Synthesis of 2-Thioxohydropyridine-3-carbonitrile, 2-Alkylthiopyridine, Thienopyridine, Pyrazolopyridine Derivatives and Their Theoretical Calculations

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Cyanothioacetamide (**1**) reacted with but-2-enal (**2**) to give the corresponding 4-methyl-2-sulfanyl-pyridine-3-carbonitrile (**7**) which was used as a good starting material for the synthesis of 1-(3-amino-4-methylthieno[2,3-b]pyridin-2-yl)ethan-1-one (**10**), 3-amino-4-methylthieno[2,3-b]pyridine-2-carboxamide (**15**), 3-amino-4-methylthieno[2,3-b]pyridine-2-carboxylate (**18**) and 3-amino-4-methylthieno[2,3-b]pyridin-2-ylarylketone **25a-c** through its reactions with each of (1-chloroacetone (**8**)**,** 3-chloropentane-2,4-dione (**11**) or ethyl 2-chloro-3-oxo-butanoate (**19**)), 2-chloroacetamide (**13**)**,** ethyl 2-chloroacetate (**16**) and 2-bromo-1-arylethan-1-one **23a-c**, respectively. Considering the data of elemental analyses, IR, ^{1}H NMR, mass spectra and theoretical calculations, structures of the newly synthesized heterocyclic compounds were elucidated.

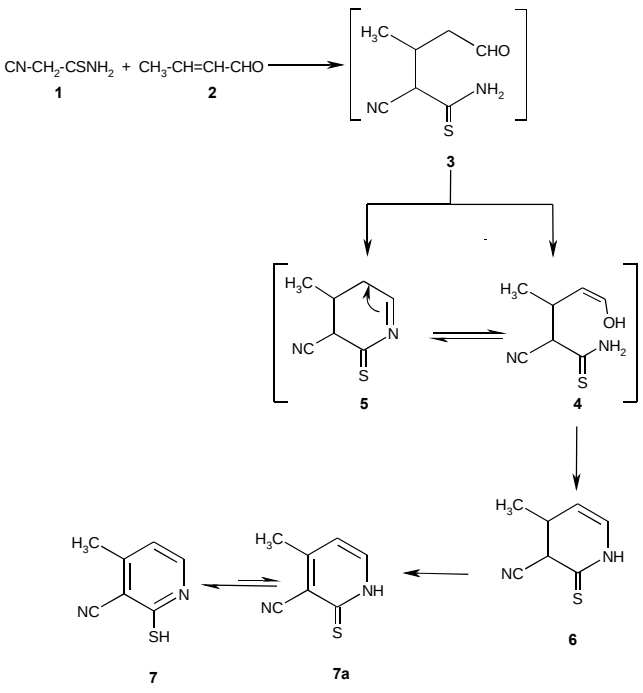
INTRODUCTION

In conjunction with our previous work[1-8] cyanothioacetamide (**1**) was used as a good synthon for the synthesis of 2-thioxohydropyridine-3-carbonitrile derivatives, which were used for building up several newly synthesized pyrazolopyridine and thienopyridine derivatives. The reported biological activities of pyridines[9-11] and thienopyridines[12-14] stimulated our interest for the synthesis of several new derivatives of these ring systems which are required for the medicinal chemistry program.

RESULTS AND DISCUSSION

It has been found that Shelyakin et al.[15] reported that cyanothioacetamide (**1**) reacted with but-2-enal (**2**) in ethanolic sodium ethoxide to afford the corresponding 4-methyl-2-thioxopyridine-3-carbonitrile (**7a**) but on carrying out such reaction in our laboratory we found that such reaction was proceeded via very low yield and an impure product. This induced our attention to change the reaction condition, and thus **1** reacted with **2** in absolute ethanol containing a catalytic amount of triethylamine to afford the reaction product via the non-isolated products **3-5**. The IR (cm^{-1}) spectrum of such reaction product showed the bands corresponding to NH, CN, C=S and C=C groups while its ^{1}H NMR spectrum revealed the signals of CH_3, pyridine H-3, H-4, H-5, H-6 and NH protons. Moreover, its mass spectrum gave *m/z* = 152 which corresponded to the molecular weight of the molecular formula $C_7H_8N_2S$ of the assigned structure (cf. Chart 1). By considering the above-mentioned data in addition to that of the elemental analyses, such reaction product could be formulated as 4-methyl-2-thioxo-1,3,4-trihydropyridine-3-carbonitrile (**6**) (cf. Chart 1). On refluxing such a reaction prod-

Chart 1



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uct in absolute ethanol containing a catalytic amount of triethylamine for three hours it gave 4-methyl-2-sulfanylpyridine-3-carbonitrile (**7**) rather than 4-methyl-2-thioxohydropyridine-3-carbonitrile (**7a**). Considering the data of IR, ^{1}H NMR and elemental analyses the structure **7** was elucidated (cf. Tables 1 and 2). Moreover, its mass spectrum gave *m/z* =

Table 1. Characterization and Analytical Data of the Newly Synthesized Compounds

Comp.	Colour	Yield (%)	M.P. (°C)	Molecular formula	% Chemical Analysis (Calcd./Found) C	H	N	S	Cl
6	Yellowish-white	72	155-7	$C_7H_8N_2S$	55.23 55.0	5.30 5.5	18.40 18.2	21.07 20.9	---- ----
7	Yellow	87	186-8	$C_7H_6N_2S$	55.98 55.7	4.03 4.1	18.65 18.7	21.35 21.5	---- ----
10	Brown	69	197-9	$C_{10}H_{10}N_2OS$	58.23 56.4	4.89 5.0	13.58 13.3	15.55 15.7	---- ----
14	Yellowish-white	70	154	$C_9H_9N_3OS$	52.16 52.3	4.38 4.5	20.27 20.0	15.47 15.2	---- ----
15	Brown	76	220-2	$C_9H_9N_3OS$	52.16 52.0	4.38 4.4	20.27 20.4	15.47 15.6	---- ----
18	Yellow	68	287-9	$C_{11}H_{12}N_2O_2S$	55.91 56.1	5.12 5.3	11.86 11.7	13.57 13.7	---- ----
20	Yellow	62	85	$C_8H_8N_2S$	58.51 58.3	4.91 5.1	17.06 16.9	19.53 19.4	---- ----
22	Pale-brown	66	238-9	$C_7H_8N_4$	56.75 56.8	5.44 5.3	37.81 37.7	---- ----	---- ----
25a	Yellow	68	297-9	$C_{14}H_{12}N_2S$	69.97 70.1	5.03 5.1	11.06 11.2	13.34 13.5	---- ----
25b	Brown	72	267-8	$C_{15}H_{14}N_2S$	70.83 70.9	5.55 5.4	11.01 10.9	12.61 12.8	---- ----
25c	Yellow	77	311-3	$C_{14}H_{11}ClN_2S$	61.20 61.4	4.04 4.2	10.20 10.3	11.67 11.7	12.90 13.1

Table 2. IR and ^{1}H NMR Spectral Data

Comp.	IR (cm^{-1})	^{1}H NMR (δ ppm)
6	3157 (NH); 3089 (olefinic CH); 2946, 2833 (sat. CH); 2222 (CN) and 1600 (C=C).	1.0 (s, 3H, CH_3); 3.1 (d, 2H, pyridine H-3, H-4); 4.1 (s, br., 1H, NH) and 6.5-6.9 (dd, 2H, pyridine H-5, H-6).
7	3143 (NH); 3081 (olefinic CH); 2934, 2852 (sat. CH); 2218 (CN) and 1605 (C=C).	1.2 (s, 3H, CH_3); 7.2-6.7 (dd, 2H, pyridine H-5, H-6) and 12.3 (s, br., 1H, S**H**).
10	3460, 3291 (NH_2); 2978 (CH sat.) and 1712 (CO-acetyl).	0.9 (s, 3H, CH_3); 2.4 (s, 3H, CO**C**$\mathbf{H_3}$); 5.2 (s, br., 2H, N$\mathbf{H_2}$); 6.8-7.3 (dd, 2H, pyridine H-5, H-6).
14	3410, 3289 (NH_2); 2985 (sat. CH); 2219 (CN); 1683 (CO amidic) and 1602 (C=C).	1.2 (s, 3H, CH_3); 3.1 (s, 2H, -SC$\mathbf{H_2}$-); 5.1 (s, br., 2H, N$\mathbf{H_2}$) and 6.7-7.0 (dd, 2H, pyridine H-4, H-5).
15	3459, 3325, 3254 (NH_2); 2982 (sat. CH); 1672 (CO amidic) and 1600 (C=C).	1.1 (s, 3H, CH_3); 5.21 (s, br., 4H, two NH_2) and 6.8-7.1 (dd, 2H, pyridine H-5, H-6).
18	3460, 3289 (NH_2); 2986 (CH sat.); 1718 (CO-ester) and 1601 (C=C).	0.9 (s, 3H, CH_3); 1.4 (t, 3H, $\mathbf{C}\mathbf{H_3}CH_2$); 4.3 (q, 2H, $CH_3\mathbf{C}\mathbf{H_2}$); 5.4 (s, br., 2H, N$\mathbf{H_2}$) and 6.8-7.3 (dd, 2h, pyridine H-5, H-6).
20	2980 (sat. CH); 2214 (CN) and 1604 (C=C).	1.2 (s, 3H, CH_3); 3.1 (s, 3H, S$\mathbf{C}\mathbf{H_3}$) and 6.7-7.1 (dd, 2H, pyridine H-5, H-6).
22	3462, 3334, 3248, 3197 (NH_2 and NH); 2982 (sat. CH) and 1600 (C=C).	1.3 (s, 3H, CH_3); 5.1 (s, br., 3H, NH, NH_2) and 6.8-7.3 (dd, 2H, pyridine H-5, H-6).
25a	3422, 3387 (NH_2); 3051 (aromatic CH); 2987 (sat. CH) and 1712 (CO ketonic) and 1603 (C=C).	1.5 (s, 3H, CH_3); 5.5 (s, br., 2H, NH_2) and 6.2-7.8 (m, 7H, aromatic and pyridine H-5, H-6 protons).
25b	3431, 3385 (NH_2); 3043 (aromatic CH); 2982 (sat. CH) and 1715 (CO ketonic) and 1600 (C=C).	1.3 (s, 6H, two CH_3); 5.7 (s, br., 2H, NH_2) and 6.5-7.6 (m, 6H, aromatic and pyridine H-5, H-6 protons).
25c	3420, 3379 (NH_2); 3063 (aromatic CH); 2988 (sat. CH) and 1717 (CO ketonic) and 1602 (C=C).	1.5 (s, 3H, CH_3); 5.3 (s, br., 2H, NH_2) and 6.5-7.6 (m, 6H, aromatic and pyridine H-5, H-6 protons).

Table 3.

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 gap (eV)	Dipole moment (D)
6	-1614.16	-1844.10	-35362.40	-180052.80	142846.30	61.38	-8.8942	-0.8599	8.0343	6.061
7	-1586.90	-1741.19	-34836.77	-165919.25	129341.30	60.05	-8.9711	-0.7531	8.2180	3.475
7a	-1586.42	-1730.16	-34836.77	-166595.00	130028.06	71.078	-8.7699	-1.1231	7.6468	7.720
9	-2346.68	-2554.90	-51535.90	-287231.00	233140.10	26.92	-8.8478	-0.8703	7.9775	4.125
10	-2347.52	-2574.40	-51535.90	-297619.60	243509.20	7.47	-8.1767	-0.8134	7.3633	6.277
12	-2950.53	-3086.20	-64923.40	-408398.70	340389.00	1.14	-9.0348	-1.0391	7.9957	6.178
14	-2412.14	-2444.90	-53154.80	-289779.30	234179.50	26.89	-8.9472	-0.9283	8.0189	4.644
15	-2413.13	-2467.80	-53154.70	-300195.20	244572.60	4.04	-8.2543	-0.7371	7.5172	5.544
17	-2823.55	-2945.60	-62137.30	-358739.30	293656.40	29.08	-8.7920	-0.8018	7.9902	2.976
18	-2824.36	-2964.10	-62137.30	-376688.30	311586.90	47.60	-8.2252	-0.8467	7.3785	5.424
20	-1742.73	-2021.46	-38148.52	-195383.40	155213.40	54.90	-8.6081	-0.6363	7.9718	3.153
20a	-1742.91	-1998.50	-38148.50	-198834.80	158687.70	77.80	-8.5723	-1.0835	7.4888	7.781
21	-1833.28	-1980.80	-40276.30	-202592.30	160335.20	84.26	-8.9876	-0.6240	8.3636	2.674
22	-1833.17	-1978.30	-40276.30	-208316.10	166061.50	86.80	-8.6083	-0.2645	8.3438	2.939
24a	-3013.86	-3477.16	-65992.30	-427441.20	357971.80	63.36	-8.6546	-0.8189	7.8327	3.728
25a	-3014.95	-3502.17	-65992.30	-440008.70	370514.30	38.35	-8.1182	-0.8783	7.2399	2.177
25b	-3170.89	-3785.04	-69304.02	-477952.77	404863.69	30.57	-8.1114	-0.8640	7.2474	1.793
25c	-3375.22	-3486.05	-74312.73	-479989.47	402190.68	31.36	-8.2214	-1.0021	7.2139	3.443

150 which corresponded to the dehydrogenated product of **6**. Furthermore, by considering the theoretical calculations (cf. Table 3) structure **7** was elucidated.

Theoretical Consideration

Table 3 presents the ground state electronic structural data of both **6** and **7**. Fig. 1 shows the prospective drawing of **6** and **7** drawn to their optimised geometry computed at the AM1 level. Compound **7** is theoretically more stable than **6** as revealed by the corresponding ΔH_f values and is much less polar. That is, the high polarity of the reaction medium shifts the reaction towards **7**. Furthermore, **7** is a stronger electron-acceptor and a weaker electron-donor than **6**. The possibility of thione-thiol tautomerism is investigated; in the case of **7** the thiol form is shown in Fig. 1 and its corresponding ground state properties are given in Table 3. **7** also, is energetically more favourable than **7a**, yet much less polar. In high polar medium, **7a** would thus predominate.

Compound **7** was used as a good starting material for the present study owing to the presence of more than one active site in its structure. Thus, it has been found that pyridine-3-carbonitrile derivative **7** reacted with 1-chloroacetone (**8**) in sodium ethoxide to give a reaction product formed via the loss of hydrogen chloride. Mass spectrum of such reaction product gave *m/z* = 206, which corresponded to the molecular weight of the molecular formula $C_{10}H_{10}N_2SO$ of the assigned structure (cf. Chart 2). Considering the above-

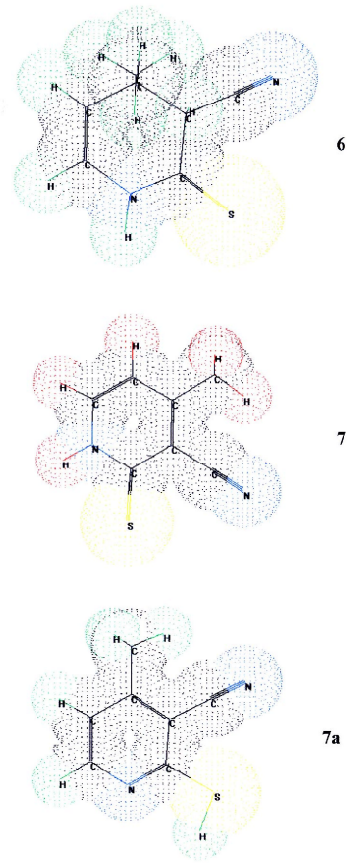
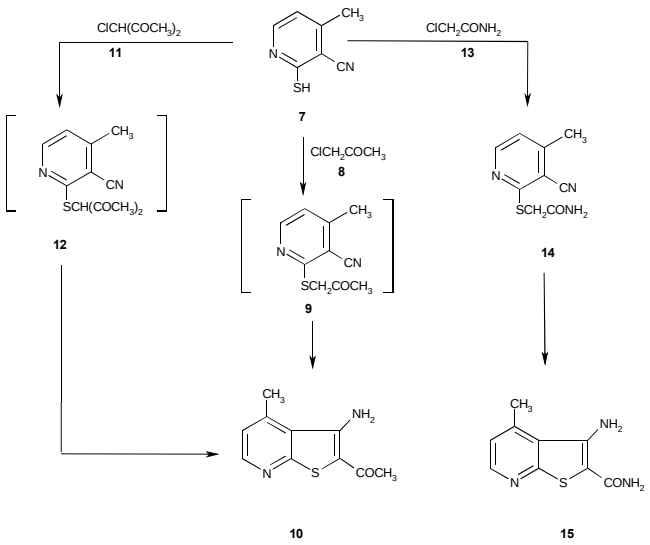


Fig. 1. Prospective drawing of compounds drawn at its AM1 geometry.

Chart 2

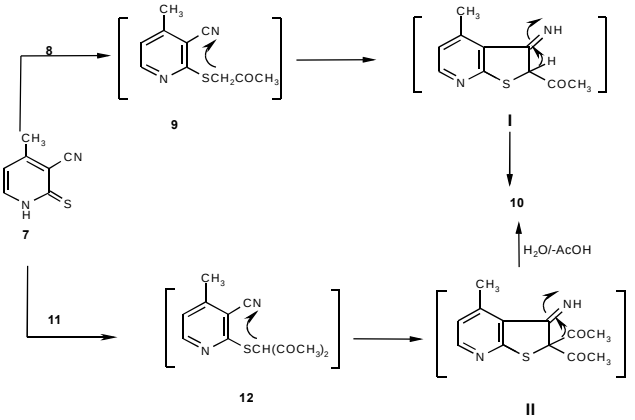


mentioned data in addition to IR, ^{1}H NMR and elemental analyses data, this reaction product was formulated as a 1-(3-amino-4-methylthieno[2,3-b]pyridin-2-yl)ethan-1-one (**10**). The formation of such a thienopyridine derivative was proposed to proceed through the non-isolated intermediate **9**.

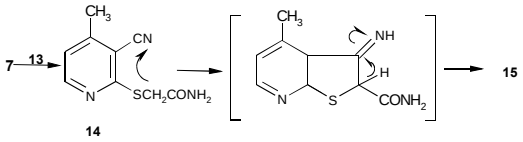
In a similar way compound **7** reacted with 3-chloropentane-2,4-dione (**11**) to give the previously isolated compound **10** with the same aspects (m.p, Mixed m.p., IR, ^{1}H NMR and mass spectra) of that obtained from the reaction of **7** with **8**. The structure of **10** was further confirmed by considering the data of elemental analyses, IR and ^{1}H NMR spectra (cf. Tables 1, 2). The IR spectra of **10** showed the absence of CN group and instead the band of the newly born NH_2 group was detected. Its ^{1}H NMR spectrum revealed no signals of -CH_2CO- protons while the NH_2 protons were detected. Based on both IR and ^{1}H-NMR spectral data it could be concluded that both the -CH_2CO- protons and the CN group were involved in the cyclization step to give the non-isolable intermediate (**I**) in case of reaction with 1-chloroacetone while the addition of the anions from the -$CH(COCH_3)_2$ to the CN groups afforded the non-isolable 3-iminothienopyridine intermediate (**II**) in case of the reaction with 3-chloropentane-2,4-dione. These intermediates, in turn, added water molecules to give **10** (cf. Equation 1).

Work was also extended to shed more light on the chemical reactivity of **7**. Thus, **7** reacted with 2-chloroacetamide (**13**) to afford 2-(3-cyano-4-methyl-2-pyridylthio)acetamide (**14**) via the loss of hydrogen chloride (cf. Chart 2). The structure of **14** was established based on the elemental analyses, IR and ^{1}H NMR spectra (cf. Chart 2 and Tables 1, 2). The mass spectra of **14** gave *m/z* = 207 which corresponded to the exact molecular weight of a molecular formula $C_9H_9N_3OS$ of an assigned structure (cf. Chart 2). More evidence for the structure **14** was given through their cyclization in an ethanolic potassium hydroxide solution. The IR spectrum of this cyclization product showed no bands for the CN group while bands of the newly born NH_2 were detected. Its ^{1}H NMR spectrum had no signals of the S-CH_2 protons and this proved that both the CN group and S-CH_2 protons were involved in the cyclization step. Considering all the above-mentioned data, this cyclization product was formulated as 3-amino-4-methylthieno[2,3-b]pyridine-2-carboxamide (**15**) (cf. Tables 1, 2, Equation 2 and Chart 2).

Equation 1

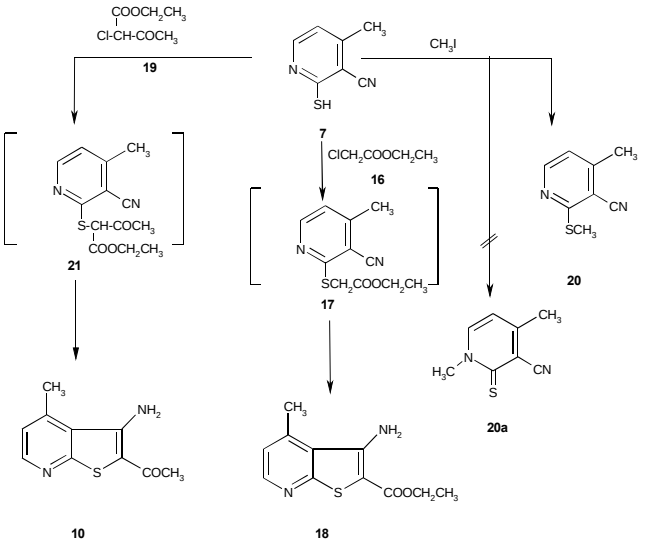


Equation 2

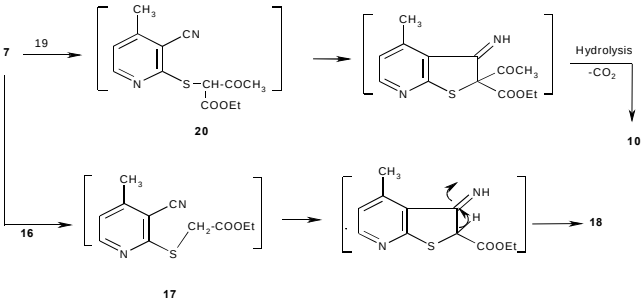


The synthetic potentiality of **7** was further demonstrated via its reaction with ethyl 2-chloroacetate (**16**) in sodium methoxide to give a reaction product formed via dehydrochlorination. The IR spectrum of this reaction product showed the bands corresponded to the NH_2 group and ester CO. Its ^{1}H-NMR spectrum revealed the signals corresponded to NH_2, CH_3 at pyridine, pyridine H-5, H-6 and CH_3CH_2-protons (cf. Table 2). Moreover, its mass spectrum gave *m/z* = 236 which corresponded to the exact molecular weight of a molecular formula $C_{11}H_{12}N_2SO_2$ of the assigned structure. Considering all the above data, this reaction product was formulated as ethyl 3-amino-4-methylthieno[2,3-b]pyridine-2-carboxylate (**18**) through the non-isolable intermediate **17** (cf. Chart 3).

Chart 3



Equation 3



Tables 1, 2 and Chart 3). A further confirmation of structure **20** was given through its reaction with hydrazine hydrate to give the sulfur-free reaction product **22**. Compound **22** was most probably formed via the substitution of the S-CH_3 group to give the non-isolable 2-hydrazino pyridine **21**. The hydrazino group was then added to the CN group to afford the corresponding 4-methylpyrazolo[3,4-b]pyridine-3-ylamine **22**. The structure of **22** was established based on elemental analyses, IR and ^{1}H NMR data (cf. Tables 1, 2 and Chart 4).

Theoretical Consideration

The reaction of **7** with **13**, would theoretically give the open structure **14** or the cyclic one **15**. Table 3 summarizes the ground state electronic properties of **14** and **15**, whereas Fig. 2 presents the two compounds drawn to their optimized geometries. While **15** seems to be energetically more stable than **14**, the energy difference is appreciable ≈ 23 Kcal/mol. Furthermore, **15** is more polar and hence would be stabilized by the reaction medium to a much higher extent. Furthermore, the energy gap ΔE (defined as the difference of energy between the HOMO and LUMO) indicates that **14** is less reactive. The reaction of **7** with **8** or **11** to finally give **10** proceeds via two routes and intermediates **9** and **12**. The ground state electronic properties of all these structures are presented in Table 3. Inspection of the data given in this table we can conclude that **10** is much more stable than **9** and also more polar.

In a similar manner, compound **7** reacted with ethyl 2-chloro-3-oxo-butanoate (**19**) to give the corresponding thienopyridine derivative **10**. The reaction product **10** was most probably formed via the addition of the anions from -CH(COOEt)$COCH_3$ to the CN group to give the non-isolable 3-iminothienopyridine intermediate. This intermediate then added water to liberate acetic acid and gave the final isolable **10** (cf. Equation 3).

Synthon **7** reacted also with methyl iodide in sodium methoxide to give the corresponding 4-methyl-2-methylthiopyridine-3-carbonitrile **20** whose structure was elucidated based on elemental analyses, IR and ^{1}H NMR data (cf.

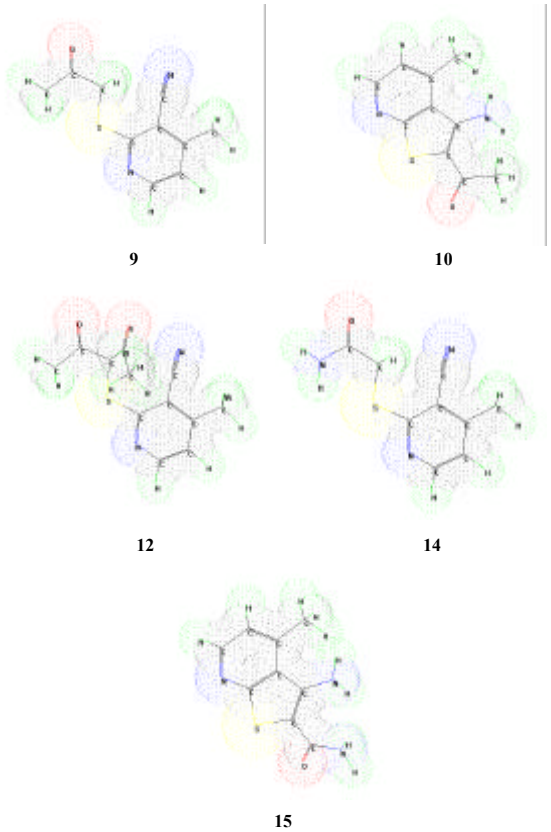
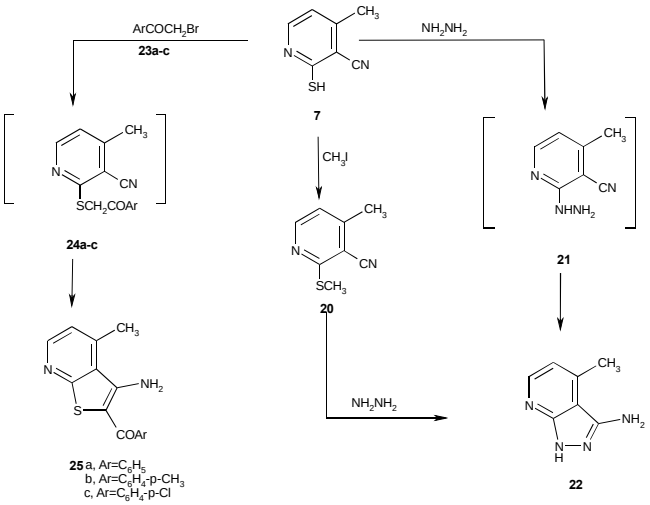


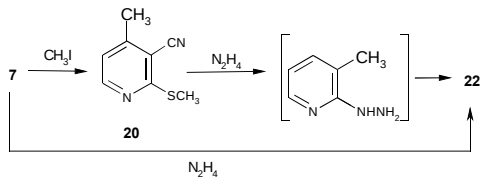
Fig. 2. Prospective drawing of compounds drawn at its AM1 geometry.

Chart 4



Moreover, the mass spectrum of **22**, gave *m/z* = 148, which corresponded to the exact molecular weight of a molecular formula $C_7H_8N_4$ of the assigned structure. Good evidence of structure **22** was given through its synthesis via another route. Thus, compound **7** reacted with hydrazine hydrate to give a reaction product which was found to be identical in all aspects with the **22** obtained from the reaction of **20** with hydrazine hydrate (cf. Chart 4 and Equation 4).

Equation 4



Theoretical Consideration

Methylation of **7** may take place to afford the $-SCH_3$ (**20**) or the $-N-CH_3$ (**20a**) derivatives. Both structures are drawn to their optimized geometries and are presented in Fig. 3, whereas the corresponding ground state properties are given in Table 3. The CH_3N- derivative seems to be energetically and thermodynamically more stable. Thus, methylation seems to occur on the HN- and then rearranged to the $-SCH_3$ form. The formation of **18** from **17** is energetically and thermodynamically favorable especially in polar solvents (cf. Table 3).

Chemical reactivity of **7** was further investigated through its reaction with 2-bromo-1-(phenyl or 4-methylphenyl, 4-chlorophenyl)ethan-1-one (**23a-c**) to give the corresponding 3-amino-4-methylthieno[2,3-b]pyridin-2-yl-(phenyl, 4-methylphenyl or 4-chlorophenyl)ketone **25a-c** via the non-isolable products **24a-c**. The structures of **25a-c** were elucidated by considering the data of elemental analyses, IR and ^{1}H NMR spectra (cf. Tables 1, 2 and Chart 4).

Theoretical Consideration

The final products of Chart 4, namely both **22** and **25**, are formed via intermediates **21** and **24**, respectively. The ground state electronic properties of all components investigated in Chart 4 are presented in Table 3. The corresponding geometrical features are shown in Fig. 4. It is interesting to note that all ground state properties of **21** and **22** are almost the same with small differences that favour **21** slightly; **22** is formed through the cyclization which occurs spontaneously. **25** is more stable than **24** by about 25 Kcal./mol. However, **24** is much more reactive as indicated by ΔE_{gap}. Fig. 5 presents free-energy relationships involving ΔH_g, E_t, μ and energy gap against the Hammet constant σ_p for the substituents a-c for compound **25**.

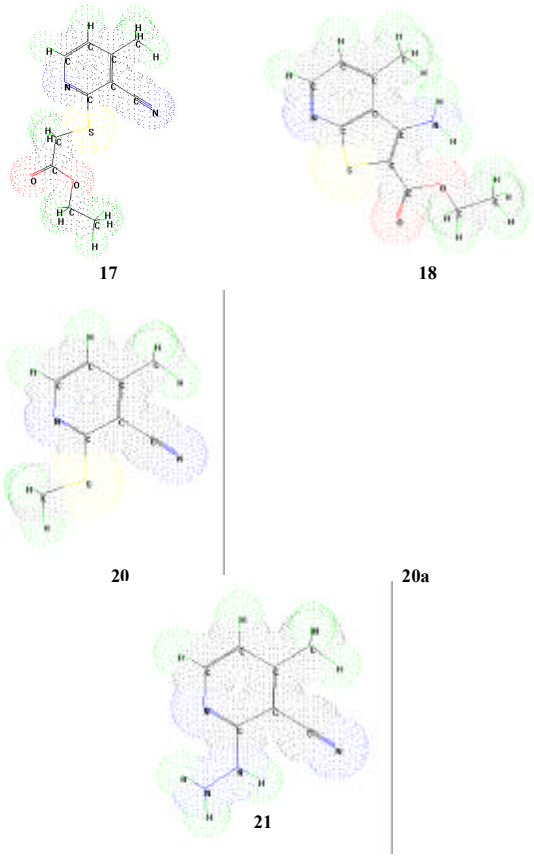


Fig. 3. Prospective drawing of compounds drawn at its AM1 geometry.

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 solvents and chemical shifts are expressed as ppm units. Mass spectra were recorded on Hewlett-Packard GC-MS type 2988 using inlet type at 70 eV. Microanalyses were performed by the Microanalytical Center of Cairo University. Molecular orbital calculations were performed by considering the Schordinger equation,[16] variational methods and Hartree-Fock theory,[17] Semi-empirical methods,[18] Modifiedneglect of the Diatomic Overlap (MNDO)[19] and Austin mode 1 (AM1).[20-22]

Synthesis of 6

A solution of **1** and buten-2-al (**2**) (0.01 mole of each) in ethanol (50 mL) containing a catalytic amount of triethylamine or piperidine (0.5 mL) was heated under reflux for 1-2 hours. The mixture was cooled and the product so formed was collected by filtration and then crystallized from ethanol to give **6** (cf. Tables 1 and 2).

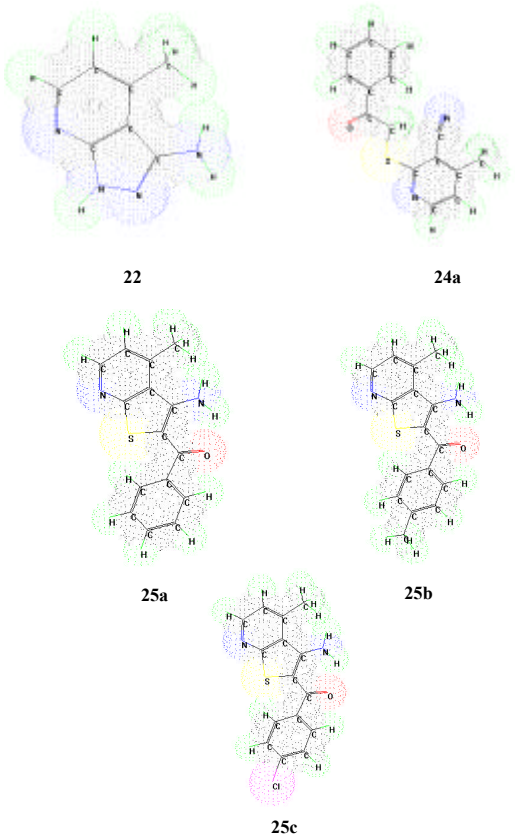


Fig. 4. Prospective drawing of compounds drawn at its AM1 geometry.

Synthesis of 7

Method (A)

A solution of **1** with buten-2-al (**2**) (0.01 mole of each) in ethanol (50 mL) containing a catalytic amount of triethylamine or piperidine (0.5 mL) was heated under reflux for 5-7 hours. The reaction mixture was cooled and the product so formed was collected by filtration and washed with cold ethanol then crystallized from ethanol to give **7** (cf. Tables 1 and 2).

Method (B)

A solution of **6** in ethanol (50 mL) containing a catalytic amount of triethylamine (0.5 mL) was heated under reflux for 3-5 hours. The reaction mixture was cooled and the product so formed was collected by filtration and then crystallized from ethanol to give **7** (cf. Tables 1 and 2).

Synthesis of 14

A mixture of **7** and chloroacetamide (**13**), 0.01 mole of each, in methanol containing sodium methoxide (prepared by 0.01 atom Na in methanol) was refluxed for 3 hours. The reaction mixture was then evaporated till dryness and then cooled. The product so formed was collected by filtration, washed with cold ethanol and then crystallized from ethanol to give **14** (cf. Tables 1 and 2).

Synthesis of 15

A solution of **14** (0.01 mole) in ethanol containing KOH 10% (10 mL) was refluxed for 3 hours. The reaction mixture was then poured onto water and acidified with hydrochloric acid. The product so formed was collected by filtration, washed with cold water and then crystallized from ethanol to give **15** (cf. Tables 1 and 2).

Synthesis 10, 18 and 25a-c: (General method)

A solution of **7** with each of (**8**, **11** or **19**), **16** and **23a-c** (0.01 mole of each) in ethanol (50 mL) containing the catalytic amounts of triethyl amine or piperidine (0.5 mL) was refluxed for 3-5 hours. The reaction mixture was then cooled and the products so formed were collected by filtration, washed with cold ethanol and then crystallized from ethanol to give **10**, **18** and **25a-c**, respectively (cf. Tables 1 and 2).

Synthesis of 20

A solution of **7** and methyl iodide (0.01 mole of each) in

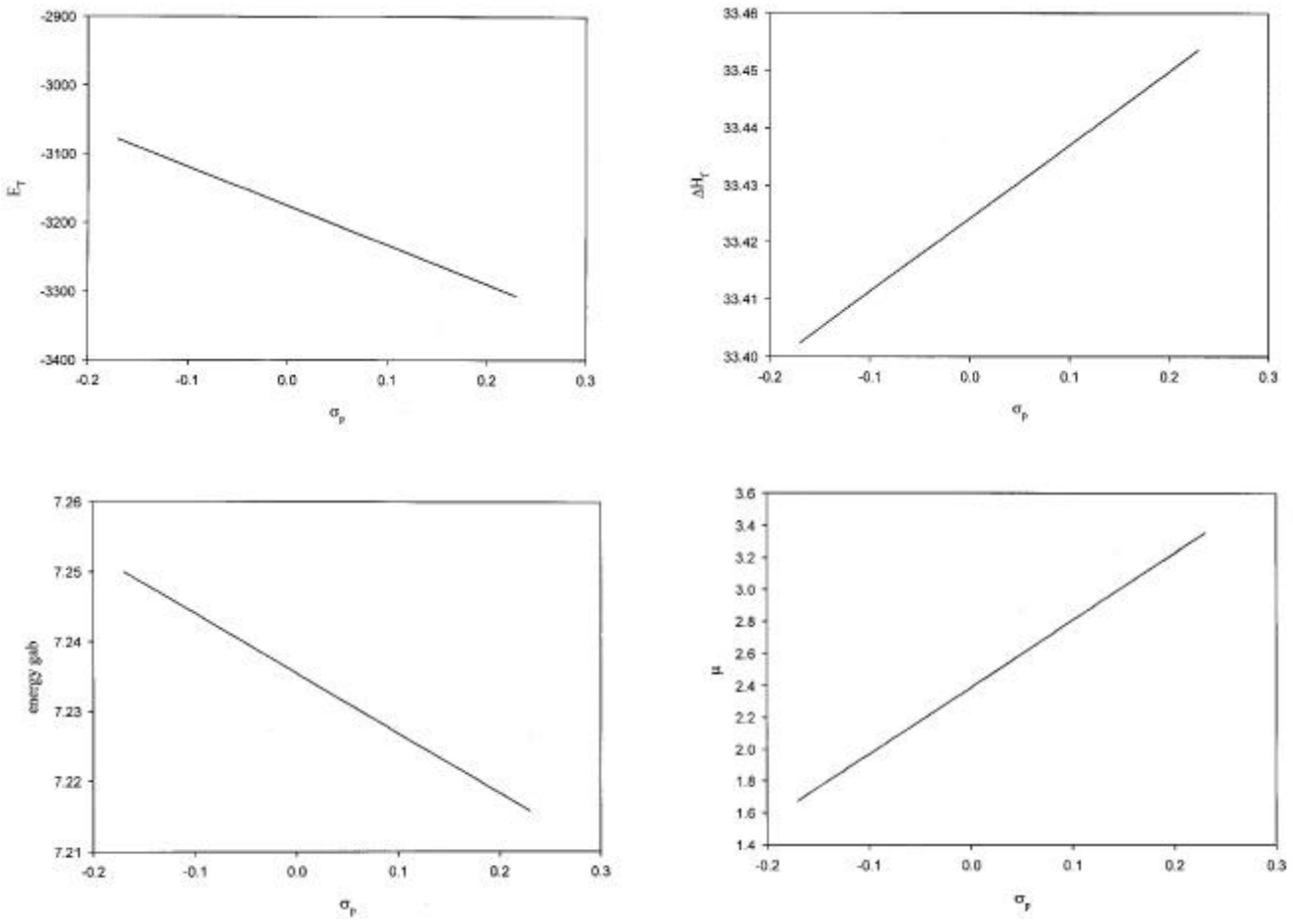


Fig. 5. Free energy relationships for E_T, ΔH_f, energy gab and μ against σ_{Hammet} constant of compound **25a-c**.

methanolic sodium methoxide (prepared by 0.01 atom of Na in 20 mL methanol) was heated under reflux for 2 hours. The reaction mixture was cooled and poured onto ice-cold water and then acidified with hydrochloric acid. The products so formed were collected by filtration, washed with water and crystallized from ethanol to give **20** (cf. Tables 1 and 2).

Synthesis of 22

A mixture of **7** or **20** (0.01 mole of each) and hydrazine hydrate (15 mL) was heated under reflux for 6 hours. The reaction mixture was then heated till dryness and then acidified with acetic acid. The product so formed after cooling, was filtrated and washed with cold ethanol then crystallized from ethanol to give **22** (cf. Tables 1 and 2).

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Key Words

Thieno[2,3-b]pyridin-2-yl)ethan-1-one; Thieno[2,3-b]pyridine-2-carboxylate; Thieno[2,3-b]pyridin-2-ylarylketone; 2-Methylthiopyridine-3-carbonitrile and pyrazolo[3,4-b]pyridine-3-ylamine.

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