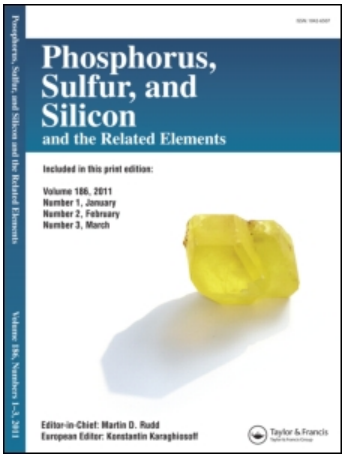


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Novel Synthesis of Condensed Pyridin-2(1H)-one and Pyrimidine Derivatives

A. M. M. Soliman[a]; A. Khodairy[a]; E. A. Ahmed[a]
[a] Chemistry Department, Faculty of Science, Sohag, Egypt

Online publication date: 27 October 2010

To cite this Article Soliman, A. M. M. , Khodairy, A. and Ahmed, E. A.(2003) 'Novel Synthesis of Condensed Pyridin-2(1H)-one and Pyrimidine Derivatives', Phosphorus, Sulfur, and Silicon and the Related Elements, 178: 4, 649 — 665
To link to this Article: DOI: 10.1080/10426500307793
URL: http://dx.doi.org/10.1080/10426500307793

Phosphorus, Sulfur and Silicon, 2003, Vol. 178:649–665

1042-6507/03 $12.00 + .00
DOI: 10.1080/10426500390197959

Taylor & Francis
Taylor & Francis Group

NOVEL SYNTHESIS OF CONDENSED PYRIDIN-2(1H)-ONE AND PYRIMIDINE DERIVATIVES

A. M. M. Soliman, A. Khodairy, and E. A. Ahmed
Chemistry Department, Faculty of Science, Sohag, Egypt

(Received February 24, 2002; accepted June 9, 2002)

The reaction of N-chloroacetyl derivatives ***6–10*** *with morpholine yielded N-morpholin-1-yl acetyl derivatives* ***11–15****, which were subjected to Thorpe-Zieler cyclization with sodium* tert*-butoxide to produce the corresponding condensed pyridin-2(1H)-one derivatives* ***16–20****. Treatment of compounds* ***1****,* ***6–10*** *with either malononitrile or* p*-chlorobenzylidinemalononitrile in presence of triethylamine, afforded the corresponding pyrimidines* ***21–25****,* ***27*** *and pyridine derivative* ***26*** *respectively. Moreover compound* $\mathbf{1_a}$ *was treated with ethyl isothiocyanoacetate to give the corresponding piprazine derivative* ***28****.*

Keywords: Pyridin-2-ones; pyrimidines; Thorpe-Ziegler cyclization

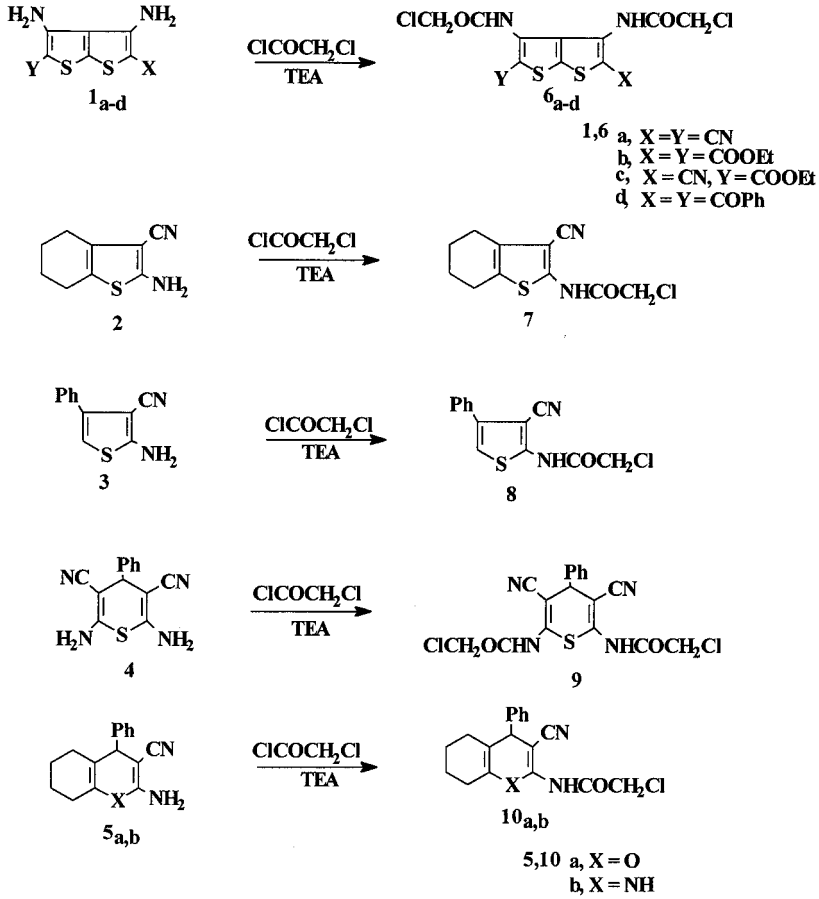
Recently, pyridin-2(1H)-one derivatives were synthesized by new procedures via the reaction of ylidinenitriles with either active methylene reagents[1] or with halocompounds and hydrazine.[2] The importance of the synthesized pyridine and pyrimidine derivatives as intermediates for the synthesis of biological active deaza and folic acid ring systems[3–6] prompted us to continue our previous work[7–11] on the synthesis of pyridine-2(1H)-one and pyrimidine derivatives.

The intramolecular ring closure reaction by Thorpe-Ziegler cyclization gives rise to amino substituted heterocycles, which otherwise would require a multistep synthesis. Electron-withdrawing groups usually activate the methylene group for an attack at the nitrile carbon.[12] Now, it was found that even electron donor substituted methylene groups undergo the Thorpe-Ziegler cyclization when a basic catalytic system like potassium *tert*-butoxide/dimethyl sulfoxide is employed.[12]

Address correspondence to A. Khodairy, Department of Chemistry, Faculty of Science, Sohag, 82524, Egypt. E-mail: khodairy@yahoo.com

RESULTS AND DISCUSSION

The starting materials, namely, 3,4-diamino-2,5-dicyano-, 3,4-diamino-2,5-dicarbethoxy-, 3,**4**-diamino-2-cyano-5-carbethoxy-, or 3,4-diamino-2,5-dibenzoyl thieno(2,3-b)thiophene $\mathbf{1}_{a-d}$,[13] 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophene **2**,[14] 2-amino-3-cyano-(5H)-4-phenylthiophene **3**,[14] 2,6-diamino-3,5-dicyano-4-phenylthiopyran **4**,[15] 2-amino-3-cyano-4-phenyl-5,6,7,8-tetrahdro-4H-chromene $\mathbf{5}_a$,[16] and 2-amino-3-cyano-4-phenyl-1,4,5,6,7,8-hexahydroquinoline $\mathbf{5}_b$[16] were treated with chloroacetyl chloride and triethylamine to afford the corresponding N-chloroacetylated derivatives **6–10** respectively, (c.f. Scheme 1, Table I), which in turn were allowed to react with morpholine



SCHEME 1

TABLE I Analytical and Spectral Data of the New Compounds

Product no.	m.p. (°C)[a]	Yield (%)	Mole. form. (mol. wt.) solvent of crystalization	Analytical data[b] cal./found					IR (cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
				C	H	N	S	Cl		
6a	280	80	$C_{12}H_6Cl_2N_4O_2S_2$ (373.34) Dioxane	38.60 36.44	1.61 1.91	15.00 15.32	17.17 17.35	19.00 19.22	3300 (NH), 2120 (CN), 1665 (C=O)	10.00 (s, 2H, 2NH), 5.20 (s, 4H, $2CH_2$)
6c	1611	60	$C_{14}H_{11}Cl_2N_3O_4S_2$ (420.14) Acetic acid	40.03 40.28	2.64 2.45	10.04 10.19	15.25 15.00	16.90 16.70	3250 (NH), 2100 (CN), 1740 (CO_{ester}), 1660 (C=O)	9.55 (s, 2H, 2NH), 5.54 (s, 4H, $2CH_2$), 4.40–4.10 (q, 4H, $2CH_{2\ ester}$), 1.3–1.0 (t, 6H, $2CH_3$)
6d	310	40	$C_{24}H_{16}N_2Cl_2O_4S_2$ (531.54) Dioxane	54.23 54.55	3.03 3.32	5.27 5.00	12.06 12.43	13.37 13.11	3300 (NH), 1743 ($C=O_{ketone}$), 1680 (C=O)	10.50 (s, 2H, 2NH), 7.70–7.00 (m, 10H, arom.), 5.40 (s, 4H, $2CH_2$)
7	151	66	$C_{11}H_{11}ClN_2OS$ (254.78) DMF	51.85 51.63	4.35 4.11	10.99 10.73	12.58 12.30	14.00 14.22	3310 (NH), 2150 (CN), 1690 (CO)	9.00 (s, 1H, NH), 5.00 (s, 2H, $COCH_2$), 3.10–2.90 (m, 4H, $2CH_2$), 2.20–1.80 (m, 4H, $2CH_2$)
8	>350	80	$C_{13}H_9ClN_2OS$ (276.79) Benzene	56.41 56.60	3.28 3.49	10.12 10.30	11.58 11.43	12.86 12.66	3100 (NH), 2200 (CN), 1690 (CO)	9.00 (s, 1H, NH), 8.00–7.60 (m, 5H, arom.), 7.00 (s, 1H, =CH), 5.00 (s, 2H, CH_2)

(Continued on next page)

TABLE I Analytical and Spectral Data of the New Compounds *(Continued)*

Product no.	m.p. (°C)[a]	Yield (%)	Mole. form. (mol.wt.) solvent of crystalization	Analytical data[b] cal./found C	H	N	S	Cl	IR (cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
9	215	45	$C_{17}H_{12}Cl_2N_4O_2S$ (407.37) Dioxane	50.12 50.32	2.97 2.75	13.75 13.53	7.87 7.55	17.42 17.31	3350 (NH), 2116 (CN), 1685 (CO)	9.00 (s, 2H, 2NH), 7.70–7.30 (m, 5H, arom.), 6.30 (s, 1H, CH), 5.00 (s, 4H, $2COCH_2$)
10_a	311	60	$C_{18}H_{17}ClN_2O_2$ (328.85) Ethanol	65.74 65.54	5.21 5.45	8.51 8.76		10.79 10.50	3350 (NH), 2216 (CN), 1690 (CO)	9.00 (s, 1H, NH), 8.00–7.60 (m, 5H, arom.), 6.00 (s, 1H, CH), 4.90 (s, 2H, $COCH_2$), 3.6–3.3 (m, 4H, $2CH_2$), 1.90–1.60 (m, 4H, $2CH_2$)
10_b	280	70	$C_{18}H_{18}ClN_3O_2$ (327.86) Dioxane	65.94 65.71	5.53 5.60	12.82 12.60		10.83 10.66	3400 (NH), 2158 (CN), 1680 (CO)	9.00 (s, 2H, 2NH), 7.70–7.30 (m, 5H, arom.), 6.10 (s, 1H, CH), 4.00 (s, 2H, $COCH_2$), 3.30–3.00 (m, 4H, $2CH_2$), 1.90–1.60 (m, 4H, $2CH_2$)
11_a	143	50	$C_{20}H_{22}N_6O_4S_2$ (474.57) DMF	50.61 50.44	4.67 4.86	17.71 17.59	13.51 13.76		3200 (NH), 2200 (CN), 1680 (C═O)	10.00 (s, 2H, 2NH), 3.90 (s, 4H, 2 $COCH_2$), 3.00–2.70 (m, 8H, $4CH_2O$) 2.10–1.80 (m, 8H, $4CH_2N$)

11$_b$	215	37	$C_{24}H_{32}N_4O_8S_2$ (568.67) Acetic acid	50.70 50.59	5.67 5.52	9.85 9.66	11.28 11.75	3150 (NH), 1740 (CO_{ester}), 1679 (C=O)	9.50 (s, 2H, 2NH), 4.20–4.00 (q, 4H, $2CH_{2\ ester}$), 3.80 (s, 4H, $2COCH_2$), 3.00–2.70 (m, 8H, $4CH_2O$), 2.10–1.80 (m, 8H, $4CH_2N$), 1.30–1.10 (t, 6H, $2CH_3$)
11$_c$	221	44	$C_{22}H_{27}N_5O_6S_2$ (521.62) Benzene	50.66 50.78	5.22 5.45	13.43 13.64	12.29 12.43	3200 (NH), 2210 (CN), 1730 (CO_{ester}), 1690 (C=O)	9.00 (s, 2H, 2NH), 4.50–4.20 (q, 2H, $CH_{2\ ester}$), 4.10 (s, 4H, $2COCH_2$), 3.20–2.90 (m, 8H, $4CH_2O$), 2.40–2.00 (m, 8H, $4CH_2N$), 1.30–1.10 (t, 3H, CH_3)
11$_d$	290	45	$C_{32}H_{32}N_4O_6S_2$ (632.77) Ethanol	60.74 60.57	5.09 5.34	8.85 8.58	10.13 10.36	3300 (NH), 1700 (CO_{ketone}), 1690 (CO)	10.00 (s, 2H, 2NH), 8.00–7.40 (m, 10H, arom.), 4.00 (s, 4H, $2COCH_2$), 3.00–2.70 (m, 8H, $4CH_2O$), 2.10–1.80 (m, 8H, $4CH_2N$)
12	201–3	44	$C_{15}H_{19}N_3O_2S$ (305.39) DMF	59.00 59.31	6.27 6.41	13.67 13.90	10.50 10.71	3400 (NH), 2200 (CN), 1690 (CO)	8.70 (s, 1H, NH), 4.00 (s, 2H, $COCH_2$), 3.40–3.00 (m, 8H, $4CH_2$), 2.40–2.00 (m, 8H, $4CH_2$)

(Continued on next page)

TABLE I Analytical and Spectral Data of the New Compounds *(Continued)*

Product no.	m.p. (°C)[a]	Yield (%)	Mole. form. (mol.wt.) solvent of crystalization	Analytical data[b] cal./found					IR (cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
				C	H	N	S	Cl		
13	183–5	60	$C_{17}H_{17}N_3O_2S$ (327.40) Dioxane	62.37 62.50	5.23 5.42	12.93 12.66	9.79 9.90		3400 (NH), 2180 (CN), 1689 (CO)	9.00 (s, 1H, NH), 7.70–7.30 (m, 5H, arom.), 6.80 (s, 1H, =CH), 4.80 (s, 2H, $COCH_2$), 3.70–3.40 (m, 4H, $2CH_2O$), 2.70–2.40 (m, 4H, $2CH_2N$)
14	>350	40	$C_{25}H_{28}N_6O_4S$ (476.54) DMF	63.01 63.34	5.92 5.75	17.63 17.44	6.74 6.92		3300 (NH), 1680 (CO)	9.00 (s, 2H, 2NH), 8.10–7.60 (m, 5H, arom.), 6.00 (s, 1H, CH), 4.08 (S, 4H, $2COCH_2$), 3.70–3.20 (m, 8H, $4CH_2O$), 2.70–2.30 (m, 8H, $4CH_2N$)
15a	201	65	$C_{22}H_{25}N_3O_3$ (379.47) Methanol	69.63 69.43	6.64 6.80	11.07 11.30			3300 (NH), 2184 (CN), 1665 (CO)	10.00 (s, 1H, NH), 8.00–7.30 (m, 5H, arom.), 6.10 (s, 1H, CH), 4.30 (s, 2H, $COCH_2$), 3.60–3.00 (m, 8H, $4CH_2O$), 2.40–1.80 (m, 8H, $4CH_2N$)

15$_b$	256	69	$C_{22}H_{26}N_4O_2$ (378.48) Acetic acid	69.81 69.66	6.92 6.70	14.80 14.63		3410, 3300 (2NH), 2200 (CN), 1675 (CO)	9.50 (s, 1H, NH), 8.00–7.40 (m, 6H, arom. + NH), 6.30 (s, 1H, CH), 4.20 (s, 2H, $COCH_2$), 3.40–3.00 (m, 8H, $4CH_2O$), 2.40–1.80 (m, 4H, $4CH_2N$)
16$_a$	311–3	80	$C_{20}H_{22}N_6O_4S_2$ (474.57) DMF	50.61 50.49	4.67 4.40	17.71 17.50	13.51 13.76	3300, 3210, 3120 (NH+ NH_2), 1690 (CO)	10.00 (s,2H, 2NH), 6.00–5.40 (br, 4H, $2NH_2$), 3.30–3.00 (m, 8H, $4CH_2O$), 2.30–2.00 (m, 8H, $4CH_2N$)
16$_b$	166	28	$C_{20}H_{20}N_4O_6S_2$ (476.53) Dioxane	50.41 50.71	4.23 4.42	11.76 11.54	13.46 13.65	3400 (OH), 3100 (NH), 1690 (CO)	9.00 (s, 2H, 2NH), 5.00 (s, 2H, 2OH), 3.30–2.00 (m, 8H, $4CH_2O$), 2.40–2.00 (m, 8H, $4CH_2N$)
16$_c$	215–7	26	$C_{20}H_{21}N_5O_5S_2$ (475.54) DMF	50.51 50.81	4.45 4.63	14.73 14.62	13.48 13.67	3350 (OH), 3210, 3135 (NH_2), 1680 (CO)	8.70 (s, 2H, 2NH), 6.00 (s, 2H, NH_2), 5.00 (s, 1H, OH), 3.50–3.20 (m, 8H, $4CH_2O$), 2.70–2.40 (m, 8H, $4CH_2N$)

(Continued on next page)

TABLE I Analytical and Spectral Data of the New Compounds *(Continued)*

Product no.	m.p. (°C)[a]	Yield (%)	Mole. form. (mol.wt.) solvent of crystalization	Analytical data[b] cal./found					IR (cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
				C	H	N	S	Cl		
16$_d$	>350	30	$C_{32}H_{28}N_4O_4S_2$ (596.74) Ethanol	64.40 64.59	4.73 4.55	9.39 9.11	10.75 10.55		3300 (NH), 1695 (C=O)	10.00 (s, 2H, 2NH), 8.00–7.50 (m, 10H, arom.), 3.70–3.40 (m, 4H, $2CH_2O$), 2.50–2.20 (m, 4H, $2CH_2N$)
17	>350	41	$C_{15}H_{19}N_3O_2S$ (305.39) Ethanol	59.00 59.30	6.23 6.00	13.74 13.60	10.50 10.70		3300, 3210, 3140 (NH+ NH_2), 1680 (CO)	9.00 (s, 1H, NH), 6.0 (s, 2H, NH_2), 3.00–2.10 (m, 8H, $4CH_2$), 2.60–1.20 (m, 8H, $4CH_2$)
18	271	35	$C_{17}H_{17}N_3O_2S$ (327.40) DMF	62.37 62.54	5.23 5.40	12.83 12.66	9.80 9.66		3300, 3210, 3140 (NH+ NH_2), 1680 (CO)	9.00 (s, 1H, NH), 8.10–7.70 (m, 5H, arom.), 6.70 (s, 1H, =CH), 5.00 (s, 2H, NH_2), 3.40–3.10 (m, 4H, $2CH_2O$), 2.30–1.90 (m, 4H, $2CH_2N$)
19	315	66	$C_{25}H_{28}N_6O_4S$ (476.54) Dioxane	63.01 63.21	5.92 5.75	17.63 17.40	6.73 6.55		3350 (NH), 3211, 3100 (NH_2), 1678 (CO)	10.00 (s, 2H, 2NH), 8.00–7.50 (m, 5H, arom.), 6.10 (s, 1H, CH), 4.50 (s, 4H, $2NH_2$), 3.50–3.20 (m, 8H, $4CH_2O$), 2.90–2.50 (m, 8H, $4CH_2N$)

20a	321–3	36	$C_{22}H_{25}N_3O_3$ (379.47) Ethanol	69.63 69.49	6.64 6.73	10.07 10.30		3315, 3200 (NH_2), 3155 (NH), 1699 (CO)	9.0 (s, 1H, NH), 8.00–7.60 (m, 5H, arom.), 6.10 (s, 1H, CH), 5.00–4.80 (br, 2H, NH_2), 3.7–3.2 (m, 8H, $4CH_2O$), 2.30–1.90 (m, 8H, $4CH_2N$)
20b	>350	40	$C_{22}H_{26}N_4O_2$ (378.48) DMF	69.81 69.59	6.92 6.75	14.80 14.60		3300, 3215, 3120 (NH+ NH_2), 1699 (CO)	8.90 (s, 2H, 2NH), 8.00–7.60 (m, 6H, arom. +NH), 6.00 (s, 1H, CH), 5.30–5.00 (br, 2H, NH_2), 3.50–3.10 (m, 8H, $4CH_2$), 2.40–2.00 (m, 8H, $4CH_2$)
21a	200	70	$C_{18}H_8N_8O_2S_2$ (432.46) Methanol	49.99 49.67	1.86 1.59	25.91 25.70	14.82 14.66	3300, 3210 (NH_2), 2100 (CN), 1695 (C=O)	6.00–5.60 (br, 4H, $2NH_2$), 5.00 (s, 4H, $2CH_2$)
21b	216	80	$C_{18}H_7N_7S_2O_3$ (433.42) Ethanol	55.44 55.73	1.63 1.75	22.62 22.45	14.74 14.57	3400 (OH), 3200, 3110 (NH_2), 2216 (CN), 1690 (C=O)	6.00 (s, 2H, NH_2), 5.30–5.00 (br, 4H, $2CH_2$), 2.3 (s, 1H, OH)
21c	203–5	75	$C_{30}H_{14}N_6O_2S_2$ (554.60) DMF	64.97 64.73	2.54 2.65	15.15 15.00	11.56 11.76	2200 (CN), 1681 (CO)	8.00–7.30 (m, 10H, arom.), 4.90–4.60 (br, 4H, $2CH_2$)
22	175	80	$C_{14}H_{12}N_4OS$ (284.34) DMF	59.14 59.30	4.25 4.48	19.70 19.90	11.28 11.40	3200, 3150 (NH_2), 2190 (CN), 1677 (CO)	6.00–5.70 (br, 2H, NH_2), 4.30 (s, 2H, CH_2CO), 3.50–3.20 (m, 4H, $2CH_2$), 2.30–2.00 (m, 4H, $2CH_2$)

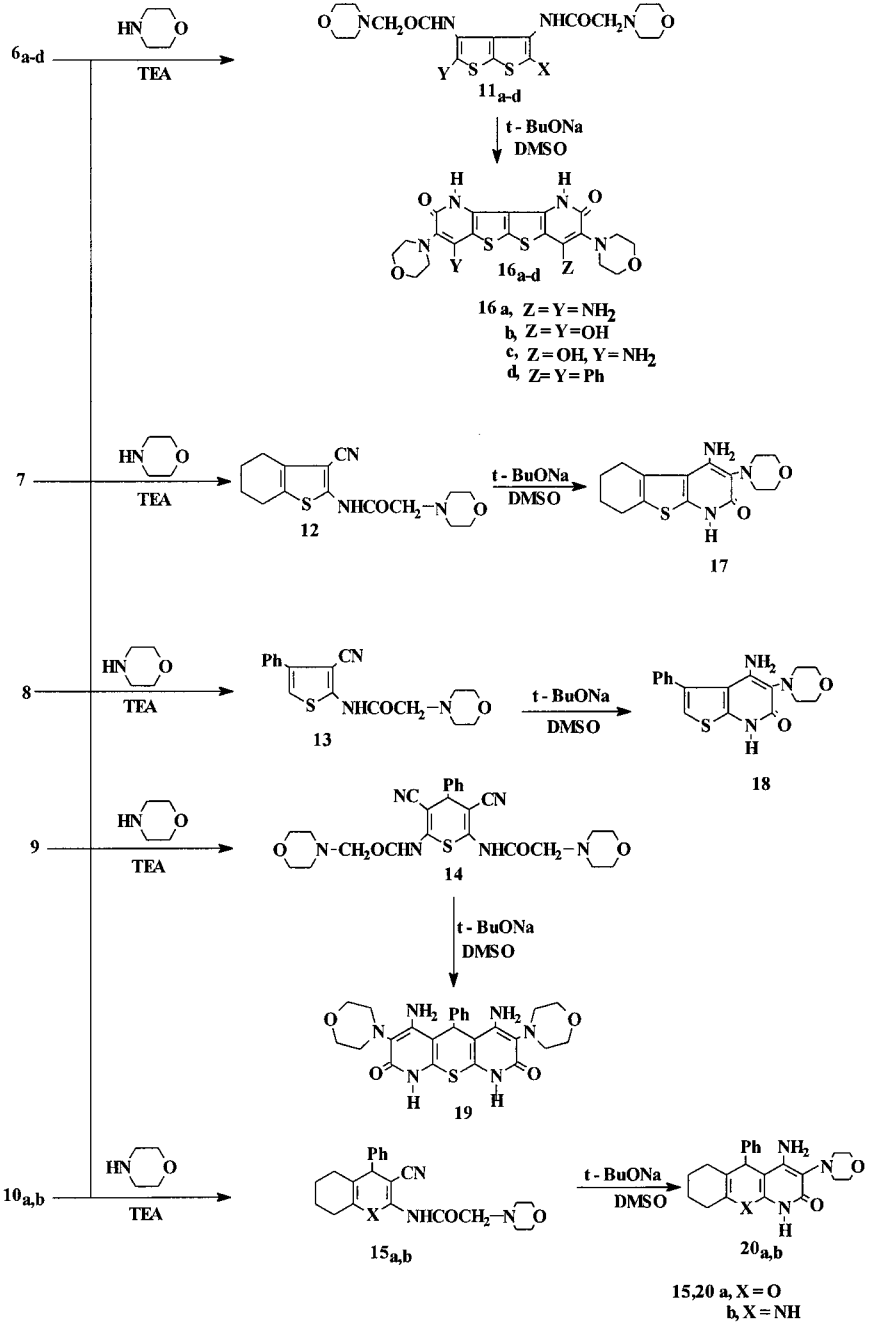
(Continued on next page)

TABLE I Analytical and Spectral Data of the New Compounds *(Continued)*

Product no.	m.p. (°C)[a]	Yield (%)	Mole. form. (mol.wt.) solvent of crystalization	Analytical data[b] cal./found C	H	N	S	Cl	IR (cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
23	190	77	$C_{16}H_{10}N_4OS$ (306.34) Ethanol	62.73 62.98	3.29 3.44	18.29 18.40	10.47 10.21		3300, 3215 (NH_2), 2210 (CN), 1690 (CO)	8.00–7.50 (m, 5H, arom.), 6.90 (s, 1H, =CH), 5.00–4.70 (br, 2H, NH_2), 4.30 (s, 2H, CH_2)
24	271	70	$C_{23}H_{14}N_8O_2S$ (466.47) Methanol	59.22 59.51	3.03 3.34	24.02 24.30	6.87 6.66		3300, 3218 (NH_2), 2100 (CN), 1690 (CO)	7.50–7.10 (m, 5H, arom.), 6.10 (s, 1H, CH), 5.50–5.20 (br, 4H, $2NH_2$), 4.40 (s, 4H, $2CH_2$)
25a	261	80	$C_{21}H_{18}N_4O_2$ (358.40) DMF	70.37 70.03	5.06 5.27	15.63 15.40			3300, 3215 (NH_2), 2200 (CN), 1690 (CO)	8.00–7.50 (m, 5H, arom.), 6.30 (s, 1H, CH), 6.00–5.80 (br, 2H, NH_2), 4.60 (s, 2H, $COCH_2$), 3.7–3.3 (m, 4H, $2CH_2$), 1.90–1.50 (m, 4H, $2CH_2$)
25b	215	61	$C_{21}H_{19}N_5O$ (357.41) Acetic acid	70.57 70.75	5.36 5.55	19.60 19.40			3340, 3215, 3100 (NH+ NH_2), 2100 (CN), 1680 (CO)	8.80 (s, 1H, NH), 8.00–7.60 (m, 5H, arom.), 6.00 (s, 1H, CH), 5.50–5.20 (br, 2H, NH_2), 3.60–3.30 (m, 4H, $2CH_2$), 1.90–1.60 (m, 4H, $2CH_2$)

26a	321	44	$C_{26}H_{10}Cl_2N_4O_2S_2$ (545.51) Dioxane	57.25 57.46	1.85 1.63	10.27 10.46	11.76 11.40	13.21 13.21	3400 (OH), 2113 (CN)	8.0–7.2 (m, 8H, arom.), 4.1 (s, 2H, 2OH)
26b	300	66	$C_{38}H_{18}Cl_2N_4S_2$ (665.71) Dioxane	68.56 68.70	2.73 2.53	8.41 8.31	9.63 9.40	10.66 10.44	2210 (CN), 1600 (C=N)	8.2–7.0 (m, 18H, arom.)
27a	290	66	$C_{32}H_{10}Cl_4N_6O_4S_2$ (748.59) Ethanol	51.34 51.54	1.35 1.50	11.23 11.55	8.57 8.39	18.96 18.79	3400 (OH), 2240 (CN), 1700 (CO)	8.4–7.2 (m, 8H, arom.), 3.1 (s, 2H, 2OH)
27b	311	70	$C_{44}H_{18}Cl_4N_6O_2S_2$ (868.79) Aetic acid	60.83 60.60	2.09 2.25	9.67 9.80	7.38 7.60	16.34 16.20	2200 (CN), 1702 (CO)	8.5–7.1 (m, 18H, arom.)
28	205	67	$C_{14}H_6N_6O_2S_4$ (418.49) Ethanol	40.18 40.35	1.45 1.66	20.08 20.23	30.65 30.40		3100 (NH), 1680 (CO), 1450 (C=S)	8.80 (s, 2H, 2NH), 4.00 (s, 4H, $2CH_2$)

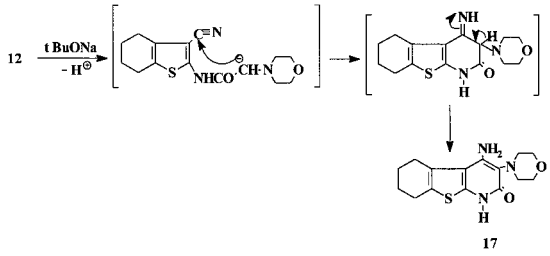
[a]Uncorrected.
[b]Satisfactory microanalysis obtained C; ±0.35, H; ±0.4, N; ±0.2, S; ±0.2, Cl; ±0.23.
[c]Measured by Nicolet FT-IR 710 spectrophotometer.
[d]Measured by a varian EM 360 L spectrometer at 60 MHZ using TMS as internal standard and DMSO as a solvent.



SCHEME 2

and triethylamine to give the corresponding N-morpholin-1-yl acetyl derivatives **11–15** respectively.

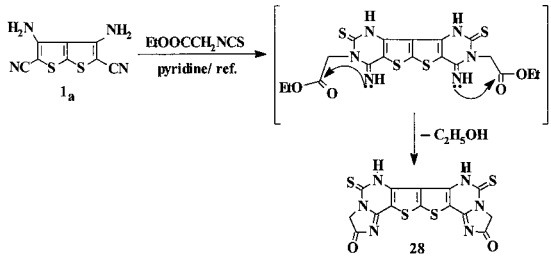
Compounds **11–15** were subjected to Thorpe-Ziegler[11] cyclization with sodium *tert*-butoxide in dimethyl sulphoxide as a solvent to yield pyridin-2(1H)-one derivatives **16–20** respectively. IR spectra of compounds **16–20** showed the presence of absorption bands corresponding to OH, NH_2 groups in addition to CO group at 3450 cm^{-1}, 3320, 3200 cm^{-1}, and 1670 cm^{-1} respectively. ^{1}H-NMR spectra showed the disappearance of the signal corresponding to the methylene group $COCH_2$-N and the appearance of new peaks at 6.50–6.00 ppm and 5.00 ppm for NH_2 and OH groups, respectively (c.f. Scheme 2, Eq. (1), Table I). The reaction pathway was assumed to involve either a nucleophilic addition of the formed carbanion of the active methylene group at the CN group or a nucleophilic attack of the methylene group at the CO_{ester} or CO_{ketone} with elimination of ethanol or water molecule (c.f. Scheme 2, Eq. (1), Table I).



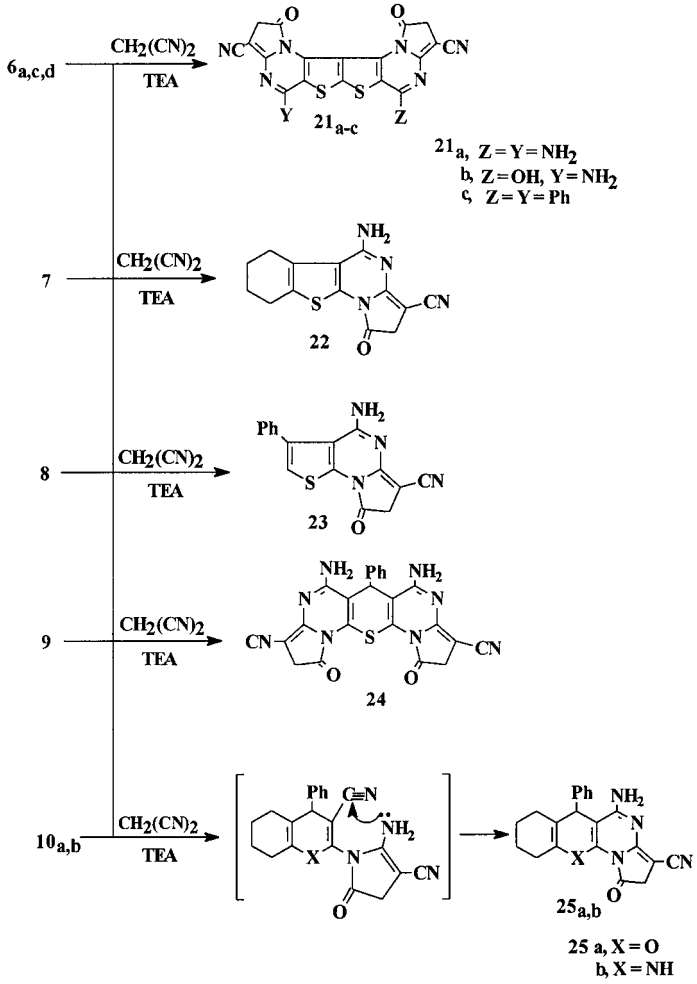
(1)

Treatment of the N-chloroacetylated derivatives **6–10** with malononitrile and triethylamine afforded the corresponding pyrimidine[7] derivatives **21–25** (c.f. Scheme 3). The pyridine **26** and pyrimidine **27** derivatives were obtained via the treatment of compound $\mathbf{1_{b,d}}$ or $\mathbf{6_{b,d}}$ with *p*-chlorobenzylidinemalononitrile. IR spectra of these compounds **21–27** showed the absorption bands corresponding of OH, NH, NH_2, CN, and CO groups at 3440, 3300, 3219–3100, 2210, and 1690 cm^{-1} respectively. ^{1}H-NMR spectra are in agreement with the proposed structures (c.f. Schemes 3 and 4, Table I).

Moreover compound $\mathbf{1_a}$ was treated with ethyl isothiocyanoacetate to give the corresponding piprazine derivative **28** (Eq. (2), Table I).



(2)

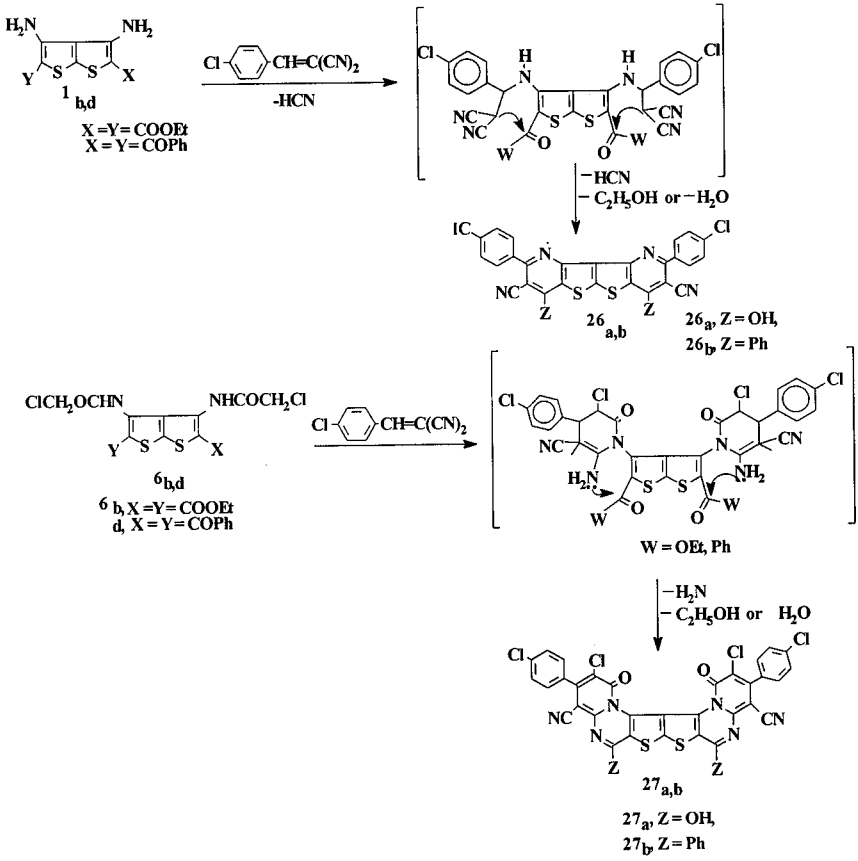


SCHEME 3

EXPERIMENTAL

Synthesis of Compounds 6–10 (General Procedure)

To a solution of compound **1–5** (0.01 mmol) in dioxan (30 ml) and triethylamine (1 ml), was added chloroacetyl chloride (0.01 mmol) dropwise with stirring. The reaction mixture was refluxed for 5 h, evaporated in vacuo and the residual solid was washed with water, dried, and crystallized from the appropriate solvent (c.f. Scheme 1, Table I). (In case of products **6** and **9**, we used double ratio of chloroacetyl chloride).



SCHEME 4

Synthesis of Compounds 11–15 (General Procedure)

An equimolar amount (0.02 mmol) of compound **6–10** and morpholine were dissolved in dioxan (30 ml). The reaction mixture was treated with triethylamine (1 ml), refluxed for 5 h and concentrated. The precipitated solid was collected by filtration, washed with water, dried, and crystallized from the appropriate solvent (c.f. Scheme 2, Table I). (In case of products **11** and **14**, the used of morpholine was 0.02 mmol).

Synthesis of Compounds 16–20 (General Procedure)

To a solution of compound **11–15** (0.005 mmol) in dry DMSO (10 ml), was added sodium *tert*-butoxide (0.006 mmol of Na in 5 ml of *tert*-butanol). The reaction mixture was stirred in an oil bath 100°C for 1 h. On cooling,

the mixture was poured into ice-water (40 ml) with 3 N HCl (10 ml), the separated solid was collected by filtration, dried, and crystallized from the appropriate solvent (c.f. Scheme 2, Table I).

Synthesis of Compounds 21–25 (General Procedure)

To a solution of compound **6–10** (0.01 mol) in dioxan (20 ml), were added malononitrile (0.01 mmol) and triethylamine (1 ml). The reaction mixture was refluxed for 3 h, evaporated in vacuo, the residual solid was washed with water, dried, and crystallized from the suitable solvent (c.f. Scheme 3, Table I). (In case of products **21** and **24**, the used of malononitrile was 0.02 mmol).

Synthesis of Compounds 26 and 27 (General Procedure)

A solution of compound $\mathbf{1_{b,d}}$ or $\mathbf{6_{b,d}}$ (0.02 mmol) in DMF (10 ml), was treated with *p*-chlorobenzylidinemalononitrile (0.02 mmol) and triethylamine (1 ml). The reaction mixture was refluxed for 8 h, evaporated in vacuo, the residual solid was washed with water, dried, and crystallized from the appropriate solvent (c.f. Scheme 4, Table I).

Synthesis of Compound 28

A mixture of compound $\mathbf{1_a}$ (0.01 mmol), isothiocyanoacetate (0.01 mmol), and pyridine (20 ml) was refluxed for 3 h. The reaction mixture was poured into ice water (20 ml) and HCl (5 ml), the precipitate was filtered off, dried, and crystallized from ethanol (c.f. Eq. (2), Table I).

REFERENCES

[1] G. E. H. El-Gemeie, F. A. Abdel-Aal, and K. Abou Hadeed, *J. Chem. Res. (S)*, 128 (1991).
[2] A. M. El-Sayed and A. Khodairy, *Synth. Commun*., **28**(18), 3331 (1998).
[3] A. Gangiee, A. Vasudevan, S. F. Queener, and R. L. Kisliuk, *J. Med. Chem*., **39,** 1438 (1996).
[4] G. E. H. El-Gemeie, E. A. Hafez, G. A. Nawwar, and M. H. El-Nagdi, *Heterocycles*, **22,** 2829 (1984).
[5] F. A. Abdel-Aal, A. M. Negm, Y. Mahfouz, and H. A. El-Fahham, *Egypt J. Pharm. Sci*., **32**, 861 (1991).
[6] G. E. H. El-Gemeie and F. A. Abdel-Aal, *Heterocycles*, **24,** 349 (1986).
[7] A. Khodairy and H. Abdel-Ghany, *Phosphorous, Sulfur, and Silicon*, **162,** 259 (2000).
[8] A. K. El-Shafei, A. M. M. El-Saghier, A. Sultan, and A. M. M. Soliman, *Phosphorous, Sulfur, and Silicon*, **72,** 73 (1992).

[9] A. K. El-Shafei, A. M. M. Soliman, A. Sultan, and A. M. M. El-Saghier, *Gazz. Chem. Ital*., 125 (1995).
[10] A. M. Soliman, *Phosphorous, Sulfur, and Silicon*, **97,** 1 (1994).
[11] A. M. Soliman, A. Sultan, and A. K. El-Shafei, *Monatshefte fur Chem*., **126,** 615 (1995).
[12] M. Rehwald, K. Gewald, Hans-Joachim Lankau, and K. Unverferth, *Heterocycles*, **45**(3), 483 (1997).
[13] A. K. El-Shafei, H. Abel-Ghany, A. A. Sultan, and A. M. M. El-Saghier, *Phosphorous, Sulfur, and Silicon*, **73,** 15 (1992).
[14] K. Gewold, *Chem. Ber*., **98,** 3571 (1965).
[15] F. M. Abdel-Galil, S. M. Serif, and M. H. El-Nagdi, *Heterocycles*, **24,** 2023 (1986).
[16] M. H. El-Nagdi, M. A. Negm, and A. W. Erian, *Leibigs. Ann. Chem*., 1255 (1989).