6.69	7.65
					57.3	4.4	6.5	7.6
	EtOH	160–2	70	$C_{18}H_{18}N_2O_5S$	57.75	4.81	7.49	8.56
					57.7	4.7	7.3	8.5
ee	EtOH	218	55	$C_{18}H_{17}ClN_4O_3S$	53.39	4.20	13.84	7.91
					53.3	4.1	13.6	7.8
	EtOH	204–6	50	$C_{16}H_{16}N_4O_4S$	53.33	4.44	15.56	8.89
					53.3	4.4	15.5	8.7

olour	Solvent of cryst.	M.P (°C)	Yield (%)	Mol. Formula	% Analysis, Calcd/Found			
					C	H	N	S
	AcOH	284–6	60	$C_{18}H_{14}ClN_3O_3S$	55.74	3.61	10.84	8.26
					55.8	3.5	10.9	8.3
	AcOH	>300	68	$C_{16}H_{13}N_3O_4S$	55.97	3.79	12.24	9.33
					55.9	3.8	12.3	9.3
	EtOH	162	62	$C_{23}H_{21}ClN_4O_3S$	58.91	4.48	11.95	6.83
					58.8	4.4	11.8	6.8
	EtOH	170	80	$C_{21}H_{20}N_4O_4S$	59.43	4.72	13.12	7.55
					59.4	7.6	13.0	7.4
	EtOH	245	68	$C_{19}H_{15}ClN_4O_3S$	55.01	3.62	13.51	7.72
					55.0	3.5	13.4	7.6
	EtOH	260–2	70	$C_{17}H_{14}N_4O_4S$	55.14	3.78	15.14	8.65
					55.1	3.7	15.0	8.5
	AcOH	276–8	79	$C_{25}H_{21}ClN_4O_3S$	60.91	4.26	11.37	6.49
					60.8	4.2	11.3	6.3
	AcOH	250	55	$C_{25}H_{20}Cl_2N_4O_3S$	56.93	3.79	10.63	6.07
					56.9	3.7	10.5	6.0
	AcOH	220	70	$C_{23}H_{20}N_4O_4S$	61.61	4.46	12.50	7.14
					61.5	4.4	12.4	7.1
	AcOH	226–8	63	$C_{23}H_{19}ClN_4O_4S$	57.20	3.94	11.61	6.63
					57.1	3.8	11.5	6.5

Furthermore, the synthetic of **1a,b** was investigated via their reaction with a variety of halogenated ketones and esters. Compounds **1a,b** reacted with – chloroacetylacetone (**11**) in methanolic sodium methoxide (cf. Chart 2) to give compound **14a,b**. The formation of **14a,b** is assumed to proceed via initial addition to the nitrile function in **12a,b** to give the corresponding non isolable 2,2- diacetyl-3-iminothieno[2,3-b]pyridine derivatives **13a,b** which then underwent acetic acid cleavage and this followed by intramolecular attack of the intermediate carbanion on the imine to afford **14a,b** respectively. In support of this idea, the H^1-NMR spectrum of 14a revealed the presence of signals at 0.98 (t, 3H, $CH_2\underline{CH_3}$); 2.6 (s, 3H, $COCH_3$); 3.0 (s, 3H, CH_3 at pyridine ring); 3.9(q, 2H, $\underline{CH_2}CH_3$); 4.5(br, 2H, NH_2lost after D_2O exchange) and 7.0–7.7 (m, 4H, ArH's).

Work was further extended to explore the synthetic potential of **1a,b** via reaction with halogenated ester, thus it has been found each of **1a,b** could be easily reacted with ethylchloroacetate (**15**) in methanolic sodium methoxide to give the corresponding 2-S-ethoxycarbonylmethylpyridine derivative **16a,b** respectively whose structures were established based on the correct elemental analyses and spectral data studies (cf. Experimental part.)

Cyclization of compounds **16a,b** via the action of ethanolic potassium hydroxide proceeded via addition of the active CH_2 group to the nitrile function to give the corresponding thieno[2,3-b]pyridine derivatives **17a,b**.

The activity of the ethoxycarbonyl group in each of **16a,b** or **17a,b** was confirmed by their reactions with hydrazine hydrate. Thus, the reaction of **16a** or **17a** with hydrazine hydrate in boiling ethanol give one and the same reaction product in each case. The reaction product of molecular formula corresponding to simple addition of one molecule of hydrazine hydrate followed by loss of one molecule of ethanol. The reaction of **16a** with hydrazine hydrate to give the final isolable product **18a** involves firstly the cyclization of **16a** to give **17a** which then reacted with hydrazine hydrate to give finally **18a**. Elemental analysis of this reaction product gave the data corresponding to a molecular formula $C_{18}H_{17}Cl\ N_4O_3S$. The IR spectrum of this reaction product showed the absence of ethoxycarbonyl absorption band and instead the bands related to the presence of NH and two NH_2 groups were clearly detected (cf.Experimental part). Moreover, the triplet and quartet signals of the ethoxycarbonyl group protons were entirely absent in the H^1-NMR spectrum of this reaction product. Collecting the above data together, this reaction product could then be

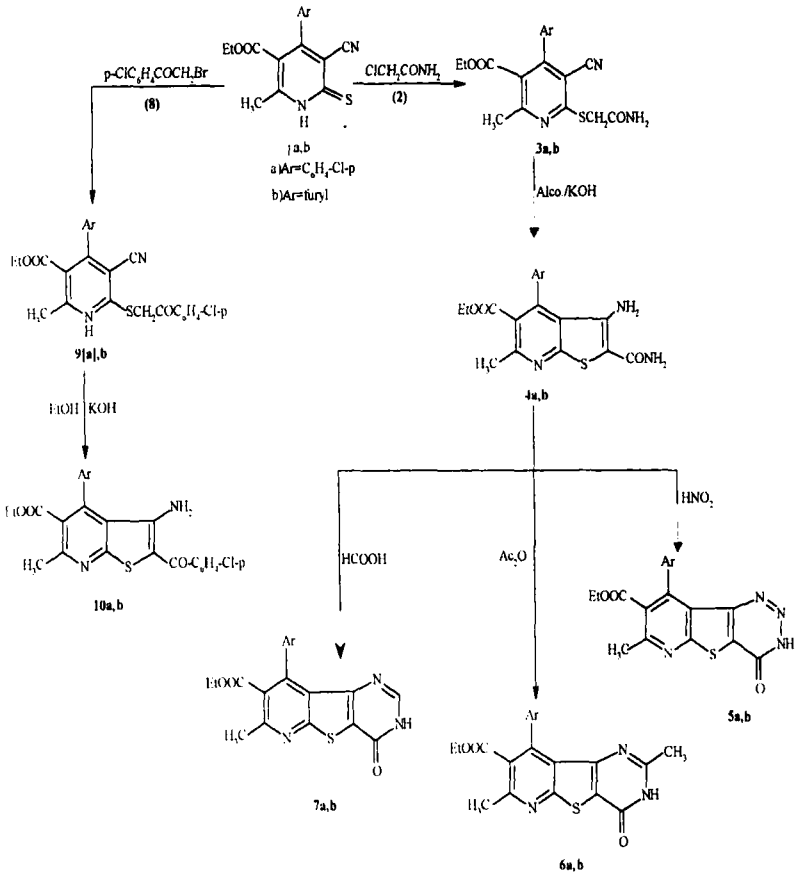

CHART1

assigned the acid hydrazidethieno[2,3-b]pyridine structure **18a** (cf Chart 2).

Following the same steps and under the same reaction conditions each of **16b** or **17b** reacted with hydrazine hydrate to furnish the corresponding acid hydrazide **18b** whose structure was also confirmed by the correct elemental analysis and spectral data studies (cf Experimental part). A further proof of the structure of **18a,b** was confirmed via their cyclization reaction with glacial acetic acid into the corresponding pyrazolino[3′,4′:4,5]thieno [2,3-b]pyridine derivatives **19a,b**.

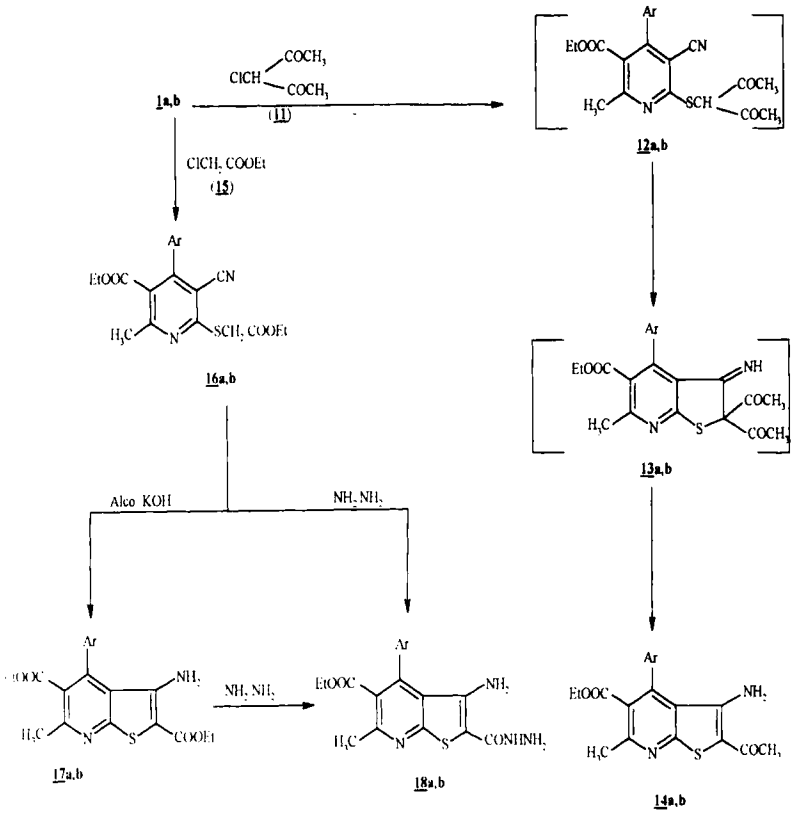

CHART 2

The activity of the acid hydrazide group in each of **18a,b** was achieved via their reactions with:

(a) Keto compound

(b) Anhydrous formic acid

(c) A variety of cinnamonitrile derivatives and aromatic aldehydes.

As follows:

(a) Compound **18a** reacted with acetyl acetone (**20**) in pyridine to afford a product of molecular formula $C_{23}H_{21}ClN_4O_3S$ which corresponded to addition of one molecule of **20** followed by loss of two molecules of water. The reaction product could be formulated as the 2-(3′,5′–dimethylpyrazol-1′-oyl)thieno[2,3-b]pyridine derivative **21a**.

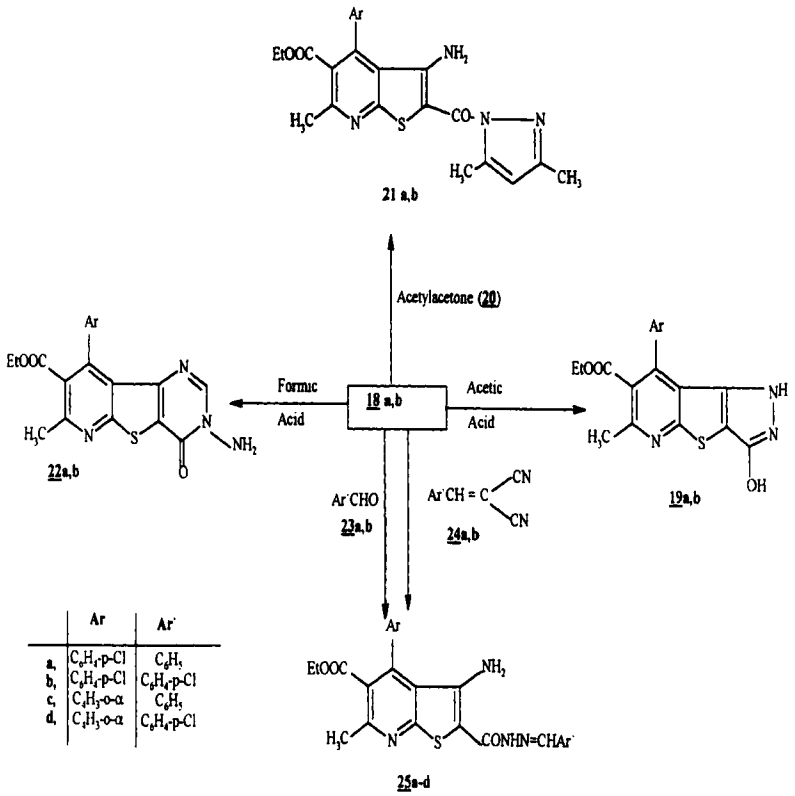

CHART 3

Similarly, **18b** reacted with **20** to afford the corresponding pyrazolo-ylthieno[2,3-b]pyridine derivative **21b**. Structure of **21b** was also established on the basis of elemental analysis, IR, ^{1}H-NMR and spectral data studies (cf. Experimental part).

(b) Compounds **18a,b** reacted with anhydrous formic acid to give products containing only one NH_2 group in each case (from IR spectra). Consequently, these reaction products were formulated as the pyrido[2′,3′–4,5]thieno[3,2-d]pyrimidinone derivatives **22a,b** respectively (cf.Experimental part).

(c) Compound **18a** reacted with α-cyanocinnamonitrile (**24a**) in pyridine to give a reaction product the elemental analysis of which indicated the presence of only one NH and one NH_2 group as detected in its IR

spectrum. Also three exchangeable NH and NH_2 protons were revealed in its ^{1}H-NMR spectrum. Accordingly, this reaction product could be formulated as the yildene group exchange product **25a**. Evidence for the yildene group exchange reaction was achieved by reacting **18a** with benzaldehyde (**23a**) in pyridine to give **25a** which was found to be completely identical in all respects with **25a** prepared as described before (cf. Chart3).

In a similar manner, compound **18a** reacted with α-cyano-p-chlorocinnamonitrile (**24b**) or p-chlorobenzaldehyde (**23b**) to yield one and the same product which could be formulated as the yildene group exchange reaction product **25b**. Its structure was also confirmed by elemental and spectral data studies (cf. Experimental part).

Similarly, **18b** reacted also with **24a,b** or **23a,b** to give one and the same reaction product in all cases which could also be formulated as the yildene group exchange reaction products **25c,d** respectively (cf. Experimental part).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr disc,) on a Pye Unicam SP-1100 and Perkin-Elmer FT-IR type 4 spectrophotometers. ^{1}H-NMR spectra were recorded on Gemini 200 MHz and Brucker WP-80 spectrometers using TMS as an internal standard and chemical shifts are expressed as δ ppm units using DMSO-d_6, $CDCl_3$ and $(CD_3)_2$ CO as solvents. Mass spectra were recorded on Hewlett-Packard GC-MS type 2988 series. A using DIP technique at 15 eV and 70 eV.

Microanalyses were performed by the Microanalytical Center at Cairo University using a Perkin-Elmer 2400 CHN Elemental analyzer.

Compounds **1a,b**[1] were prepared according to literature procedure.

Reaction of 1a,b with different reagents in methanolic sodium methoxide

General procedure

A solution of each of **1a,b** (0.01mole) and each of the reagents **2, 8, 11** and **15** was heated under reflux in methanolic sodium methoxide (prepared from 0.01 g-atom of sodium metal in 30 ml of methanol) for 5 hours. The reaction products obtained after cooling were filtered off and crystallized from the proper solvents to yield **3a,b, 9a,b, 10b, 14a,b** and **16a,b** respectively. (cf. Tables 1 and 2).

TABLE II IR and ^{1}H-NMR Spectral Data

IR (KBr, Cm^{-1})	*^{1}H-NMR (δ ppm)*
4, 3285(NH_2); 3053(aromatic CH); 2985, 2917(Sat. CH); 2220 N; 1714(ester CO); 1687(amidic CO) and 1600(C=C).	0.98(t, 3H, $CH_2\underline{CH_3}$); 2.3(s, 3H, CH_3); 4.1(q, 2H, $\underline{CH_2}CH_3$); 4.5(s, 2H, -S-$\underline{CH_2}$); 5.9(br, 2H, NH_2)* and 7.1 7.8(m, 4H, ArH
2, 3279(NH_2); 3057(aromatic CH); 2962, 2935(Sat. CH); 0, (C≡N); 1712(ester CO); 1692(amidic CO) and 1609(C=C).	0.98(t, 3H, $CH_2\underline{CH_3}$); 2.5(s, 3H, CH_3); 4.1(q, 2H, $\underline{CH_2}CH_3$); 4.5(s, 2H, -S-$\underline{CH_2}$); 5.9(br, 2H, NH_2)* and 7.0 7.8(m, 3H, Fury
4, 3478, 3313, 3167(two NH_2); 2980(Sat. CH); 1724(ester CO); 8(amidic CO); 1644(C=N) and 1600(C=C).	1.0(t, 3H, $CH_2\underline{CH_3}$); 2.3(s, 3H, CH_3); 4.1(q, 2H, $\underline{CH_2}CH_3$); 5.5(br, 2H, NH_2)*; 5.8(br, 2H, $CONH_2$) and 7.0 7.5(m, 4H, Ar
6, 3388, 3336, 3182(two NH_2); 2966, 2933(Sat. CH); 0(ester CO); 1660(amidic CO) and 1607(C=C).	0.99(t, 3H, $CH_2\underline{CH_3}$); 3.1(s, 3H, CH_3); 4.1(q, 2H, $\underline{CH_2}CH_3$); 5 2H, NH_2)*; 5.6(br, 2H, $CONH_2$) and 7.0–7.4(m, 3H, Furyl H's
6(NH); 2928(Sat. CH); 1731 (ester CO); 1703(CO of triazinone) 1609(C=C).	1.0(t, 3H, $CH_2\underline{CH_3}$); 3.1(s, 3H, CH_3); 4.1(q, 2H, $\underline{CH_2}CH_3$); 6.5(br, 1H, NH)* and7.2 7.5(m, 4H, ArH's).
3(NH); 3073(aromatic CH); 2928 (Sat. CH); 1731(ester CO); 5(CO of triazinone) and 1605(C=C).	0.98(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 3.9(q, 2H, $\underline{CH_2}CH_3$); 6.4(br, 1H, NH)* and 7.1 7.8(m, 3H, Furyl H's).
2(NH); 2932, 2857(Sat. CH); 1729(ester CO); 1658(amidic CO yrimidinone) and 1601(C=C).	0.98(t, 3H, $CH_2\underline{CH_3}$); 1.5(s, 3H, CH_3 at pyrimidinone); 3.0(s, 3 CH_3 at pyridine ring); 3.9(q, 2H, $\underline{CH_2}CH_3$); 6.6(br, 1H, NH)* and 7.0–7.8(m, 4H,ArH's).
1(NH); 3032(aromatic CH); 2920 (Sat. CH); 1725(ester CO); 1-(amidic CO of pyrimidinone) and 1605(C=C).	0.95(t, 3H, $CH_2\underline{CH_3}$); 1.4(s, 3H, CH_3 at pyrimidinone); 3.0(s, 3 CH_3 at pyridine ring); 4.0(q, 2H, $\underline{CH_2}CH_3$); 6.2(br, 1H, NH)* and 7.2–7.5(m, 3H, Furyl H's).
3(NH); 2960, 2832(Sat. CH); 1732(ester CO); 1658(amidic CO yrimidinone) and 1596(C=C).	0.95(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3 at pyridine ring); 4.1(q, 2 $\underline{CH_2}CH_3$); 6.5(br, 1H, NH)* and 6.9–7.5(m, 5H, ArH's and pyrimidinone H-2).
5(NH); 2970(Sat. CH); 1725 (ester CO); 1660(amidic CO yrimidinone) and 1600(C=C).	1.0(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 3.9(q, 2H, $\underline{CH_2}CH_3$); 6.6(br, 1H, NH) and 7.0 7.6(m, 4H, Furyl H's and pyrimidinone
9(aromatic CH); 2999, 2963(Sat. CH); 2213(C≡N); 1725(ester CO); 1 (aroyl CO) and 1604(C=C).	0.95(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 3.2(s, 2H, CH_2); 3.9(q, 2H, $\underline{CH_2}CH_3$) and 6.9 8.0(m, 7H, FurylH's).

IR (KBr, Cm^{-1})	*^{1}H-NMR (δ ppm)*
79 3289(NH_2); 3070(aromatic CH); 2928 (Sat. CH); 1730(ester CO) 1600(C=C).	0.99(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 4.0(q, 2H, $\underline{CH_2}CH_3$); 6.8(br, 2H, NH_2)* and 7.0 8.2 (m, 8H, ArH's).
79 3289(NH_2); 3056(aromatic CH); 2901(Sat. CH); 1725(ester CO) 1600(C=C).	1.1(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 4.2(q, 2H, $\underline{CH_2}CH_3$); 7.1(br, 2H, NH_2) and 7.3 7.8(m, 7H, ArH's and Furyl H's).
89 3317(NH_2); 3046(aromatic CH); 2984(Sat. CH); 1717(ester CO); 30 CO acetyl at thiophene with H-bonding) and 1605(C=C).	0.92(t, 3H, $CH_2\underline{CH_3}$); 2.6(s, 3H, $COCH_3$); 3.0(s, 3H, CH_3 at pyri ring); 3.9(q, 2H, $\underline{CH_2}CH_3$); 4.5(br, 2H, NH_2)* and 7.0–7.7(m, 4H
80 3350(NH_2); 2950(Sat. CH); 1719(ester CO); 1635(CO acetyl hiophene with H-bonding) and 1602 (C=C).	0.99(t, 3H, $CH_2\underline{CH_3}$); 2.5(s, 3H, $COCH_3$); 3.0(s, 3H, CH_3 at p ring); 4.1(q, 2H, $\underline{CH_2}CH_3$); 4.7(br, 2H, NH_2)* and 7.2–7.6(m, Furyl H's).
56 aromatic CH); 2980, 2954(Sat. CH); 2221(C≡N); 1735(ester CO); 2 ester CO at pyridine and 1596 (C=C).	0.98(t, 3H, $CH_2\underline{CH_3}$ at pyridine); 1.5 (t, 3H, $CH_2\underline{CH_3}$); 3.0(s, CH_3); 3.8(s, 2H, -S-CH_2); 4.3(q, 2H, $\underline{CH_2}CH_3$ at pyridine); 4.6(q, 2H, $\underline{CH_2}CH_3$) and 7.3 8.0(m, 4H, ArH's).
20 aromatic CH); 2980(Sat. CH); 2220(C≡N); 1740(ester CO); 24 ester CO at pyridine) and 1600 (C=C).	0.96(t, 3H, $CH_2\underline{CH_3}$at pyridine); 1.5 (t, 3H, $CH_2\underline{CH_3}$); 3.0(s, CH_3); 3.7(s, 2H, -S-CH_2); 4.2(q, 2H, $\underline{CH_2}CH_3$ at pyridine); 4.9(q, 2H, $\underline{CH_2}CH_3$) and 7.3 7.9(m, 3H, Furyl H's).
49 3320(NH_2); 3050(aromatic CH); 2975(Sat. CH); 1724(ester CO yridine); 1673(ester CO with H-bonding) and 1600(C=C).	0.95(t, 3H, $CH_2\underline{CH_3}$ at pyridine); 1.2 (t, 3H, $CH_2\underline{CH_3}$); 3.0(s, CH_3); 3.9(q, 2H, CH_2CH_3 at pyridine); 4.1 (q, 2H, $\underline{CH_2}CH_3$); 5.7(br, 2H, NH_2)* and 7.3 8.0(m, 4H, ArH's).
06 3350(NH_2); 3081(aromatic CH); 2932(Sat. CH); 1725(ester CO yridine); 1673(ester CO with H-bonding) and 1603(C=C).	1.0(t, 3H, $CH_2\underline{CH_3}$at pyridine); 1.5 (t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H 4.3(q, 2H, $\underline{CH_2}CH_3$ at pyridine); 4.6 (q, 2H, $\underline{CH_2}CH_3$); 5.7(br, NH_2)* and 7.0 7.7(m, 3H, FurylH's).
79 3355, 3326, 3208(two NH_2 and NH); 3020(aromatic CH); 2976 t. CH); 1718(ester CO); 1630(CO hydrazide with H-bonding) 1608 (C=C).	1.0(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 4.0 (br, 2H, NH_2 at thiophene)*; 4.1(q, 2H, $\underline{CH_2}CH_3$); 5.7(br, 2H, $CONH\underline{NH_2}$)*; 6.9($CO\underline{NH}NH_2$) and 7.0–7.6(m, 4H, Ar H's)
22 3329, 3249, 3202(two NH_2 and NH); 3020(aromatic CH); 2966 t. CH); 1720(ester CO); 1630(CO; hydrazide with H-bonding) 1600 (C=C).	0.98(t, 3H, $CH_2\underline{CH_3}$); 3.0(s,3H, CH_3); 3.9(q, 2H,$\underline{CH_2}CH_3$); 4.2(br, 2H, NH_2 at thiophene); 5.8(br, 2H, $CONH\underline{NH_2}$)*; 6.9(b $CO\underline{NH}NH_2$)and 7.5 7.8(m, 3H, Furyl H's).

IR (KBr, Cm^{-1})	*^{1}H-NMR (δ ppm)*
70(OH); 3220(NH); 2935(Sat.CH); 1724(ester CO) and 1604(C=C).	0.98(t, 3H, $CH_2\underline{CH_3}$); 3.0(s,3H, CH_3); 4.0(q, 2H, $\underline{CH_2}CH_3$); 5.4(br, 1H,NH)*; 7.0–7.7(m, 4H, Ar H's)and 12.2(s, 1H, OH)*
70(OH); 3220(NH); 2950(Sat.CH); 1730(ester CO) and 1604(C=C).	1.0(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 4.0(q, 2H, $\underline{CH_2}CH_3$); 5.6(br. 1H, NH)*; 7.0-7.5(m, 3H, furyl H's) and 12.1(s, 1H, O
93,3339(NH_2); 3053(aromatic CH); 2980(Sat. CH); 1727(ester CO); 79(CO at thiophene); 1640(C=N) and 1594(C=C).	0.87(t, 3H, $CH_2\underline{CH_3}$); 2 3(s, 3H, CH_3 at 3-pyrazole); 2.6(s-3H, 5- pyrazole); 3.0(s, 3H, CH_3); 3.7(q, 2H, $\underline{CH_2}CH_3$); 5.9(s, 1H, pyrazole H-4); 6.3(br, 2H, NH_2)*; and 7.5 8.0(m, 4H, ArH's).
3316(NH_2); 3066(aromatic CH); 2981(Sat. CH); 1725(ester CO); 3(CO at thiophene); 1640(C=N) and 1595(C=C).	0.9(t, 3H, $CH_2\underline{CH_3}$); 2.3(s, 3H, CH_3 at 3-pyrazole); 2.6(s-3H, 5-pyrazole); 3.0(s, 3H, CH_3); 3.8(q, 2H, $\underline{CH_2}CH_3$); 5.8(s, 1H, pyrazole H-4) 6.3(br, 2H, NH_2)*; and 7.0 7.5(m, 3H, Furyl H's
6,3210(NH_2); 3059(aromatic CH); 2959, 2932(Sat. CH); 1731 er CO); 1674(pyrimidinone CO) and 1606(C=C).	1.0(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 4.0(q, 2H, $\underline{CH_2}CH_3$); 6.5(br, 2H, NH_2)* and 7.3–7.8(m, 5H, ArH's and pyrimidinone
5,3211(NH_2); 2958, 2932(Sat. CH); 1713(ester CO); 1674 rimidinone CO) and 1606(C=C).	0.98(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 3.9(q, 2H, $\underline{CH_2}CH_3$); 6 (br, 2H, NH_2)* and 7.0–7.5(m, 4H, Furyl H's and pyrimidinone
5,3328, 3145(NH_2 and NH); 3054(aromatic CH), 2938(Sat. CH); 7(ester CO); 1630(CO hydrazide with H-bonding); 1620(C=N) 1603(C=C).	0.98(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 4.0(q, 2H, $\underline{CH_2}CH_3$); 5.8(br, 2H, NH_2)*; 6.7(br, 1H, NH)* and 7.2 7.8(m, 10H, ArH and Ar- $\underline{CH}$=N).
0,3330, 3152(NH_2 and NH); 3050(aromatic CH), 2936(Sat. CH); 7(ester CO); 1634(CO hydrazide with H-bonding); 1620(C=N) 1600(C=C).	0.95(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 4.1(q, 2H, $\underline{CH_2}CH_3$); 5.7(br, 2H, NH_2); 6.8(br, 1H, NH)* and 7.1 7.9(m, 9H, ArH's and Ar-$\underline{CH}$=N).
9,3315, 3151(NH_2 and NH); 3040 (aromatic CH), 2947(Sat. CH); 5(ester CO); 1630(CO hydrazide with H-bonding); and 1600(C=C).	0.95(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 4.0(q, 2H, $\underline{CH_2}CH_3$); 5.6(br, 2H, NH_2)*; 6.5(br, 1H, NH)* and 7.0 7.7(m, 9H, Furyl Ar-H's and Ar-$\underline{CH}$=N).
8,3321, 3147(NH_2 and NH); 3031(aromatic CH), 2930(Sat. CH); 0(ester CO); 1630(CO hydrazide with H-bonding); and 1600(C=C).	0.98(t, 3H, $CH_2\underline{CH_3}$); 3.0(s, 3H, CH_3); 4.0(q, 2H, $\underline{CH_2}CH_3$); 5.4(br, 2H, NH_2)*; 6.4(br, 1H, NH)* and 7.0 7.8(m, 8H, Furyl ArH's and Ar-$\underline{CH}$=N).

r D_2O exchange.

Cyclization reactions with ethanolic potassium hydroxide

General procedure

A solution of each of the reactants **3a,b**, **9b** and **16a,b** in ethanol (30mL) was heated under reflux for 3–5 hrs with potassium hydroxide (0.01mole). The reaction mixture was then cooled, acidified with dilute hydrochloric acid and the precipitated solid products were filtered off, washed with water then crystallized from the proper solvents to yield the cyclized products **4a,b, 10b** and **17a,b** respectively (cf.Tables land 2).

Reactions with hydrazine hydrate

A solution of **16a,b** or **17a,b** (0.01 mole) in ethanol (30ml) was treated with hydrazine hydrate (10 ml) and then heated under reflux for 6 hrs. The solid products obtained on hot or after cooling were filtered off and crystallized from the proper solvents to give **18a,b** (cf.Tables Iand II).

Reactions of 18a,b with different cinnamonitriles, acetylacetone or aromatic aldehydes in boiling ethanol in the presence of pyridine

General Procedure

A solution of each of **18a,b** (0.01 mole) in ethanol (30 mL) containing pyridine (5 mL) was heated with the appropriate acetylacetone **(20)**, cinnamonitriles **24a,b** and aromatic aldehydes **23a,b** for four hours. The solid obtained either while the solution was still boiling or after cooling were filtered off and crystallized from the proper solvents to give the reaction products **21a,b** and **25a-d** respectively (cf. Tables I and II).

Reaction with Formic acid

A solution of each of **4a,b** or **18a,b** (0.01 mole) and formic acid (30 mL) was heated under reflux for five hrs. The solid products obtained after cooling were filtered off and crystallized from the proper solvents to give the reaction products **7a,b** and **22a,b** respectively (cf. Tables I and II).

Acetylative cyclization with acetic anhydride

A solution of **4a,b** (0.01 mole) in acetic anhydride (30 mL) was heated under reflux for five hours. The solid products obtained after cooling were filtered off and crystallized from the proper solvents to give the reaction products **6a,b** (cf. Tables I and II).

Reaction with nitrous acid

A cold solution of **4a,b** (0.01 mole) in concentrated hydrochloric acid was treated with a cold saturated solution of sodium nitrite (0.015 mole) and then stirred in ice-cold bath for one hr. The solid products obtained were filtered off, washed with water and crystallized from the proper solvents to yield the reaction products **5a,b** (cf. Tables I and II).

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