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Synthesis of Thiazole, Triazole, Pyrazolo[3,4-b]-Pyridinyl-3-Phenylthiourea, Aminopyrazolo[3,4-b]Pyridine Derivatives and Their Biological Evaluation

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SYNTHESIS OF THIAZOLE, TRIAZOLE, PYRAZOLO[3,4-b]-PYRIDINYL-3-PHENYLTHIOUREA, AMINOPYRAZOLO[3,4-b]PYRIDINE DERIVATIVES AND THEIR BIOLOGICAL EVALUATION

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The pyrazolopyridine derivatives **1a,b** reacted with phenylisothiocyanate (**2**), nitrous acid and cinnamonitrile derivatives **5a,b** to afford the corresponded pyrazolo[3,4-b]-pyridinyl-3-phenylthiourea derivatives **3a,b**, 3-diazotized aminopyrazolo[3,4-b]-pyridine derivatives **4a,b** and Schiff bases **7a-d** in a respective manner. Compounds **3a,b**, **4a,b** and **7a-d** were taken as the starting materials for the present study owing to the presence of more than one active site. Compounds **3a,b** reacted with the halogen-containing reagents e.g. **11a,b**, **13** and **15** to give the corresponded thiazole derivatives **12a-d**, **14a,b** and **16a,b** respectively. Compounds **4a,b** coupled with the active hydrogen-containing reagents **17a-j** to afford the corresponding 3-hydrazino derivatives **18a-t** which could be cyclized to give the corresponding triazines **19a-t** respectively. Compounds **7a-d** reacted with thioglycolic acid (**9**) to give the corresponding thiazole derivative **10a-d** in a good yield. The assigned structures of the newly synthesized compounds are based on their elemental analyses, IR, ^{1}H NMR and mass spectra. The biological activity of some of these compounds was tested.

Keywords: Phenylisothiocyanate; Thiazole; Triazole; Pyrazolo[3,4-b]pyridinyl-3-phenylthiourea and Aminopyrazolo[3,4-b]pyridine

INTRODUCTION

In continuation of our previous work [1–6] and owing to biological activity of pyrazolopyridine as antiolytics [7], hypnotics [8] and as inhibitors

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for nucleotide phosphodiesterase cycle [9]. Due to the reported biological activity of triazines as herbicides [10], fungicides [10], antiepileptic agents [11], antioxidant [12] and antagonists at adenosine receptors [13], it was of interest to synthesize some new species of these heterocyclic compounds.

RESULTS AND DISCUSSION

It has been found that our recently synthesized pyrazolo[3,4-b]pyridine derivatives **1a,b** have more than one active site [6]. Thus, 3-amino-4(p-chlorophenyl)-6-methylpyrazolo[3,4-b]pyridine (**1a**) reacted with phenylisothiocyanate (**2**) in pyridine to give the corresponding 4-(p-chlorophenyl)-6-methylpyrazolo[3,4-b]pyridin-3-ylphenylthiourea (**3a**) whose structure was established based on the data of IR, ^{1}H NMR and elemental analyses (cf. Tables I and II). Moreover, its mass spectrum gave the parent peak at m/z = 393 (23%) which agrees with a molecular weight of a formula $C_{20}H_{16}N_5SCl$ of the assigned structure (cf. Chart 1). In addition to the above mentioned peak, other peaks appeared at m/z = 242 (100%), 301 (34%) and 257 (57%) which agreed with the following fragments: -NHCSNHPh, -NHPh and -CSNHPh. Other peaks at low % of abundance appeared at m/z = 151 (18%), 136 (13%), 92 (11%) and 77 (9%).

TABLE I Physical and analytical data of the newly synthesized compounds

Comp.	*M.P [°C]*	*Yield [%]*	*Molecular Formula*	*% of Analysis Calcd./Found*				
				C	*H*	*N*	*S*	*Cl*
3a	145	75	$C_{20}H_{16}N_5SCl$	61.07	4.07	17.81	8.14	8.91
				61.2	4.1	17.9	8.2	9.0
3b	163	87	$C_{18}H_{15}N_5SO$	61.89	4.30	20.06	9.17	----
				61.90	4.0	19.9	9.2	----
7a	187	54	$C_{20}H_{15}N_4Cl$	69.26	4.33	16.16	----	10.25
				69.4	4.4	16.3	----	10.3
7b	193	77	$C_{20}H_{14}N_4Cl_2$	62.99	3.67	14.70	----	18.64
				63.1	3.8	14.5	----	18.8
7c	212	66	$C_{18}H_{14}N_4O$	71.52	4.64	18.54	----	----
				71.7	?.8	18.3	----	----

Comp.	M.P [°C]	Yield [%]	Molecular Formula	% of Analysis Calcd./Found				
				C	H	N	S	Cl
7d	227	71	$C_{18}H_{13}N_4OCl$	64.19	3.86	16.64	----	10.55
				63.9	4.0	16.8	----	10.7
10a	140	77	$C_{22}H_{17}N_4SOCl$	62.78	4.04	13.32	7.61	8.44
				63.0	4.3	13.5	7.8	8.6
10b	172	78	$C_{22}H_{16}N_4SOCl_2$	58.02	3.52	12.31	7.03	15.60
				58.2	3.3	12.5	6.9	15.8
10c	183	87	$C_{20}H_{16}N_4SO_2$	63.83	4.26	14.89	8.51	----
				63.9	4.4	15.0	8.6	-----
10d	191	76	$C_{20}H_{15}N_4SO_2Cl$	58.47	3.65	13.64	7.80	8.65
				58.6	3.4	13.8	8.0	8.5
12a	169	80	$C_{23}H_{18}N_5SCl$	63.96	4.17	16.22	7.42	8.23
				64.1	3.9	16.5	7.6	8.0
12b	252	82	$C_{25}H_{20}N_5SOCl$	63.36	4.22	14.78	6.76	7.50
				63.5	4.4	14.6	7.0	7.6
12c	220	67	$C_{21}H_{17}N_5SO$	65.12	4.39	18.09	8.27	---
				65.0	4.5	17.8	8.5	----
12d	188	77	$C_{23}H_{19}N_5SO_2$	64.34	4.43	16.32	7.46	---
				64.6	4.6	16.4	7.6	----
14a	122	65	$C_{28}H_{20}N_5SCl$	68.09	4.05	14.18	6.48	7.19
				68.2	3.9	13.9	6.5	7.3
14b	185	81	$C_{26}H_{19}N_5SO$	69.49	4.23	15.59	7.13	---
				69.6	4.4	15.5	7.4	----
16a	169	73	$C_{22}H_{16}N_5SOCl$	60.90	3.69	16.15	7.38	8.19
				61.0	3.8	16.3	7.5	8.4
16b	195	69	$C_{20}H_{15}N_5SO_2$	61.70	3.86	17.99	8.23	---
				61.7	3.6	18.1	8.2	----
18a	182	65	$C_{18}H_{16}N_5O_2Cl$	58.46	4.33	18.94	---	9.61
				58.6	4.6	19.2	----	9.8
18b	155	75	$C_{19}H_{18}N_5O_3Cl$	57.07	4.51	17.52	---	8.89
				57.2	4.6	17.7	----	9.0
18c	173	72	$C_{24}H_{20}N_5O_3Cl$	62.41	4.33	15.17	---	7.69
				62.5	4.6	15.3	----	7.4

Comp.	M.P [°C]	Yield [%]	Molecular Formula	% of Analysis Calcd./Found				
				C	H	N	S	Cl
18d	138	73	$C_{21}H_{15}N_5OBrCl$	53.79	3.20	14.94	---	7.58
				53.9	3.2	15.0	----	7.6
18f	152	69	$C_{18}H_{15}N_6O_2Cl$	56.47	3.92	21.96	----	9.28
				56.5	4.1	22.2	----	9.2
18g	180	77	$C_{16}H_{12}N_7SCl$	51.96	3.25	26.52	8.66	9.61
				52.1	3.2	26.5	8.6	9.7
18h	193	78	$C_{16}H_{12}N_7OCl$	54.31	3.39	27.72	----	10.04
				54.4	3.5	27.6	----	10.2
18i	135	81	$C_{22}H_{14}N_7SCl$	59.53	3.16	22.10	7.22	8.00
				59.7	3.3	22.0	7.5	8.2
18j	174	56	$C_{20}H_{20}N_5O_4Cl$	55.88	4.66	16.30	----	8.27
				56.0	4.4	16.5	----	8.4
18k	290	55	$C_{16}H_{15}N_5O_3$	59.08	4.62	21.54	----	----
				58.8	4.6	21.6	----	----
18l	209	64	$C_{17}H_{17}N_5O_4$	57.46	4.79	19.72	----	----
				57.6	4.8	19.8	----	----
18m	285	71	$C_{22}H_{19}N_5O_4$	63.31	4.56	16.79	----	----
				63.1	4.6	16.9	----	----
18n	213	55	$C_{19}H_{14}N_5O_2Br$	53.77	3.30	16.51	----	----
				53.5	3.4	16.6	----	----
18p	223	67	$C_{16}H_{14}N_6O_3$	56.80	4.14	24.85	----	----
				56.9	4.1	24.9	----	----
18q	291	59	$C_{14}H_{11}N_7SO$	51.69	3.38	30.15	9.85	----
				51.6	3.5	30.0	10.0	----
18r	300	82	$C_{14}H_{11}N_7O_2$	54.37	3.56	31.72	----	----
				54.5	3.7	31.7	----	----
18s	195	73	$C_{20}H_{13}N_7SO$	60.15	3.26	24.56	8.02	----
				59.9	3.3	24.7	8.1	----
18t	287	66	$C_{18}H_{19}N_5O_5$	56.10	4.94	18.18	----	----
				56.0	5.0	18.3	----	----
19a	197	74	$C_{18}H_{14}N_5OCl$	61.45	3.98	19.91	----	10.10
				61.6	4.1	20.2	----	10.3

Comp.	M.P [°C]	Yield [%]	Molecular Formula	% of Analysis Calcd./Found				
				C	H	N	S	Cl
19b	176	80	$C_{19}H_{16}N_5O_2Cl$	59.76	4.19	18.35	----	9.31
				59.8	4.0	18.1	----	9.0
19c	211	86	$C_{24}H_{18}N_5O_2Cl$	64.94	4.06	15.78	----	8.00
				65.1	4.2	15.5	----	8.2
19d	185	66	$C_{21}H_{13}N_5BrCl$	55.94	2.89	15.54	----	7.88
				56.2	3.1	15.3	----	8.1
19e	>300	74	$C_{16}H_{10}N_7Cl$	57.23	2.98	29.21	----	10.58
				57.1	3.2	28.9	----	10.7
19f	187	66	$C_{18}H_{15}N_6O_2Cl$	56.47	3.92	21.96	----	9.28
				56.3	4.1	22.1	----	9.4
19g	225	69	$C_{16}H_{12}N_7SCl$	51.96	3.25	26.52	8.66	9.61
				52.2	3.3	26.3	8.8	9.8
19h	248	58	$C_{16}H_{12}N_7OCl$	54.31	3.39	27.72	----	10.04
				54.1	3.4	27.5	----	10.2
19i	179	68	$C_{22}H_{14}N_7SCl$	59.53	3.16	22.10	7.22	8.00
				59.7	3.1	22.1	7.4	8.2
19j	223	65	$C_{18}H_{14}N_5O_3Cl$	56.32	3.65	18.25	----	9.26
				56.5	3.4	18.0	----	9.5
19k	>300	71	$C_{16}H_{13}N_5O_2$	62.54	4.23	22.80	----	----
				62.7	4.5	23.0	----	----
19l	243	59	$C_{17}H_{15}N_5O_3$	60.53	4.45	20.77	----	----
				60.7	4.4	20.5	----	----
19m	310	65	$C_{22}H_{17}N_5O_3$	66.17	4.26	17.54	----	----
				66.0	4.4	17.5	----	----
19n	258	77	$C_{19}H_{12}N_5OBr$	56.16	2.96	17.24	----	----
				56.3	3.1	17.4	----	----
19o	>300	71	$C_{14}H_9N_7O$	57.73	3.09	33.68	----	----
				57.9	2.9	33.5	----	----
19p	265	65	$C_{16}H_{14}N_6O_3$	56.80	4.14	24.85	----	----
				57.1	4.2	24.8	----	----
19q	>300	58	$C_{14}H_{11}N_7SO$	51.69	3.38	30.15	9.85	----
				51.4	3.4	30.1	9.8	----

Comp.	M.P [°C]	Yield [%]	Molecular Formula	% of Analysis Calcd./Found				
				C	H	N	S	Cl
19r	>300	77	$C_{14}H_{11}N_7O_2$	54.37	3.56	31.72	---	----
				54.5	3.5	31.7	----	----
19s	297	86	$C_{20}H_{13}N_7SO$	60.15	3.26	24.56	8.02	----
				60.1	3.4	24.5	7.9	----
19t	>300	76	$C_{16}H_{13}N_5O_4$	56.64	3.83	20.65	----	----
				56.4	4.0	20.6	----	----

Compounds **18d**, **18n**, **19d** and **19n** the % at Br Calcd/Found 17.10/17.30; 18.87/18.60; 17.72/17.60; 19.70/20.00.

TABLE II IR and ^{1}H NMR of the newly synthesized compounds

Comp.	IR (cm^{-1})	^{1}H NMR (δppm)
3a	3227, 3200, 3187 (NH); 3079 (aromatic CH); 2978 (sat. CH); 1615 (C=N); 1604 (C=C) and 1554 (C=S).	1.1 (s, 3H, CH_3); 4.9 (s, 1H, pyridine H-5); 6.2*(s, br., 3H, three NH) and 7.0–7.9 (m, 9H, ArH's).
3b	3239, 3218, 3188 (NH); 3077 (aromatic CH); 2985 (sat. CH); 1610 (C=N); 1600 (C=C) and 1558 (C=S).	1.3 (s, 3H, CH_3); 5.3 (s, 1H, pyridine H-5); 6.3*(s, br., 3H, three NH) and 6.9–7.8 (m, 8H, Furyl and ArH's).
7a	3193 (NH); 3083 (aromatic CH); 2982 (sat. CH); 1613 (C=N) and 1600 (C=C).	1.0 (s, 3H, CH_3); 5.3 (s, 1H, pyridine H-5); 6.3*(s, br., 1H, NH); 7.0–7.8 (m, 9H, ArH's) and 9.1 (s, 1H, -N=CH-).
7d	3187 (NH); 3079 (aromatic CH); 2979 (sat. CH); 1611 (C=N) and 1602 (C=C).	1.2 (s, 3H, CH_3); 5.6 (s, 1H, pyridine H-5); 6.4*(s, br., 1H, NH); 7.1–8.2 (m, 7H, Furyl and ArH's) and 9.5 (s, 1H, -N=CH-).
10b	3185 (NH); 3077 (aromatic CH); 2979 (sat. CH); 1718 (C=O); 1613 (C=N) and 1605 (C=C).	1.3 (s, 3H, CH_3); 3.7 (s, 2H, thiazole-CH_2-); 5.3 (s, 1H, pyridine H-5); 5.7 (s, 1H, thiazole H-2); 6.3*(s, br., 1H, NH) and 7.0–7.8 (m, 8H, ArH's).
10c	3213 (NH); 3085 (aromatic CH); 2978 (sat. CH); 1720 (C=O); 1612 (C=N) and 1602 (C=C).	1.2 (s, 3H, CH_3); 3.5 (s, 2H, thiazole-CH_2-); 5.1 (s, 1H, pyridine H-5); 5.8 (s, 1H, thiazole H-2); 6.4*(s, br., 1H, NH) and 6.7–7.9 (m, 8H, Furyl and ArH's).
12a	3200 (NH); 3080 (aromatic CH); 2978 (sat. CH); 1612 (C=N) and 1600 (C=C).	1.2 (s, 6H, two CH_3); 5.1 (s, 1H, pyridine H-5); 6.4*(s, br., 1H, NH) and 7.1–8.2 (m, 10H, thiazole and ArH's).

Comp.	*IR* (cm^{-1})	^1H *NMR* (δ*ppm*)
12d	3208 (NH); 3076 (aromatic CH); 2982 (sat. CH); 1714 (C=O); 1609 (C=N) and 1601 (C=C).	1.1 (s, 6H, two CH_3); 2.3 (s, 3H, $COCH_3$); 5.2 (s, 1H, pyridine H-5); 6.3*(s, br., 1H, NH) and 6.7–7.9 (m, 8H, Furyl and ArH's).
14a	3197 (NH); 3080 (aromatic CH); 2987 (sat. CH); 1612 (C=N) and 1600 (C=C).	1.1 (s, 3H, CH_3); 5.2 (s, 1H, pyridine H-5); 6.3*(s, br., 1H, NH) and 7.0–8.1 (m, 15H, thiazole and ArH's).
14b	3200 (NH); 3080 (aromatic CH); 2979 (sat. CH); 1611 (C=N) and 1602 (C=C).	1.2 (s, 3H, CH_3); 4.9 (s, 1H, pyridine H-5); 6.2*(s, br., 1H, NH) and 6.8–7.7 (m, 14H, Furyl, thiazole and ArH's).
16a	3195 (NH); 3069 (aromatic CH); 2980 (sat. CH); 1717 (C=O); 1613 (C=N) and 1604 (C=C).	1.3 (s, 3H, CH_3); 4.5 (s, 2H, thiazole $-CH_2-$); 5.1 (s, 1H, pyridine H-5); 6.3* (s, br., 1H, NH) and 7.1–7.9 (m, 9H, ArH's).
16b	3205 (NH); 3078 (aromatic CH); 2982 (sat. CH); 1720 (C=O); 1611 (C=N) and 1600 (C=C).	1.5 (s, 3H, CH_3); 4.3 (s, 2H, thiazole $-CH_2-$); 5.2 (s, 1H, pyridine H-5); 6.2* (s, br., 1H, NH) and 6.7–7.9 (m, 8H, Furyl and ArH's).
18a	3225, 3200 (NH); 3073 (aromatic CH); 2978 (sat. CH); 1700 (C=O); 1615 (C=N) and 1602 (C=C).	1.1 (s, 3H, CH_3); 1.9 (s, 6H, two $COCH_3$); 5.0 (s, 1H, pyridine H-5); 6.5*(s, br., 2H, two NH) and 7.0–7.8 (m, 4H, ArH's).
18c	3217, 3195 (NH); 3082 (aromatic CH); 2977 (sat. CH); 1728 (C=O); 1612 (C=N) and 1600 (C=C).	1.0 (s, 3H, CH_3); 1.3 (t, 3H, $\underline{CH_3}CH_2$); 3.6 (q, 2H, $CH_3\underline{CH_2}$); 5.1 (s, 1H, pyridine H-5); 6.1*(s, br., 2H, two NH) and 7.0–8.2 (m, 9H, ArH's).
18f	3220, 3197 (NH); 3079 (aromatic CH); 2980 (sat. CH); 2218 (CN); 1735 (C=O); 1614 (C=N) and 1603 (C=C).	1.0 (s, 3H, CH_3); 1.5 (t, 3H, $\underline{CH_3}CH_2$); 3.8 (q, 2H, $CH_3\underline{CH_2}$); 5.0 (s, 1H, pyridine H-5); 6.3*(s, br., 2H, two NH) and 7.0–7.9 (m, 4H, ArH's).
18j	3212, 3187 (NH); 3077 (aromatic CH); 2981 (sat. CH); 1733 (C=O); 1614 (C=N) and 1600 (C=C).	1.1 (s, 3H, CH_3); 1.5 (t, 6H, two $\underline{CH_3}CH_2$); 4.0 (q, 4H, two $CH_3\underline{CH_2}$); 5.1 (s, 1H, pyridine H-5); 5.8*(s, br., 2H, two NH) and 7.0–7.9 (m, 4H, ArH's).
18l	3222, 3197 (NH); 3083 (aromatic CH); 2985 (sat. CH); 1733 (ester CO); 1700 (acetyl CO); 1610 (C=N) and 1604 (C=C).	1.2 (s, 6H, two CH_3); 1.6 (t, 3H, $\underline{CH_3}CH_2$); 4.1 (q, 2H, $CH_3\underline{CH_2}$); 5.1 (s, 1H, pyridine H-5); 5.8*(s, br., 2H, two NH) and 6.6–7.3 (m, 3H, Furyl H's).
18n	3200, 3182 (NH); 3087 (aromatic CH); 2989 (sat. CH); 1703 (C=O); 1611 (C=N) and 1602 (C=C).	1.0 (s, 3H, CH_3); 5.2 (s, 1H, pyridine H-5); 5.8*(s, br., 2H, two NH) and 6.7–7.9 (m, 8H, Furyl and ArH's).

Comp.	*IR* (cm^{-1})	^1H *NMR* (δ*ppm*)
18q	3212, 3189 (NH); 3080 (aromatic CH); 2981 (sat. CH); 2220 (CN); 1613 (C=N); 1602 (C=C) and 1557 (C=S).	1.1 (s, 3H, CH_3); 5.1 (s, 1H, pyridine H-5); 5.6*(s, br., 2H, two NH); 6.3 (s, br., 2H, NH_2) and 6.7–7.2 (m, 3H, Furyl H's).
18s	3220, 3192 (NH); 3085 (aromatic CH); 2979 (sat. CH); 2219 (CN); 1613 (C=N) and 1600 (C=C).	1.2 (s, 3H, CH_3); 5.0 (s, 1H, pyridine H-5); 5.6*(s, br., 2H, two NH) and 6.7–8.1 (m, 7H, Furyl and ArH's).
19a	3098 (aromatic CH); 2976 (sat. CH); 1712 (C=O); 1613 (C=N) and 1600 (C=C).	1.1 (s, 6H, two CH_3); 1.7 (s, 3H, $COCH_3$); 5.3 (s, 1H, pyridine H-5); and 7.0–7.6 (m, 4H, ArH's).
19c	3087 (aromatic CH); 2982 (sat. CH); 1732 (C=O); 1610 (C=N) and 1602 (C=C).	1.0 (s, 3H, CH_3); 1.5 (t, 3H, $CH_2\underline{CH_3}$); 4.0 (q, 2H, $\underline{CH_2}CH_3$); 5.4 (s, 1H, pyridine H-5); and 7.1–8.2 (m, 9H, ArH's).
19e	3346, 3320, 3242 (NH_2); 3079 (aromatic CH); 2978 (sat. CH); 2222 (CN); 1617 (C=N) and 1603 (C=C).	1.1 (s, 3H, CH_3); 4.5*(s, br., 2H, NH_2); 5.2 (s, 1H, pyridine H-5); and 7.0–7.9 (m, 4H, ArH's).
19f	3320, 3196, 3175 (NH_2); 3082 (aromatic CH); 2978 (sat. CH); 1730 (C=O); 1617 (C=N) and 1602 (C=C).	1.1 (s, 3H, CH_3); 1.6 (t, 3H, $CH_2\underline{CH_3}$); 3.9 (q, 2H, $\underline{CH_2}CH_3$); 4.6*(s, br., 2H, NH_2); 5.3 (s, 1H, pyridine H-5); and 7.0–7.8 (m, 4H, ArH's).
19j	3188 (NH); 3068 (aromatic CH); 2976 (sat. CH); 1730 (ester CO); 1693 (ring CO); 1612 (C=N) and 1604 (C=C).	1.0 (s, 3H, CH_3); 1.4 (t, 3H, $CH_2\underline{CH_3}$); 4.1 (q, 2H, $\underline{CH_2}CH_3$); 5.3 (s, 1H, pyridine H-5); 7.0–7.8 (m, 4H, ArH's) and 8.4* (s, br., 1H, NH).
19l	3087 (aromatic CH); 2978 (sat. CH); 1722 (C=O); 1612 (C=N) and 1600 (C=C).	1.1 (s, 6H, two CH_3); 1.5 (t, 3H, $CH_2\underline{CH_3}$); 4.0 (q, 2H, $\underline{CH_2}CH_3$); 5.1 (s, 1H, pyridine H-5); and 6.6–7.4 (m, 3H, FurylH's).
19n	3076 (aromatic CH); 2977 (sat. CH); 1613 (C=N) and 1601 (C=C).	1.2 (s, 3H, CH_3); 5.0 (s, 1H, pyridine H-5); and 6.8–7.6 (m, 8H, Furyl and ArH's).
19o	3352, 3265, 3201 (NH_2); 3091 (aromatic CH); 2982 (sat. CH); 2217 (CN); 1613 (C=N) and 1600 (C=C).	1.3 (s, 3H, CH_3); 4.7*(s, br., 2H, NH_2); 5.3 (s, 1H, pyridine H-5); and 6.7–7.3 (m, 3H, FurylH's).
19q	3387, 3365, 3226, 3200 (NH_2); 3077 (aromatic CH); 2989 (sat. CH); 1615 (C=N) and 1602 (C=C).	1.2 (s, 3H, CH_3); 4.6*(s, br., 2H, NH_2 at position 5 of triazine ring); 5.2 (s, 1H, pyridine H-5); 5.8*(s, br., 2H, $CS\underline{NH_2}$ and 6.7–7.5 (m, 3H, FurylH's).
19s	3365, 3271, 3187 (NH_2); 3090 (aromatic CH); 2978 (sat. CH); 1612 (C=N) and 1600 (C=C).	1.1 (s, 3H, CH_3); 4.5*(s, br., 2H, NH_2); 5.5 (s, 1H, pyridine H-5); and 6.9- 7.6 (m, 7H, Furyl and ArH's).

All astride signals disappeared on D_2O addition.

Similarly, **1b** reacted under the same experimental conditions with phenylisothiocyanate (**2**)to afford the corresponding 4(2′-furyl)-6-methylpyrazolo[3,4-b]pyridin-3-ylphenylthiourea (**3b**). The structure of **3b** was established on the basis of IR, ^{1}H NMR and the elemental analyses (cf. Tables I and II). Moreover, its mass spectrum gave parent peak at m/z = 349 (27%) which agreed with a molecular weight of a formula $C_{18}H_{15}N_5SO$ of the assigned structure (cf. Chart 1). Other peaks were detected at m/z = 198 (100%), 213 (58%), 257 (38%), 151 (30%), 136 (19%), 92 (12%) and 77 (9%) which agreed with the following fragments: -NHCSNHPh, -NHPh, -CSNHPh and Ph-.

Synthon **1a** reacted with cinnamonitriles **5a,b** in ethanol containing a catalytic amount of piperidine to afford the corresponding Schiff bases of the pyrazolopyridine derivatives **7a,b**. The compounds **7a,b** formed through an arylidine group exchange. This is further supported by synthesis of authentic samples of **7a,b** *via* the reaction of **1a** with the appropriate aldehyde **6a,b** in ethanol containing the catalytic amount of piperidine. It is remarkable that **7a,b** synthesized by the different pathways are identical in all aspects. Compounds **7a,b** reacted with thioglycollic acid (**9**) in anhydrous benzene to afford the corresponding 3-(2′-arylthiazolidin-4′-on-3′-yl)pyrazolo[3,4-b]pyridine derivatives **10a,b** respectively.

Similarly, the analogue **1b** reacted with **5a,b** to afford **7c,d** which resulted also, *via* the reaction of **1b** with the appropriate aldehyde **6a,b**. Compounds **7c,d** reacted similarly with **9** to give the corresponding **10c,d** respectively (cf. Chart 1). A chemical support of the structures of **7a-d** was given by preparation of an authentic sample of **1a,b** *via* the reaction of **7a-d** with ethyl cyanoacetate (**8**) (cf. Exp. Part and Chart 1). Structures **7a-d** and **10a-d** were established on the basis data of IR, ^{1}H NMR data and elemental analyses (Tables I and II).

Compound **3a** reacted with both chloroacetone (**11a**) and chloroacetylacetone (**11b**) in the presence of sodium acetate to give products formed *via* dehydrochlorination followed by cyclization through elimination of a molecule of water in each case. The IR spectra of these products showed the presence of NH, acetyl-CO and groups. Their ^{1}H NMR spectra revealed only one D_2O-exchangeable NH proton (cf. Table II). By considering the above data these reaction products were formulated as 3-(3′-phenyl-4′-methyl-4′-thiazolin-2′-yl)-amino-4-(p-chlorophenyl)-5-methylpyrazolo[3,4-b]pyridine (**12a**) and 3-(3′-phenyl-4′-methyl-5′-acetyl-4′-thiazolin-2′-yl)amino-4-(p-chlorophenyl)-5-methylpyrazolo- [3,4-b]pyridine

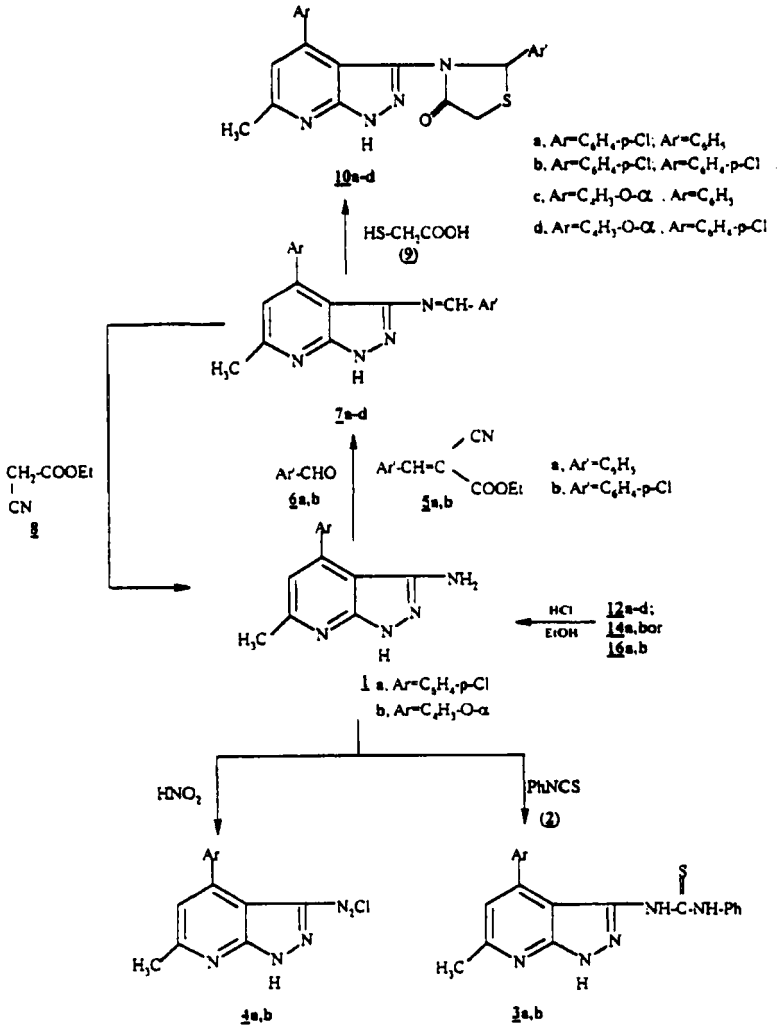


CHART I

(**12b**) species. Under the same experimental conditions, compound **3b** reacted with **11a,b** to afford **12c,d** whose structure was established on the basis of IR, ^{1}H NMR data and elemental analyses (cf. Tables I and II).

Compounds **3a,b** reacted also with ω-bromoacetophenone (**13**) in boiling ethanol in the presence of sodium acetate to afford products which could be formulated as 3-(3′,4′-diphenylthiazolin-2′-yl)amino-4-(p-chlorophenyl)-6-methylpyrazolo[3,4-b]pyridine **14a** and 3-(3′,4′-diphenylthiazolin-2′-yl)amino-4(2′-furyl)-6-methylpyrazolo[3,4-b]pyridine **14b**. The structure assignment of **14a**,b was confirmed by evaluation the data of IR, ^{1}H NMR and elemental analyses (cf. Tables I and II).

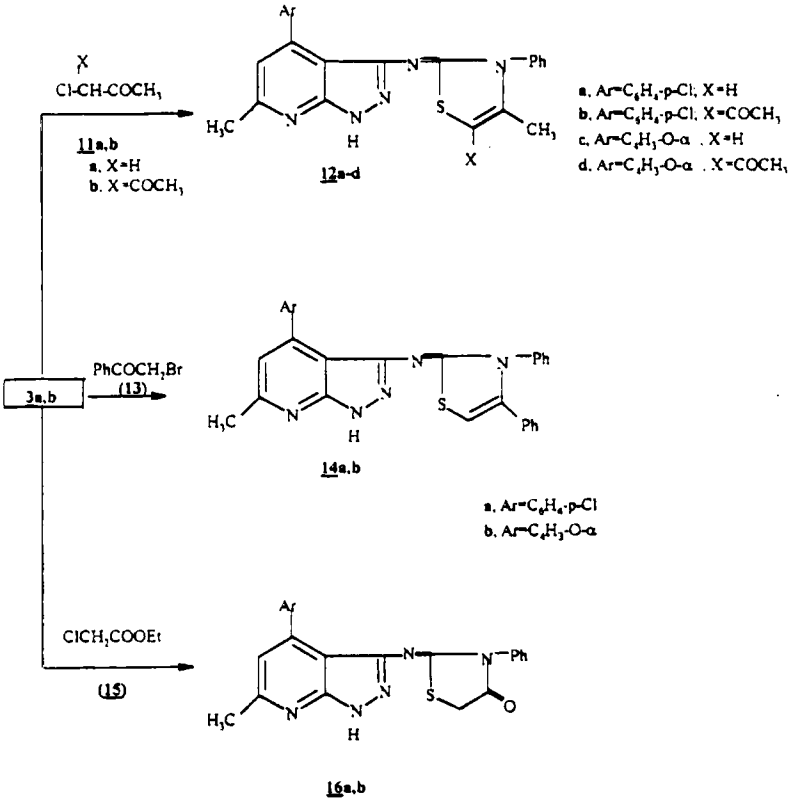
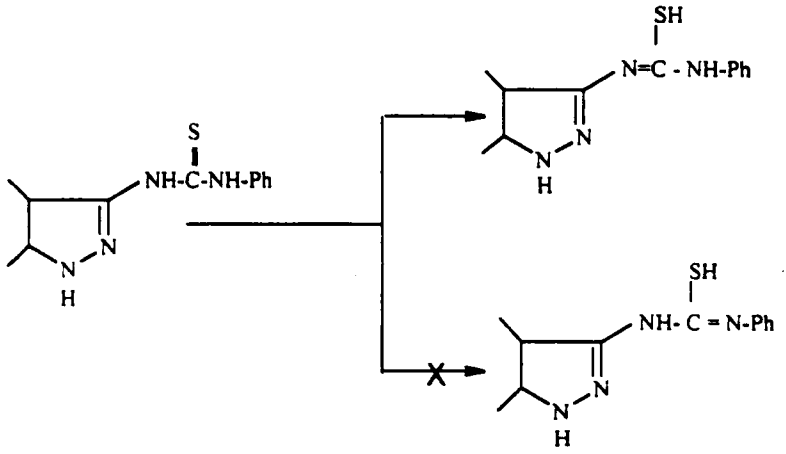


CHART 2

Synthons **3a**,b reacted in a similar manner with ethyl chloroacetate (**15**) to afford products formed through dehydrochlorination followed by elimination of one molecule of ethanol. By considering the data of IR, ^{1}H NMR and elemental analyses these reaction products could be formulated as

3-(3′-phenylthiazolidin-4′-on-2′-yl)aminopyrazolo[3,4-b]pyridine derivatives **16a,b** respectively (cf. Chart 2, Tables I and II). Compounds **12a-d, 14a,b**, and **16a,b** were most probably formed through the formation of thioenol *via* the migration of the hydrogen atom of the NH group adjacent to the pyrazolopyridine residue. This can be illustrated as follows:



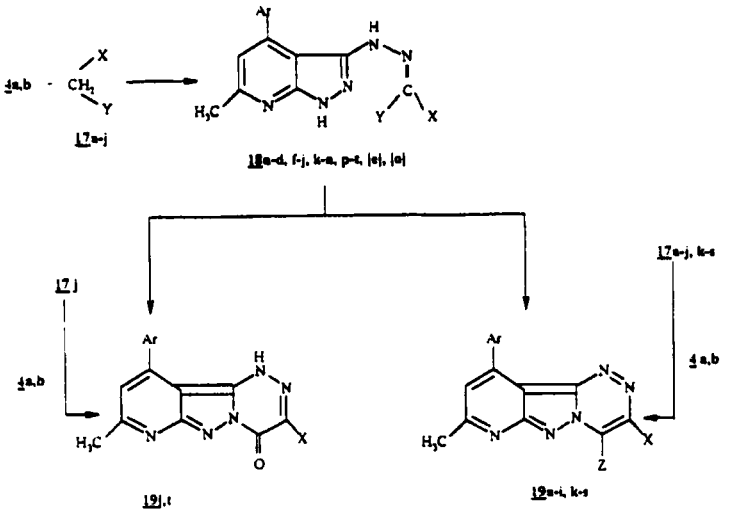
Enolization according to the above mentioned step facilitate the reaction of **3a,b** through their enolic -SH groups *via* dehydrochlorination in case of **11a,b** and **15**and *via* dehydrobromination in case of **13**. Dehydrochlorination and dehydrobromination followed by cyclization *via* loss of water to form **12a-d** and **14a,b** while this dehydrochlorination followed by elimination of a molecule of ethanol yielded **16a,b**.

The previously mentioned results were supported by the preparation of **1a,b** *via* hydrolysis of each of **12a-d, 14a,b** or **16a,b** in an ethanolic hydrochloric acid solution. It is important to note that the hydrolysis products in each case were similar in all aspects with **1a,b** synthesized according to our literature procedure [6] (cf. Exp. Part and Chart 1).

The isolation of polyfunctionallized diazotized aminopyrazolo[3,4-b]-pyridine derivatives **4a,b** stimulated the interest to shed more light on their chemical reactivity and synthetic potential. Reactions with active methylene-containing reagents **17a-i** constitute an easy and direct route for the synthesis of several hydrazones and their fused triazines. These triazines appear highly promising for biological activity studies as

well as for further chemical transformations. Compounds **4a,b** reacted with acetylacetone **17a**, ethyl acetoacetate **17b**, ethyl benzoylactate **17c** and ω-bromoacetophenone **17d** in cold solution of ethanol containing sodium acetate to give compounds **18a-d** and **18k-n** which were formed *via* dehydrochlorination. These compounds cyclized in boiling ethanol contains a catalytic amount of triethylamine to afford the corresponding pyridopyrazolotriazine derivatives **19a-d** and **19k-n** *via* dehydration. The structures of **18a-d; 18k-n; 19a-d** and **19k-n** were established based on IR, ^{1}H NMR data and elemental analyses (cf. Tables I and II). No D_2O-exchangeable protons were detected in the ^{1}H NMR spectra of **19a-d** and **19k-n**. Moreover, the mass spectra of **18a, 19a, 18l** and **19l** as examples gave m/z = 369, 351, 355 and 337 which corresponding to the molecular weights of the molecular formulas $C_{18}H_{16}N_5O_2Cl$, $C_{18}H_{14}N_5OCl$, $C_{17}H_{17}N_5O_4$, and $C_{17}H_{15}N_5O_3$ of the assigned structures (cf. Chart 3). An additional confirmation for the structure of **19a-d** and **19k-n** arose from their synthesis *via* another route by conducting the reaction between **17a-d** and **4a,b** in boiling ethanol in the presence of triethylamine to afford **19a-d** and **19k-n** directly without isolation of the corresponding hydrazones **18a-d** and **18k-n**.

The study was extended to investigate further reactions of **4a,b** with other active methylene containing reagents. Thus, **4a,b** was reacted with ethyl cyanoacetate, cyanothioacetamide, cyanoacetamide and 2-cyanomethylbenzthiazole **17f-i** in cold ethanol containing sodium acetate to afford the corresponding hydrazones **18f-i** and **18p-s** respectively. Compounds **18f-i** and **18p-s** cyclized in boiling ethanol containing the catalytic amount of triethylamine to afford **19f-i** and **19p-s**. Compounds **19f-i** and **19p-s** were synthesized *via* another route by reacting **17f-i** with **4a,b** in boiling ethanol containing a catalytic amount of triethylamine to afford **19f-i** and **19p-s**directly without isolation of **18f-i** and **18p-s**. It is remarkable to report here that **4a,b** reacted with **17e** either in cold ethanol containing triethylamine to afford directly **19e,o** without isolation of the hydrazones **18e,o**. All trials to isolate **18e,o** under a variety of conditions failed. The structures **18f-i; 18p-s; 19e-i** and **19o-s** were established based on IR, ^{1}H NMR data and elemental analyses (cf. Tables I and II). The formation of **19f-i** and **19p-s** were proceeded through the cyclization reaction between CN and two NH groups. This supported by the absence of CN and NH bands in IR and the presence of NH_2 group in both IR and ^{1}H-NMR. Moreover, The mass spectra of **18f,q** and **19f,q** gave m/z = 382



17-19	Ar	X	Y	Z
a	C_6H_4-p-Cl	$COCH_3$	$COCH_3$	CH_3
b	C_6H_4-p-Cl	COOEt	$COCH_3$	CH_3
c	C_6H_4-p-Cl	COOEt	COPh	Ph
d	C_6H_4-p-Cl	Br	COPh	Ph
e	C_6H_4-p-Cl	CN	CN	NH_2
f	C_6H_4-p-Cl	COOEt	CN	NH_2
g	C_6H_4-p-Cl	$CSNH_2$	CN	NH_2
h	C_6H_4-p-Cl	$CONH_2$	CN	NH_2
i	C_6H_4-p-Cl	BT	CN	NH_2
j	C_6H_4-p-Cl	COOEt	COOEt	—
k	C_6H_5-O-α	$COCH_3$	$COCH_3$	CH_3
l	C_6H_5-O-α	COOEt	$COCH_3$	CH_3
m	C_6H_5-O-α	COOEt	COPh	Ph
n	C_6H_5-O-α	Br	COPh	Ph
o	C_6H_5-O-α	CN	CN	NH_2
p	C_6H_5-O-α	COOEt	CN	NH_2
q	C_6H_5-O-α	$CSNH_2$	CN	NH_2
r	C_6H_5-O-α	$CONH_2$	CN	NH_2
s	C_6H_5-O-α	BT	CN	NH_2
t	C_6H_5-O-α	COOEt	COOEt	—

BT =

CHART 3

for **18f** and **19f** while m/z = 325 for **18q** and **19q** which agreed with the molecular weight of a formula $C_{18}H_{15}N_6O_2Cl$ for **18f** and **19f** and $C_{14}H_{11}N_7SO$ for **18q** and **19q** (cf. Chart 3).

Final investigation of the synthetic potential of **4a,b** was came from their reaction with diethyl malonate **17j** in cold ethanolic sodium acetate solution to afford the corresponding hydrazones **18j,t** respectively. The hydrazones **18j,t** cyclized in boiling ethanol-triethylamine to afford the corresponding triazines **19j,t** respectively, which were synthesized authentically by reactions of each of **4a,b** with **17j** in a boiling ethanol triethylamine solution to give **19j,t** directly without isolation of **18j,t**. Structures **18j,t** and **19j,t** were established based on data given from their IR and ^1H NMR spectra and their elemental analyses (cf. Tables I and II). Moreover, the mass spectra of **18j** and **19j** are reported as selective examples for this reaction. The parent peak of m/z = 429 and 383 agreed with the molecular weights of the formulas $C_{20}H_{20}N_5O_4Cl$ and $C_{18}H_{14}N_5O_3Cl$ of the assigned structures (cf. Chart 3). The peak at m/z = 383 confirmed that the cyclization step involved elimination of one ethanol molecule (Molecular weight = 46).

ANTIMICROBIAL ACTIVITY

The preliminary antimicrobial evaluation of a number of representative examples of the newly synthesized heterocyclic compounds against Grame-positive, Grame-negative bacteria, yeast and fungi compared with NA using the cup-plate method [14] showed strong activity of compounds **3a; 7b; 10b**; **18d,n,q,s** and **19d,g,i,n,q,s** against *Bacillus subtilis and Staphylococcus aureas*. Compounds **7a,d; 10a,d; 12a,b; 14a; 16a; 18g,h,i,r** and **19h,r** showed a moderate activity against *Aspergillus niger*. Compounds **3b; 7c; 10c; 18f,p,t** and **19e,f,o,p,t** were only slightly active while the rest of the compounds, **12c,d**; **14b; 16b; 18a-c,j,k-m** and **19a-c,j,k-m** are inactive against the tested organisms (cf. Table III).

TABLE III Antimicrobial activity

Comp.	*Aspergillus niger (Fungi)*	*Candida Albicans (Yeast)*	*Bacillus Subtilis (Gr+ve)*	*Staphylococus aureus (Gr -ve)*	*Escherichia Coli (Gr -ve)*	*Pseudomonas aeruginosa (Gr-ve)*
3a	–	–	+++	+++	+	–
3b	+	–	–	–	++	+
7a	++	–	–	–	+	–
7b	–	+	+++	+++	+	–

Comp.	*Aspergillus niger (Fungi)*	*Candida Albicans (Yeast)*	*Bacillus Subtilis (Gr+ve)*	*Staphylococus aureus (Gr -ve)*	*Escherichia Coli (Gr -ve)*	*Pseudomonas aeruginosa (Gr-ve)*
7c	+	+	–	–	+	–
7d	++	–	–	–	–	–
10a	++	–	–	–	–	–
10b	–	+	+++	+++	–	–
10c	+	+	–	–	+	+
10d	++	+	–	–	+	+
12a	++	–	–	–	+	+
12b	++	+	–	–	+	+
14a	++	–	–	–	++	++
16a	++	-	-	-	-	–
18d	–	–	+++	+++	+	+
18f	+	+	–	–	+	+
18g	++	–	–	–	+	+
18h	++	–	–	–	–	–
18i	++	+	-	-	+	+
18n	–	–	+++	+++	+	+
18p	+	+	–	–	–	–
18q	–	–	+++	+++	+	+
18r	++	+	–	–	–	–
18s	–	+	+++	+++	–	–
18t	+	–	–	–	–	–
19d	–	–	–	+++	+++	–
19e	+	+	–	+	–	++
19f	+	–	–	+	–	–
19g	+	+	+	+++	+++	–
19h	++	–	–	–	–	+
19i	–	–	–	+++	+++	–
19n	–	+	+	+++	+++	+
19o	+	–	–	+	+	–
19p	+	++	++	–	–	–
19q	–	–	–	+++	+++	+
19r	++	-	-	-	-	–
19s	–	–	–	+++	+++	+
19t	+	–	–	–	–	–

Highly active (+++), Moderately active (++), Slightly active (+), Inactive (-)

Thanks are due to Prof. Dr. Y. E. Saleh, Department of Botany, Faculty of Science, Cairo University for carrying out the biological evaluation of the newly synthesized compounds.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were recorded in KBr discs on Perkin-Elmer FT-IR type 4 and Pye Unicam SP-1100 spectrophotometers. The ^{1}H NMR spectra were recorded on Varian EM 390–90 MHz, Varian Gemini, 200 and Brucker WP-80 spectrometers using $CDCl_3$, DMSO-d_6 and $(CD_3)_2CO$ as solvents and TMS as an internal standard. Chemical shifts are expressed as δ ppm units. Mass spectra were recorded on Hewlett-Packard GC-MS type 2988 series A using DIP technique at 70 eV. Microanalyses were performed at the Microanalytical Center of Cairo University using Perkin-Elmer 2400 CHN Elemental Analyzer.

Synthesis of 3a,b

A solution of **1a,b** (0.01 mole) and phenyl isothiocyanate **2** (0.01 mole) in pyridine (30 mL) was refluxed for 2 hrs and then allowed to cool. The solid products were filtered off and crystallized from ethanol to afford **3a,b** respectively (cf. Tables I and II).

Synthesis of 7a-d

A solution of **1a,b** (0.01 mole) and cinnamonitriles **5a,b** or aromatic aldehydes **6a,b** (0.01 mole of each) in ethanol (50 mL) and piperidine (0.5 mL) was refluxed for 6 hrs. The reaction mixture was allowed to cool, the solid products obtained were collected and crystallized from the proper solvent to afford **7a-d** respectively (cf. Tables I and II).

Synthesis of 10a-d

A solution of **7a-d** (0.01 mole) and thioglycollic acid **9** (0.01 mole) in dry benzene (50 mL) was refluxed for 9–12 hrs. The reaction mixture was allowed to cool, the solid products were filtered off and crystallized from the proper solvent to afford **10a-d** respectively (cf. Tables I and II).

Reactions of 7a-d with ethyl cyanoacetate (8)

To a solution of each of **7a-d** (0.01 mole) and ethyl cyanoacetate (**8**) (0.01 mole) in ethanol (50 mL), 0.5 mL of triethylamine were added. The reaction mixture was heated under reflux for 5 hrs, allowed to cool and the solid products were collected. By fractional crystallization from petroleum ether, the dissolved was identified as the cinnamonitriles **5a,b** and non-dissolved portion was identified as **1a,b**. Both **5a,b** and **1a,b** were compared with their authentic samples and they were identical in all aspects (m.p, mixed m.p., IR and ^{1}H NMR).

Synthesis of 12a-d, 14a,b and 16a,b (General Procedure)

A solution of each of **3a,b; 11a,b; 13** and **15** (0.01 mole) and sodium acetate (0.02 mole) in ethanol (50 mL) was heated under reflux for 4 hrs. The reaction mixture was allowed to cool, filtered off, washed with water and crystallized from the proper solvent to afford **12a-d, 14a,b** and **16a,b** respectively (cf. Tables I and II).

Synthesis of 18a-d; 18f-j; 18k-n and 18p-t (General Procedure)

A solution of each of **17a-d; 17f-j; 17k-n** and **17p-t** (0.01 mole each) in ethanol (50 mL) was treated with **4a,b** (0.01 mole) and the whole was stirred in the presence of sodium acetate in the ice chest for 2 hrs. The solid products thus obtained were filtered off, washed with water and crystallized from the proper solvent to afford **18a-d; 18f-j; 18k-n** and **18p-t** respectively (cf. Tables I and II).

Synthesis of 19a-t

Route A

A solution of each of **18a-d; 18f-j; 18k-n** and **18p-t** ($\cong$ 0.01 mole) in ethanol (50 mL) containing the catalytic amount of triethylamine (0.5 mL) was heated under reflux for 5 hrs. The solid products obtained on hot or after cooling were crystallized from the proper solvent to afford **19a-d; 19f-j; 19k-n** and **19p-t** respectively (cf. Tables I and II).

Route B

A solution of each of **17a-j** and **4a,b** (0.01 mole) in ethanol (50 m containing the catalytic amount of triethylamine (0.5 mL) was heated under reflux for 8 hrs. The solid products obtained on hot or after cooling were filtered off and crystallized from the proper solvent to afford **19a-t** respectively (cf. Tables I and II).

Acknowledgements

Thanks are due to Prof. Dr. Y. E. Saleh, Department of Botany, Faculty of Science, Cairo University for carrying out the biological evaluation of the newly synthesized compounds.

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