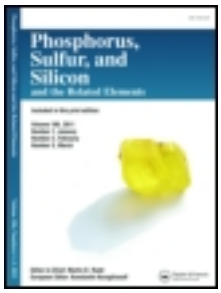

Phosphorus, Sulfur, and Silicon and the Related Elements

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Cyanothioacetamide in Heterocyclic Chemistry: Synthesis of Piperidine-3-carbonitrile, Pyrazolopyridine, Thiinopyridine-3-carbonitrile Derivatives, and Their Theoretical Calculations

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CYANOTHIOACETAMIDE IN HETEROCYCLIC CHEMISTRY: SYNTHESIS OF PIPERIDINE-3-CARBONITRILE, PYRAZOLOPYRIDINE, THIINOPYRIDINE-3-CARBONITRILE DERIVATIVES, AND THEIR THEORETICAL CALCULATIONS

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*Cyanothioacetamide (**1**) reacted with acrylonitrile (**2**) to afford the corresponding 6-oxo-2-sulfanylpiperidine-3-carbonitrile (**6**), which oxidized to give compounds **7** and **8** under different conditions. Moreover, compound **6** was used as a starting material to synthesize **12a–c**, **16a–d**, **26a–c**, **27a–c**, and **30a–c** via reactions with aromatic aldehydes **9a–c**, diazonium chlorides **13a–d**, and 3-arylpropennitrile derivatives **18a–i** respectively. Considering the data of IR, ^{1}H NMR, mass spectra, elemental analyses, and theoretical calculations, all the structures of the newly synthesized heterocyclic compounds were elucidated.*

Keywords: 5,6-Dihydrothiino[2,3-b]pyridine-3-carbonitrile; 6-oxo-2-sulfanyl-piperidine-3-carbo-nitrile; acrylonitrile; cyanothioacetamide; pyrazolo[4,3-c]pyridin-6-one

INTRODUCTION

Although several publications[1–17] have appeared concerning the reactions and synthetic potential of cyanothioacetamide (**1**) no approach concerning its reaction with acrylonitrile (**2**) has been published. This induced our interest to carry out this reaction to isolate pyridine derivative and, in turn, use it as a good synthon to prepare several heterocyclic compounds with promising biological activities. In addition, the reported biological activities of each of pyridines[18–19] and pyrazolopyridines[20–22] stimulated our interest for the synthesis of several new derivatives of these ring systems which are required for the chemical transformations and medicinal chemistry program.

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TABLE I

Comp.	Color	Yield (%)	m.p. (°C)	Molecular formula	% Chemical analysis (calcd./found)				
					C	H	N	S	Cl
6	Pale-yellow	75	156	$C_6H_6N_2OS$	46.74	3.92	18.17	20.80	—
					46.5	4.1	18.3	20.6	—
7	Brown	66	220–220	$C_{12}H_{10}N_4O_2S_2$	47.05	3.29	18.29	20.93	—
					46.9	3.1	18.4	21.1	—
8	Brown	82	287–289	$C_6H_4N_2OS$	47.36	2.65	18.41	21.07	—
					47.5	2.5	18.6	21.2	—
12a	White	67	211–213	$C_{13}H_{10}N_2OS$	64.44	11.56	13.23	—	
					64.6	11.7	13.4	—	
12b	Yellow	65	237–239	$C_{13}H_9ClN_2OS$	56.42	3.28	10.12	11.59	12.81
					56.6	3.4	10.3	11.7	12.6
12c	Gray	77	198	$C_{14}H_{12}N_2O_2S$	61.75	4.44	10.29	11.78	—
					61.9	4.6	10.1	11.9	—
14a	White	59	178	$C_{12}H_{10}N_4OS$	55.80	3.90	21.69	12.41	—
					55.6	4.1	21.8	12.2	—
14b	Green	69	235–237	$C_{12}H_9ClN_4OS$	49.23	3.01	19.14	10.95	12.11
					49.4	3.2	19.3	11.1	12.3
14c	Brown	81	220–220	$C_{13}H_{12}N_4O_2S$	54.15	4.20	19.43	11.12	—
					54.3	4.0	19.6	11.3	—
14d	Gray	66	199	$C_{13}H_{12}N_4OS$	57.34	4.44	20.57	11.78	—
					57.5	4.5	20.3	11.5	—

16a	Brown	68	266–268	$C_{12}H_{10}N_4OS$	55.80	3.90	21.69	12.41	—
					56.0	3.7	21.5	12.6	—
16b	Gray	69	311–313	$C_{12}H_9ClN_4OS$	49.23	3.01	19.14	10.95	12.11
					49.0	2.8	18.9	10.8	11.9
16c	Yellow	81	297–299	$C_{13}H_{12}N_4O_2S$	54.15	4.20	19.43	11.12	—
					53.9	4.4	19.2	11.1	—
16d	White	66	225–227	$C_{13}H_{12}N_4OS$	57.34	4.44	20.57	11.78	—
					57.1	4.6	20.7	11.9	—
26a	Yellow	71	287–289	$C_{15}H_{11}N_3OS$	64.04	3.39	14.94	11.40	—
					64.2	3.5	15.1	11.2	—
26b	Green	79	235–237	$C_{15}H_{10}ClN_3OS$	57.05	3.19	13.31	10.16	11.23
					57.2	3.0	13.5	10.3	11.5
26c	Yellow	66	300–302	$C_{16}H_{13}N_3O_2S$	61.72	4.21	13.50	10.30	—
					61.9	4.4	13.3	10.1	—
28a	Yellow	69	187–189	$C_{17}H_{16}N_2O_3S$	62.18	4.91	8.53	9.77	—
					62.3	5.1	8.6	9.5	—
28b	White	74	225–227	$C_{17}H_{15}ClN_2O_3S$	56.28	4.17	7.72	8.84	9.77
					56.1	4.3	7.9	8.6	9.5
28c	Yellowish-white	59	>300	$C_{18}H_{18}N_2O_4S$	60.32	5.06	7.82	8.95	—
					60.1	5.2	7.6	9.1	—

RESULTS AND DISCUSSION

It has been found that cyanothioacetamide (**1**) reacted with acrylonitrile (**2**) in an aqueous solution of potassium hydroxide (10%) to afford the corresponding 6-oxo-2-thioxopiperidine-3-carbonitrile (**5**), which was present in equilibrium with the more stable structure 6-oxo-2-sulfanyl-3,4,5-trihydropyridine-3-carbonitrile (**6**). Formation of **6** was assumed to proceed via the addition of a proton from **1** on the olefinic double bond of **2** to give the nonisolable intermediate **3**, which, in turn, hydrolyzed to give **4** that underwent ammonia elimination (ammonia removal detected by its odor in addition to the formation of the white clouds with glass rod moistened with hydrochloric acid) to afford **5**⇌**6**. Considering both IR and ^{1}H NMR data and the solubility in alkali, the structure **5** is eliminated. The IR spectrum of the reaction product showed the bands of SH, CN, and CO groups, and its ^{1}H NMR spectrum revealed signals of H-3, H-4, H-5 pyridine and SH or piperidine protons (cf. Tables I, II, and Experimental Part). Moreover, the mass spectrum of **6** gave m/z = 154 that corresponding to the exact molecular weight of a molecular formula $C_6H_6N_2SO$ of the assigned structure (cf. Chart 1).

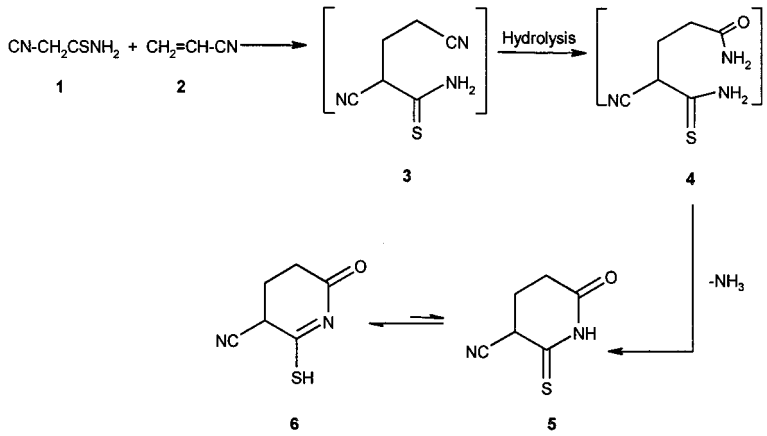

CHART 1

Theoretical Consideration

The reaction products in Chart 1 imply the possible tautomeric equilibrium between **5** and **6**. The ground state electronic properties of these two forms are given in Table III. The **6** is thermodynamically more stable. In a polar medium, **6** would be more stabilized due to its greater dipole moment. For structure **6**, two active methylene centres

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

Comp.	IR (KBr, cm^{-1})	^{1}H NMR (δ ppm)
6	2987 (sat CH); 2569 (SH); 2218 (CN); 1692 (CO amidic); 1629 (C═N) and 1600 (C═C)	2.3 (s, br., 1H, SH); 2.9 (t, 1H, pyridine H-3); 3.5 (m, 2H, pyridine H-4) and 4.7 (t, 2H, pyridine H-5)
7	2982 (sat. CH); 2221 (CN); 1687 (CO amidic); 1635 (C═N) and 1604 (C═C)	2.7 (t, 2H, at H-3 of the two pyridine rings); 3.6 (m, 4H, at H-4 of the two pyridine rings) 5.2 (t, 4H, at H-5 of the two pyridine rings)
8	3267–3442 (OH); 3079 (═C─H stretch); 2568 (SH); 2215 (CN); 1624 (C═N) and 1600 (C═C)	2.1 (s, br., 1H, SH) and 5.7 (dd, 2H, at Pyridine H-4, H-5)
12a	3098 (═C─H streth.); 2979 (sat C─H); 2559 (SH); 2218 (CN); 1624 (C═N) and 1600 (C═C)	2.2 (s, br., 1H, SH); 2.8 (s, 1H, pyridine H-3); 4.8 (s, 2H, pyridine H-5) and 6.9–7.3 (m, 6H, aromatic and ═C**H**─ protons)
12b	3087 (═C─H streth.); 2985 (sat C─H); 2560 (SH); 2214 (CN); 1636 (C═N) and 1602 (C═C)	2.5 (s, br., 1H, SH); 3.1 (s, 1H, pyridine H-3); 5.2 (s, 2H, pyridine H-5) and 7.0–7.9 (m, 5H, aromatic and ═C**H**─ protons)
12c	3112 (═C─H streth.); 2989 (sat C─H); 2552 (SH); 2222 (CN); 1640 (C═N) and 1607 (C═C)	1.3 (s, 3H, CH_3); 2.4 (s, br., 1H, SH); 2.9 (s, 1H, pyridine H-3); 5.3 (s, 2H, pyridine H-5) and 7.0–7.9 (m, 5H, aromatic and ═C**H**─ protons)
14a	3187 (NH); 2982 (sat. CH); 2552 (SH); 2220 (CN); 1687 (CO amidic); 1623 (C═N) and 1602 (C═C)	2.6 (s, br., 1H, SH); 3.2 (s, 1H, pyridine H-3); 5.1 (s, 2H, pyridine H-5); 5.9 (s, br., 1H, NH) and 6.9–7.8 (m, 5H, aromatic protons)
14b	3191 (NH); 2987 (sat. CH); 2556 (SH); 2218 (CN); 1690 (CO amidic); 1631 (C═N) and 1600 (C═C)	2.4 (s, br., 1H, SH); 3.1 (s, 1H, pyridine H-3); 4.9 (s, 2H, pyridine H-5); 5.7 (s, br., 1H, NH) and 7.0–7.9 (m, 4H, aromatic protons)
14c	3197 (NH); 2977 (sat. CH); 2560 (SH); 2221 (CN); 1690 (CO amidic); 1633 (C═N) and 1605 (C═C)	1.7 (s, 3H, OC**H**$_3$); 2.2 (s, br., 1H, SH); 3.3 (s, 1H, pyridine H-3); 5.3 (s, 2H, pyridine H-5); 5.9 (s, br., 1H, NH) and 7.3–8.2 (m, 5H, aromatic protons)
14d	3196 (NH); 2989 (sat. CH); 2555 (SH); 2220 (CN); 1690 (CO amidic); 1631 (C═N) and 1600 (C═C)	0.9 (s, 3H, CH_3); 2.5 (s, br., 1H, SH); 3.4 (s, 1H, pyridine H-3); 4.7 (s, 2H, pyridine H-5); 5.6 (s, br., 1H, NH) and 6.9–7.5 (m, 4H, aromatic protons)
16a	3545–3207 (broad, OH and NH_2); 3087 (═**C**─**H**); 2556 (SH); 2221 (CN); 1635 (C═N) and 1601 (C═C)	2.3 (s, br., 1H, SH); 5.7 (s, br., 2H, NH_2); 6.9–8.1 (m, 6H, aromatic and pyridine H-5) and 12.4 (s, br., 1H, O**H**)
16b	3556–3221 (broad, OH and NH_2); 3101 (═**C**─**H**); 2562 (SH); 2218 (CN); 1630 (C═N) and 1600 (C═C)	2.0 (s, br., 1H, SH); 5.8 (s, br., 2H, NH_2); 7.0–8.1 (m, 5H, aromatic and pyridine H-5) and 12.5 (s, br., 1H, O**H**)

(Continued on next page)

TABLE II IR and ^{1}H NMR Spectral Data *(Continued)*

Comp.	IR (KBr, cm^{-1})	^{1}H NMR (δ ppm)
16c	3551–3218 (broad, OH and NH_2); 3080 (=**C**–**H**); 2981 (sat. CH); 2552 (SH); 2214 (CN); 1628 (C=N) and 1602 (C=C)	1.5 (s, 3H, OC**H$_3$**); 2.2 (s, br., 1H, SH); 5.5 (s, br., 2H, NH_2); 6.9–8.3 (m, 5H, aromatic and pyridine H-5) and 12.3 (s, br., 1H, O**H**)
16d	3582–3224 (broad, OH and NH_2); 3076 (=**C**–**H**); 2551 (SH); 2222 (CN); 1630 (C=N) and 1600 (C=C)	1.0 (s, 3H, CH_3); 2.3 (s, br., 1H, SH); 5.3 (s, br., 2H, NH_2); 6.8–7.2 (m, 5H, aromatic and pyridine H-5) and 12.7 (s, br., 1H, O**H**)
26a	3432, 3253 (NH_2); 2976 (sat CH); 2217 (CN); 1687 (CO amidic); 1633 (C=N) and 1604 (C=C)	2.7 (t, 2H, at pyridine H-4); 4.8 (t, 2H, at pyridine H-3); 5.6 (s, br., 2H, NH_2) and 6.9–7.7 (m, 5H, aromatic protons)
26b	3421, 3249 (NH_2); 2978 (sat CH); 2218 (CN); 1691 (CO amidic); 1630 (C=N) and 1600 (C=C)	3.1 (t, 2H, at pyridine H-4); 4.5 (t, 2H, at pyridine H-3); 5.8 (s, br., 2H, NH_2) and 7.0–7.8 (m, 4H, aromatic protons)
26c	3441, 3258 (NH_2); 2982 (sat CH); 2222 (CN); 1695 (CO amidic); 1623 (C=N) and 1601 (C=C)	1.5 (s, 3H, OC**H$_3$**); 3.3 (t, 2H, at pyridine H-4); 4.8 (t, 2H, at pyridine H-3); 5.3 (s, br., 2H, NH_2) and 7.0–7.9 (m, 4H, aromatic protons)
28a	3452, 3224 (NH_2); 2987 (sat CH); 2218 (CN); 1721 (CO ester); 1690 (CO amidic); 1630 (C=N) and 1602 (C=C)	1.0 (t, 3H, **CH$_3$**CH_2); 2.8 (t, 2H, at pyridine H-4); 4.2 (q, 2H, CH_3**CH$_2$**); 5.0 (t, 2H, at pyridine H-3); 5.7 (s, br., 2H, NH_2) and 6.8–7.8 (m, 5H, aromatic protons)
28b	3434, 3218 (NH_2); 2980 (sat CH); 2214 (CN); 1719 (CO ester); 1684 (CO amidic); 1635 (C=N) and 1605 (C=C)	1.2 (t, 3H, **CH$_3$**CH_2); 3.1 (t, 2H, at pyridine H-4); 4.3 (q, 2H, CH_3**CH$_2$**); 4.9 (t, 2H, at pyridine H-3); 5.8 (s, br., 2H, NH_2) and 6.9–7.6 (m, 4H, aromatic protons)
28c	3441, 3223 (NH_2); 2987 (sat CH); 2217 (CN); 1723 (CO ester); 1693 (CO amidic); 1632 (C=N) and 1601 (C=C)	0.9 (t, 3H, **CH$_3$**CH_2); 1.6 (s, 3H, O**CH$_3$**); 3.3 (t, 2H, at pyridine H-4); 4.1 (q, 2H, CH_3**CH$_2$**); 5.2 (t, 2H, at pyridine H-3); 5.9 (s, br., 2H, NH_2) and 7.1–8.2 (m, 4H, aromatic protons)

are available for consideration, viz., atoms 4 and 5. The net charge on the two atoms is 0.067e and 0.033e respectively. These charge densities would thus favor C_4 over C_5. The electrostatic potential map (EPM) for **6** is given in Figure 1. This map supports our conclusion that C_4 is the most favorable center of consideration.

Compound **6** was oxidized by refluxing in ethanol containing a catalytic amount of triethylamine for 3 h to give a reaction product corresponding to dehydrogenation. The IR spectrum of this reaction product showed bands corresponding to the CN and CO groups, and its ^{1}H NMR spectrum revealed the signals of only pyridine protons.

TABLE III

Comp. no.	Total energy (eV)	Binding energy (Kcal)	Isolated A.E. (Kcal)	Electronic energy (Kcal)	Nuclear-nuclear repulsion (Kcal)	Heat of formation (Kcal)	E_{HOMO} (IP) (eV)	E_{LUMO} (EA) (eV)	Energy gab (eV)	Dipole moment (D)
5	−1779.69	−1681.50	−39340.20	−181770.70	140748.90	8.37	−9.2462	−1.2854	7.9608	3.756
6	−1779.16	−1669.40	−39340.20	−182122.30	141112.70	20.51	−9.8353	−0.8882	8.9471	5.457
7	−3530.58	−3225.04	−78154.80	−486525.30	405145.40	50.57	−9.3738	−2.8695	6.5043	6.616
8	−1751.58	−1559.20	−38814.60	−168712.20	128338.00	26.50	−9.0791	−0.8828	8.1963	1.645
10a	−2729.56	−3021.90	−59894.40	−365815.50	302899.10	72.60	−9.3653	−1.0370	8.3283	4.390
11a	−3679.82	−4371.30	−80448.60	−613166.80	528346.90	127.80	−8.9187	−1.1023	7.8164	4.059
12a	−2729.60	−3022.80	−59894.30	−367205.90	304288.70	71.73	−9.4363	−0.8645	8.5718	4.835
12b	−3089.87	−3008.84	−68214.85	−406409.06	335185.36	64.92	−9.4464	−0.9646	8.4818	4.475
12c	−3205.79	−3397.84	−70495.72	−448244.21	374350.65	33.39	−9.0422	−0.8488	8.1934	4.428
14a	−3014.82	−3047.80	−66443.70	−407480.90	339789.30	101.70	−8.8699	−0.9619	7.9080	3.810
15a	−3014.70	−3045.20	−66443.70	−419307.70	349818.70	104.45	−9.2491	−0.9261	8.3230	8.219
16a	−3015.07	−3053.60	−66443.70	−418494.90	348997.60	96.05	−8.0645	−0.7089	7.3556	5.087
16b	−3375.33	−3037.10	−74764.20	−457872.50	380071.20	89.50	−8.1592	−0.8869	7.2723	4.389
16c	−3490.79	−3417.60	−77045.00	−500115.10	419652.40	66.69	−8.2809	−0.9906	7.2903	6.107
16d	−3171.01	−3336.30	−69755.50	−455663.20	382571.40	88.41	−8.0507	−0.7098	7.3409	5.280
17a	−3014.99	−3051.90	−66443.70	−403389.50	333893.80	97.70	−8.7841	−1.0746	7.7095	3.124
18a	−3776.87	−3995.90	−83061.00	−617475.30	530418.40	112.10	−9.0289	−1.1159	7.9130	9.333
19a	−3554.93	−3827.20	−78113.80	−561692.10	479751.00	110.20	−9.3478	−1.1354	8.2124	3.664
19d	−3554.59	−3819.60	−78113.90	−548703.80	466770.60	−118.08	−9.7160	−1.1148	8.6012	5.798
19g	−4315.00	−4549.10	−94911.60	−728675.30	629214.50	−3.32	−9.5454	−0.9811	8.5643	8.665
20a	−3777.21	−4003.60	−83061.00	−638969.30	551904.70	104.40	−8.8828	−1.1350	7.7470	6.159
21a	−3777.28	−4005.30	83061.00	−634087.50	547021.10	102.70	−8.5637	−1.0200	7.5437	4.242
22a	−3206.48	−3512.10	−70397.20	−472812.90	398903.50	89.25	−9.1806	−1.4205	7.7601	4.446
23a	−3429.80	−3712.50	−75344.30	−539833.80	460777.00	59.57	−8.3783	−1.2915	7.0868	8.323
24a	−3429.29	−3700.80	−75344.30	−541732.70	462687.50	71.18	−8.4775	−1.0443	7.4332	6.199
26a	−3206.77	−3518.80	−70397.20	−470924.00	397008.90	82.62	−8.7806	−1.6198	7.1608	5.071
26b	−3567.02	−3502.20	−78717.70	−511817.90	429598.10	76.12	−8.8584	−1.7728	7.0856	4.615
26c	−3682.89	−3892.20	−80998.50	−555417.40	470526.60	43.89	−8.7295	−1.5603	7.1692	6.279
27a	−3966.76	−4239.10	−87194.90	−644063.30	552629.30	−29.216	−9.0912	−1.2763	7.8149	6.458
28a	−3967.27	−4252.97	−87194.93	−642876.90	551429.00	−40.75	−8.6872	−1.3641	7.3231	7.681
29a	−3306.16	−2450.60	−72756.30	−478615.70	402408.80	45.25	−9.4322	−1.3926	8.0396	4.671

Moreover, its mass spectrum gave m/z = 306 which corresponding to the exact molecular weight of a molecular formula $C_{12}H_{10}N_4S_2O_2$. Considering the above data, in addition to the elemental analyses, this reaction product could be formulated as the corresponding disulphide derivative **7**. Compound **6** was aromatized by stirring in cold ethanol containing a

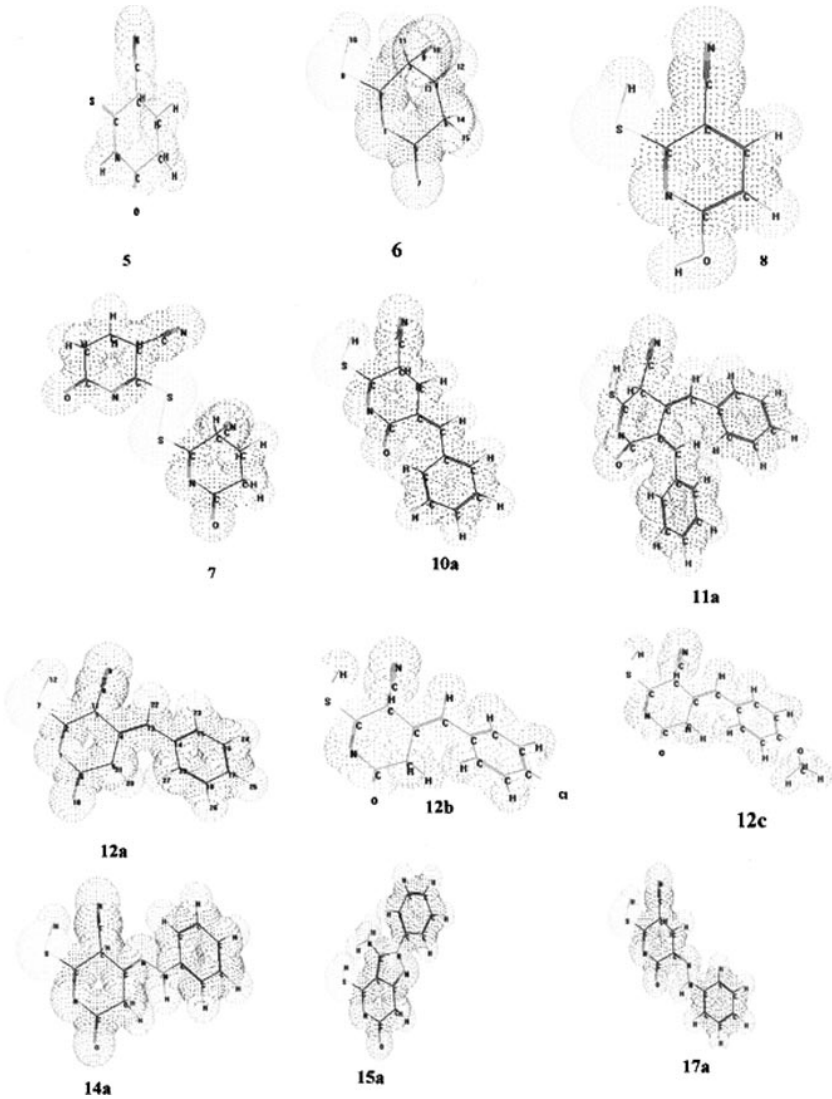

FIGURE 1 Prospective drawing of compounds drawn at its AM1 geometry. *(Continued)*

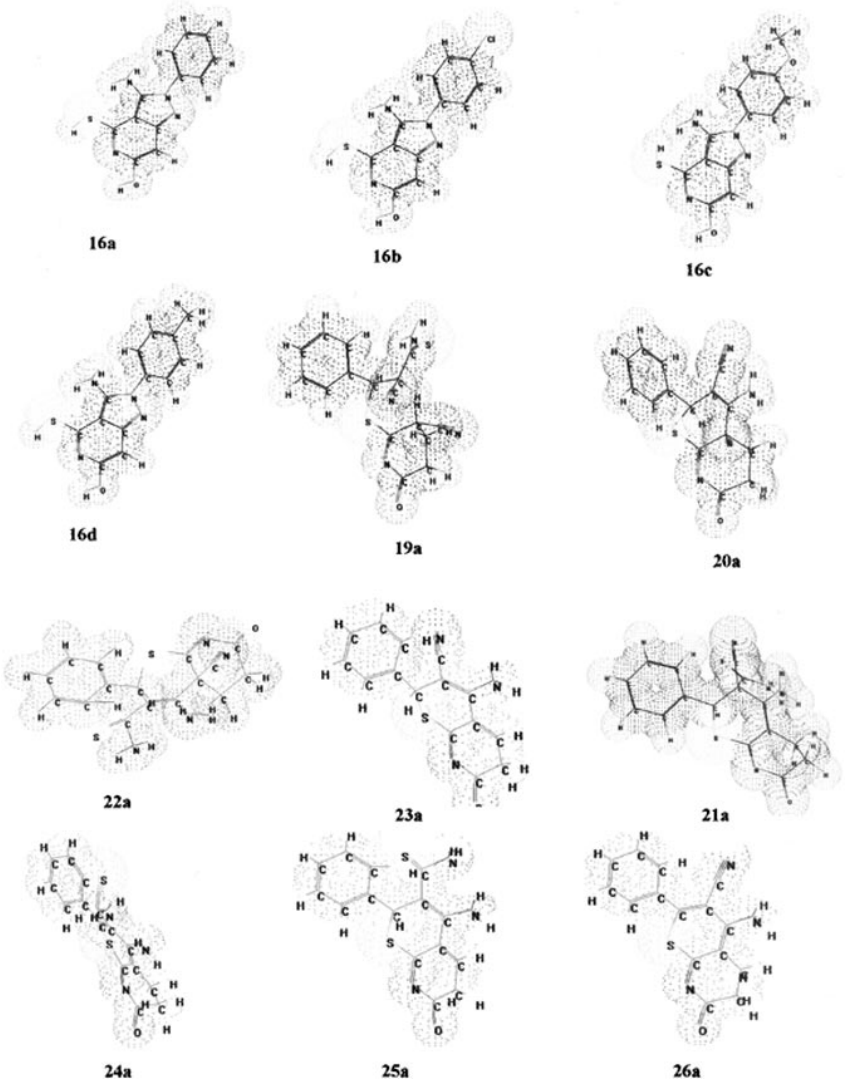

FIGURE 1 (Continued)

catalytic amount of triethylamine to give the corresponding 6-hydroxy-2-sulfanylpyridine-3-carbonitrile (**8**). The structure of **8** was elucidated by considering the data of IR and ^{1}H NMR spectra in addition to its mass spectrum which gave m/z = 152 and which corresponded to the molecular weight of a molecular formula $C_6H_4N_2SO$ of the assigned structure (cf. Chart 2).

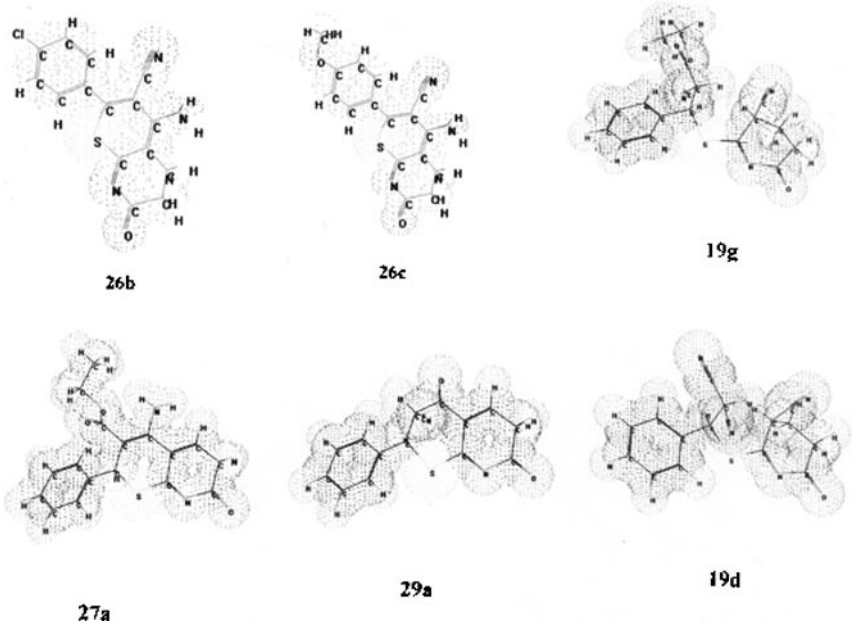

FIGURE 1 (Continued)

An investigation of the $-CH_2$-activity in **6** was examined through its reaction with aromatic aldehydes **9a–c**. It was found that **6** reacted with benzaldehyde (**9a**) in ethanol containing a catalytic amount of triethylamine under reflux for 5 h to afford a condensation product **12a**. The elemental analyses, IR, and ^{1}H NMR data were the basis on which the structure of **12a** was established and the structures **10a** and **11a** were eliminated (cf. Tables I and II). Similarly, **6** reacted with both p-chlorobenzaldehyde and p-methoxybenzaldehyde **9b**,**c** to afford the corresponding condensation products **12b**,**c** respectively.

Theoretical Consideration

Condensation reactions on **6** may yield the ArCH= derivative either **10** or **12** depending on the condensation site. The ground state electronic structural properties of **10–12** are presented in Table III. Careful inspection of these data reveals that condensation at C_4 or C_5 are equally probable and perhaps allows simultaneous attack on the two centres (cf. Figure 1). Figure 2 plots free energy relationships of E_t, ΔH_f, μ, and ΔE_{gap} against the (σ_p) Hammet constant for substituents **a–c** of **12**.

Work was extended to shed more light on the $-CH_2$-activity in **6** through its coupling reaction with aryl diazonium chlorides. Thus, it was found that a cold solution of **6** in ethanol containing sodium

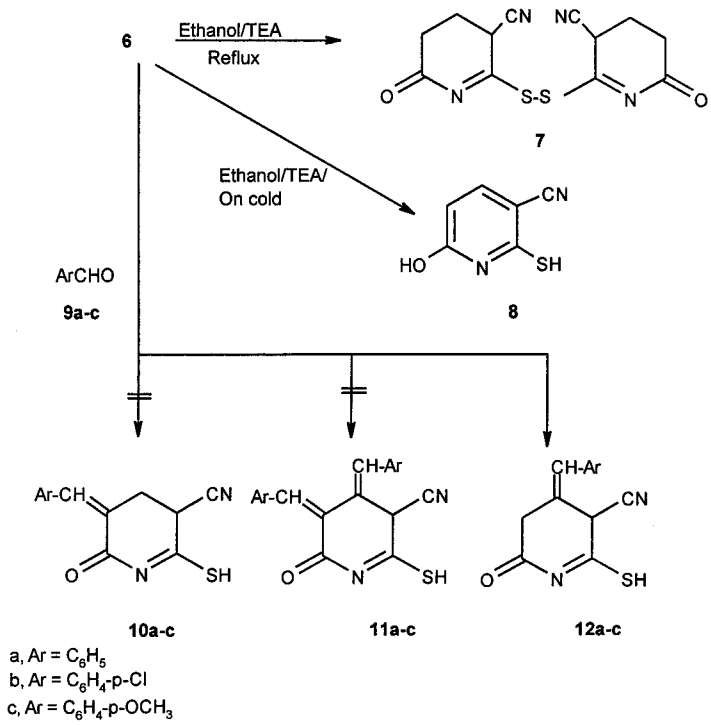

CHART 2

acetate was stirred with a cold solution of diazotized aromatic amines **13a–d** for 3 h to afford the corresponding hydrazo derivatives **14a–d** respectively. The IR spectra of **14a–d** showed bands for NH, SH, CN, and CO groups and the ^{1}H NMR spectra revealed signals of pyridine H-3, H-5, NH, SH, and aromatic protons (cf. Tables I and II). Moreover, the mass spectra of **14a**,**c** as typical examples, gave m/z = 258 and 288 which corresponds to the exact molecular weights of the molecular formulas $C_{12}H_{10}N_4SO$ and $C_{13}H_{12}N_4SO_2$ of the assigned structures (cf. Chart 3). The structures of **14a–d** were further confirmed through their cyclization in ethanol containing catalytic amounts of triethylamine under reflux for 3–5 h to give 3-amino-2-(phenyl-, 4-chlorophenyl, 4-methoxyphenyl and 4-methylphenyl)-4-sulfan-yl-7-hydro-pyrazolo[4,3-c]pyridin-6-one **15a–d** respectively. The IR spectra of these products showed no bands for the CN group and, instead, the newly formed NH_2 group was detected in each case. The absence of C=O band and the presence of newly formed OH group were detected. This proves the presence of **16a–d** rather than **15a–d** (c.f. Tables I, II and Chart 3).

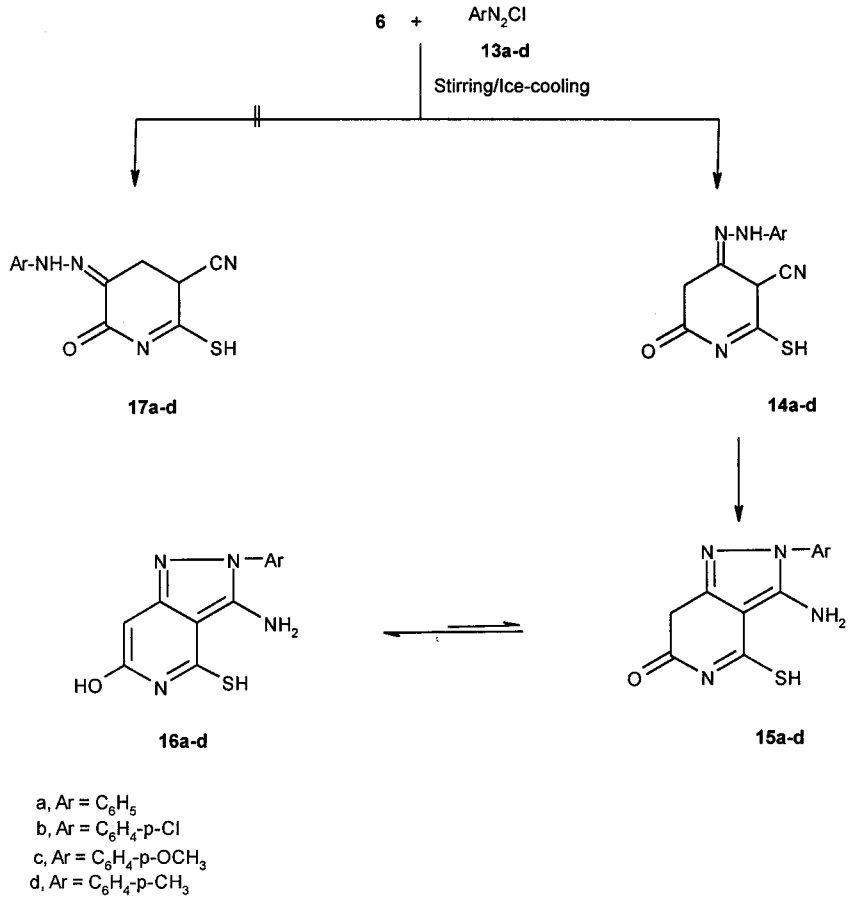

CHART 3

Theoretical Consideration

The reaction of **6** with ArN_2Cl may yield **14** or **17** depending on the rate of condensation. The **14** is thermodynamically and energetically more stable than **17** and **14** is stabilized by its cyclization to **15**, which is further stabilized by its tautomeric equilibrium with **16**. The ground state properties of the formed compounds are given in Table III. The effect of substituents is best visualized via analysis of the free-energy relationships (cf. Figure 1). Figure 3 presents such relationships for compounds **a–d** for the most stable compound **16**.

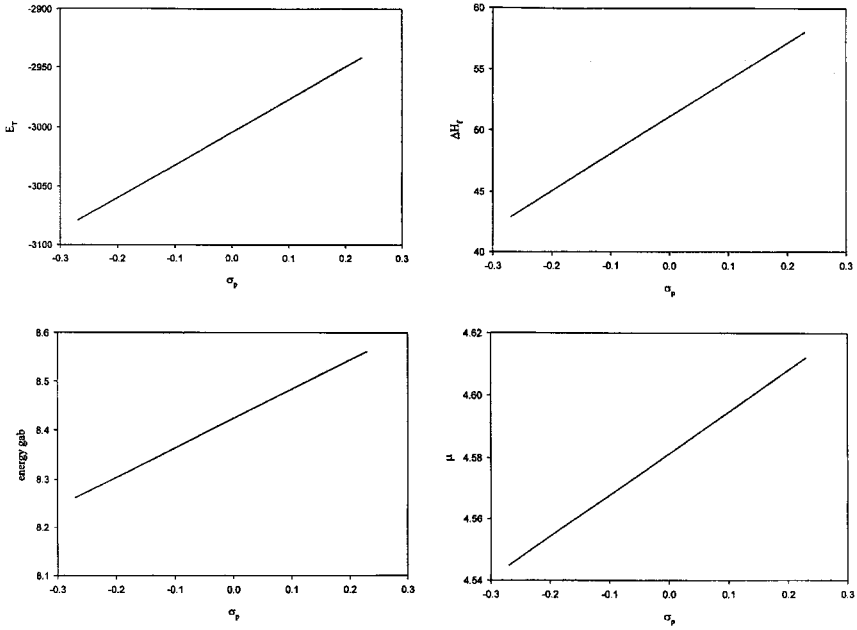

FIGURE 2 Free energy relationships for E_T, ΔH_f, energy gab, and μ as plotted against the σ_{Hammet} constant of compounds **12a–c**.

Synthon **6** reacted with 2-(aminothioxomethyl)-3-phenylprop-2-ennitrile (**18a**) in ethanol containing a catalytic amount of piperidine to afford the corresponding 4-amino-7-oxo-2-phenyl-5,6-dihydrothiino-[2,3-b]pyridine-3-carbonitrile (**26a**). This reaction product formed via the addition of the SH group in **7** to the double bond of **18a** afforded the nonisolable product **19a** which underwent elimination of hydrogen sulphide followed by elimination of hydrocyanic acid to give **23a** that rearranged to give **26a**. The IR and ^{1}H NMR spectrum of this reaction product confirmed its structure (cf. Table II). Moreover, the mass spectrum of reaction product gave m/z = 281 which corresponds to the molecular weight for a molecular formula $C_{15}H_{11}N_3OS$ of the assigned structure (cf. Chart 8). Similarly, other analogues 2-(amino-thioxomethyl)-3-(4-chlorophenyl and 4-methoxyphenyl)-prop-2-ennitrile (**18b**,**c**) reacted with **6** under the same reaction condition to afford the corresponding 4-amino-7-oxo-2(4-chlorophenyl and 4-methoxyphenyl)-5,6-dihydrothiino[2,3-b]pyridine-3-carbonitrile **26b**,**c**, respectively via the nonisolable **20b**,**c** and **23b**,**c**. By considering the data of IR and ^{1}H NMR data and the elemental analyses, structures **24a–c** and **25a–c** were eliminated (cf. Tables I, II, and Chart 4).

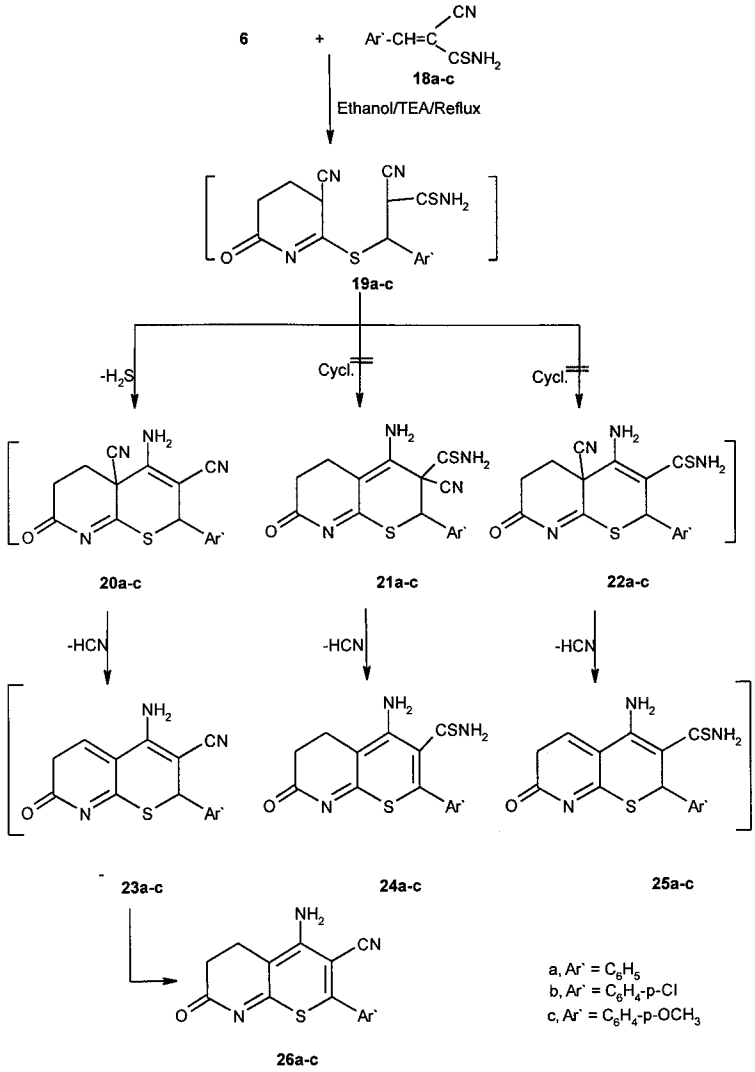

CHART 4

Theoretical Consideration

Chart 4 reveals **26** may be formed from the reaction of **6** with **18** via three main possible intermediate products, namely **20–22**. The intermediate **20** is thermodynamically the most stable as revealed by the ΔH values presented in Table III. Furthermore the loss of HCN would lead to compounds **23–25** of which **23** is thermodynamically much more

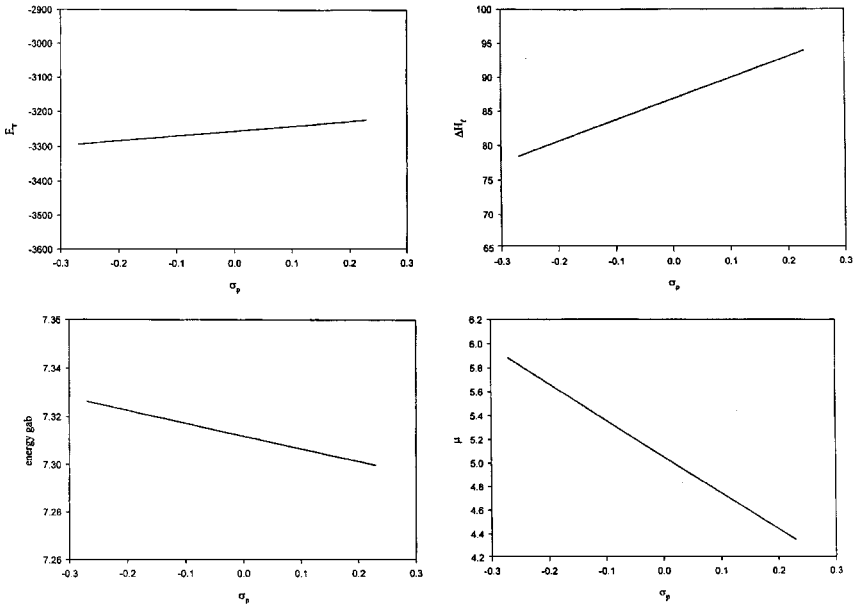

FIGURE 3 Free energy relationships for E_T, ΔH_f, energy gab, and μ as plotted against the σ_{Hammet} constant of compounds **16a–d**.

favorable than **24** and **25**. It is interesting to note that the more favorable route **6** > **20** > **23** involves the less polar components (cf. Figure 1). Figures 4 plots the free-energy relationships between the σ_p-Hammet substituent constants for substituted **26a–c** and E_t, E_{gap}, μ, and ΔH_f.

In a surprise reaction, synthon **6** reacted with each of (phenyl-, 4-chloro-phenyl and 4-methoxyphenylmethylene)methane-1,1-dicarbonitrile **18d–f** under the same previously mentioned conditions to afford the reaction products which were identical in all aspects with that given from the reaction of **18a–c** with **6**. The obtained reaction products **26a–c** were formed via the non-isolable intermediates **19d–f** respectively. It is important to report here that compounds **26a–c** obtained by this route were identical in all aspects with that given from the reaction of **6** with **18a–c**. Moreover, compound **6** reacted with each ethyl-3-(phenyl, 4-chlorophenyl and 4-methoxyphenyl)-2-cyanoprop-2-enoate **18g–i** to give the corresponding ethyl 4-amino-7-oxo-2-(phenyl-, 4-chlorophenyl and 4-methoxyphenyl)-5,6-dihydrothiino[2,3-b]pyridine-3-carboxylate (**28a–c**) via the nonisolable products **19g–i** and **27a–c**. The IR, ^{1}H NMR spectra, and the elemental analyses data were the basis on which the structures **28a–c** were confirmed, and the structures **29a–c** were eliminated. Further confirmation of

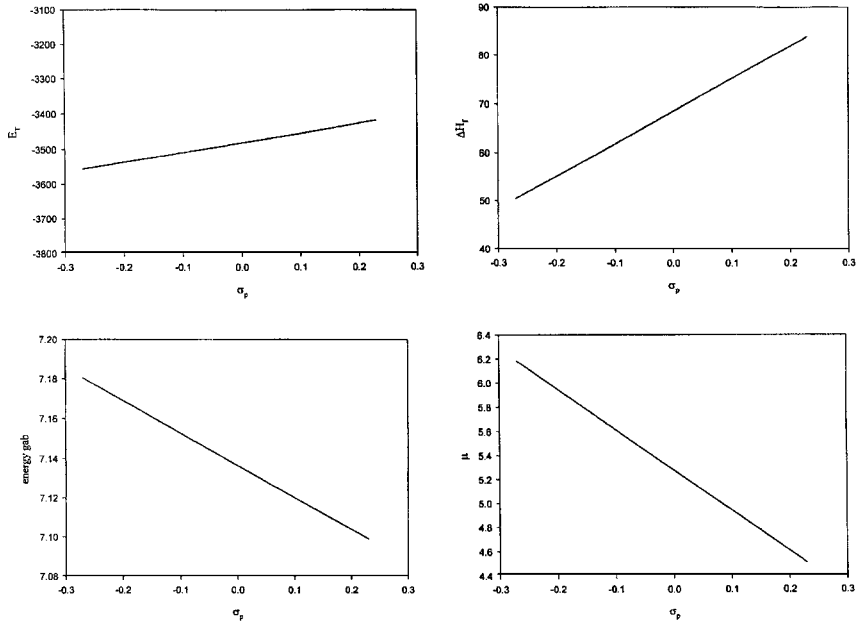

FIGURE 4 Free energy relationships for E_T, ΔH_f, energy gab, and μ as plotted against the σ_{Hammet} constant of compounds **26a–c**.

28a–c structures was given from their mass spectra. The m/z = 328, 362 and 358 corresponded to the molecular weights of the molecular formulae $C_{17}H_{16}N_2O_3S$, $C_{17}H_{15}ClN_2O_3S$, and $C_{18}H_{18}N_2O_4S$ of the assigned structures **28a–c**, respectively (cf. Chart 5).

Theoretical Consideration

The ground state electronic properties for **27–29** are given in Table III and Figure 1. The **27** is much more stable energetically and thermodynamically than **29**. In the polar reaction medium **27** is further stabilized. Once **27** is formed, it would be stabilized by tautomeric equilibrium with **28**.

EXPERIMENTAL

All melting points were uncorrected. IR spectra (KBr discs) were recorded on Brucker Vector 22 and Perkin-Elmer FT-IR type 4 spectrophotometers. ^{1}H NMR spectra were recorded on Varian EM 390 MHz, Gemnai-200 MHz and Brucker WP-80 spectrometers using TMS as an internal standard and $CDCl_3$, DMSO-d_6 and $(CD_3)_2CO$ as

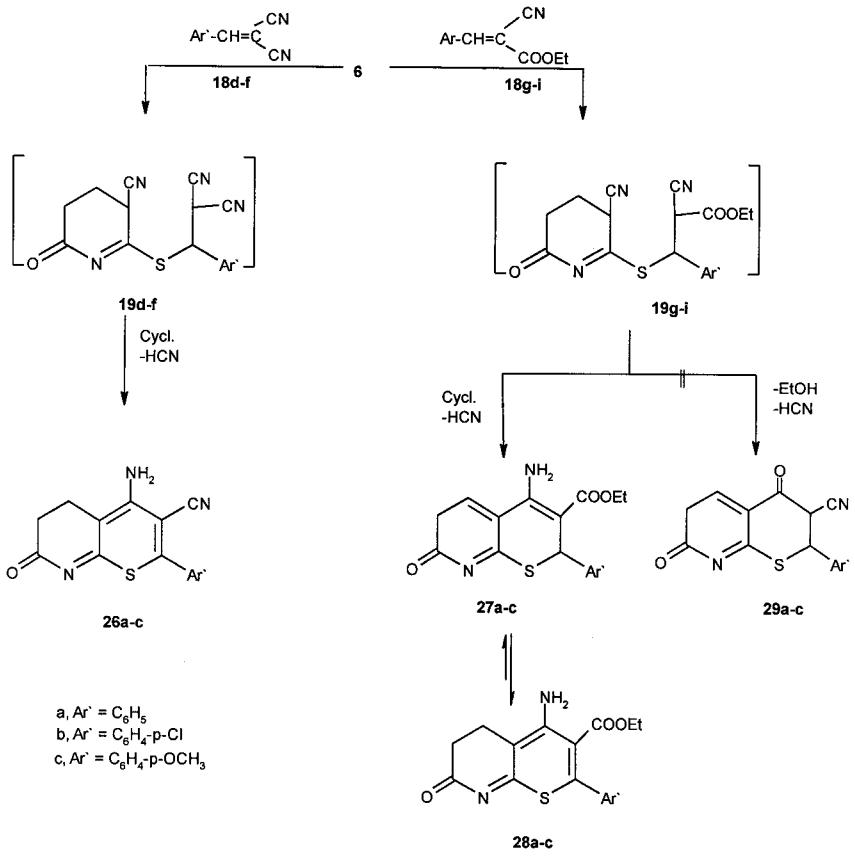

CHART 5

solvents. Chemical shifts are expressed as δ ppm units. Mass spectra were recorded on Hewlett-Packard GC-MS type 2988 using an inlet type at 70eV. Microanalyses were performed by the Microanalytical Center of Cairo University. Molecular orbital calculations were performedby considering the Schrodinger equation,[23] variational methods, and Hartree-Fock theory,[24] and semiempirical methods,[25] Modified neglect of the Diatomic Overlap (MNDO)[26] and Austin mode 1 (AM1).[27–30]

Synthesis of 6-Oxo-2-sulfanyl-3,4,5-trihydropyridine-3-carbonitrile (6)

A solution of cyanothioacetamide (**1**) and acrylonitrile (**2**) (0.01 mmol of each) in potassium hydroxide (25 mL, 10%) was refluxed for 5 h. The reaction mixture was then cooled and acidified with hydrochloric acid.

The product formed was collected by filtration, washed with cold water, and then crystallized from ethanol to give **6** (cf. Tables I and II).

Synthesis of 7

A solution of 2-sulfanylpyridine derivative **6** in ethanol (50 mL) containing a catalytic amount of triethyl amine (0.05 mL) was refluxed for 5 h. The reaction mixture was then cooled, and the product formed was collected by filtration, washed with cold water, and then crystallized from ethanol to give **7** (cf. Tables I and II).

Synthesis of 6-Hydroxy-2-sulfanylpyridine-3-carbonitrile (8)

A solution of 2-sulfanylpyridine derivative **6** in ethanol (50 mL) containing a catalytic amount of triethylamine (0.05 mL) was stirred for 1 h at room temperature. The product formed was collected by filtration, washed with cold water, and then crystallized from ethanol to give **8** (cf. Tables I and II).

Synthesis of 12a–c

A solution of 2-sulfanylpyridine derivative **6** was refluxed for 5 h with each aromatic aldehyde **9a–c** in ethanol (50 mL) containing a catalytic amount of triethylamine (0.5 mL). The reaction mixture was then cooled, and the products formed were collected by filtration, washed with cold water, and then crystallized from proper solvent to give **12a–c** respectively (cf. Tables I and II).

Synthesis of 14a–d

To a cold solution of 2-sulfanylpyridine derivative **6** (0.01 mmol) in ethanol (50 mL) was added 0.01 mmol sodium acetate. The solution was stirred, and then each of diazonium chlorides **13a–d** (0.01 mmol of each) was added dropwise. Stirring was continued for 2–3 h. The products formed were collected by filtration and washed with water, followed by cold ethanol. The isolated compounds were crystallized from ethanol to give the products **14a–d**, respectively (cf. Tables I and II).

Synthesis of 16a–d

A solution of each of hydrazones **14a–d** in ethanol (50 mL) containing a catalytic amount of triethylamine (0.5 mL) was refluxed for 3 h. The

reaction mixture was then cooled, and the products formed were collected by filtration, washed with water, and then crystallized from the proper solvent to give **16a–d** respectively (cf. Tables I and II).

Synthesis of 26a–c and 28a–c

A solution of **36** with 2-(aminothioxomethyl)-3-(phenyl or subs. phenyl)prop-2-ennitrile **18a–c** or (phenyl-or subs. phenylmethylene)-methane-1,1-dicarbonitrile **18d–f** and **18g–i** in ethanol (50 mL) containing the catalytic amounts of triethylamine or piperidine (0.5 mL) was refluxed for 4–7 h. The reaction mixture was then cooled and acidified with acetic acid and, the products formed were collected by filtration and crystallized from the proper solvent to afford **26a–c** and **28a–c** respectively (cf. Tables I and II).

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