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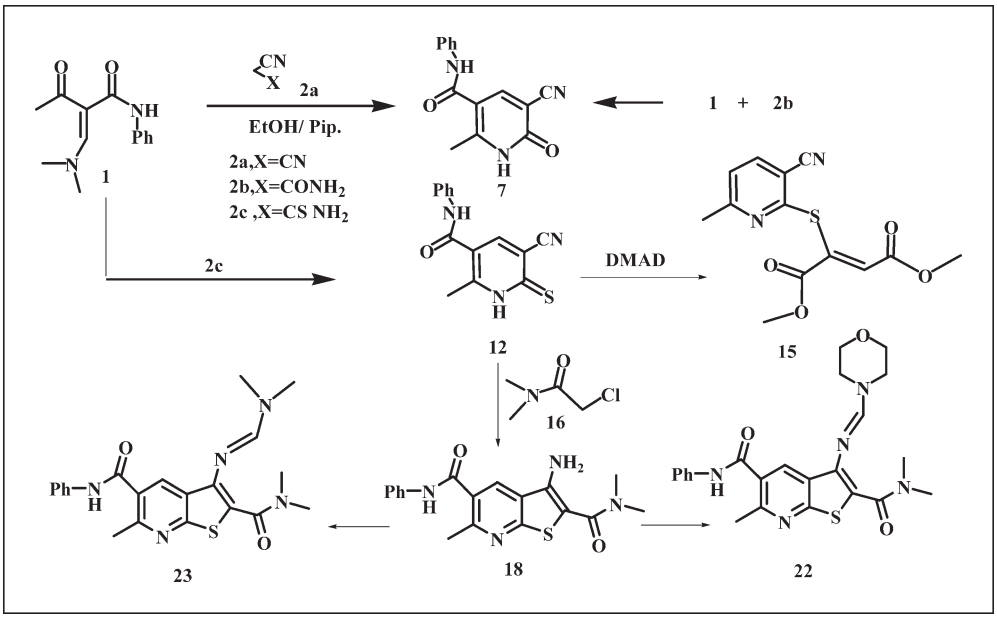

2-Dimethylaminomethylene-3-oxo-*N*-phenylbutyramide **1** reacts with malononitrile **2a** to afford the pent-2-enedioic acid 1-amide 5-phenylamide derivative **6**, which could be cyclized to give the 6-methyl-pyridone derivative **7**. Compound **1** reacts with cyanoacetamide **2b** to afford the same pyridone **7** and with cyanothioacetamide **2c** to afford the analogous pyridinethione **12**. Compound **12** reacts with DMAD to afford the pyridine derivative **15** and with *N*,*N*-dimethylchloroacetamide **16** to afford the thieno[2,3-d]pyridine derivative **18**. Compound **18** reacts with morpholine-4-carboxaldehyde **19**, *N*,*N*-diemthylformamide **20**, and 2,5-dimethoxy-tetrahydrofuran **21** to afford the fully aromatic thieno[2,3-d]pyridine derivatives **22**, **23**, and **24**, respectively.

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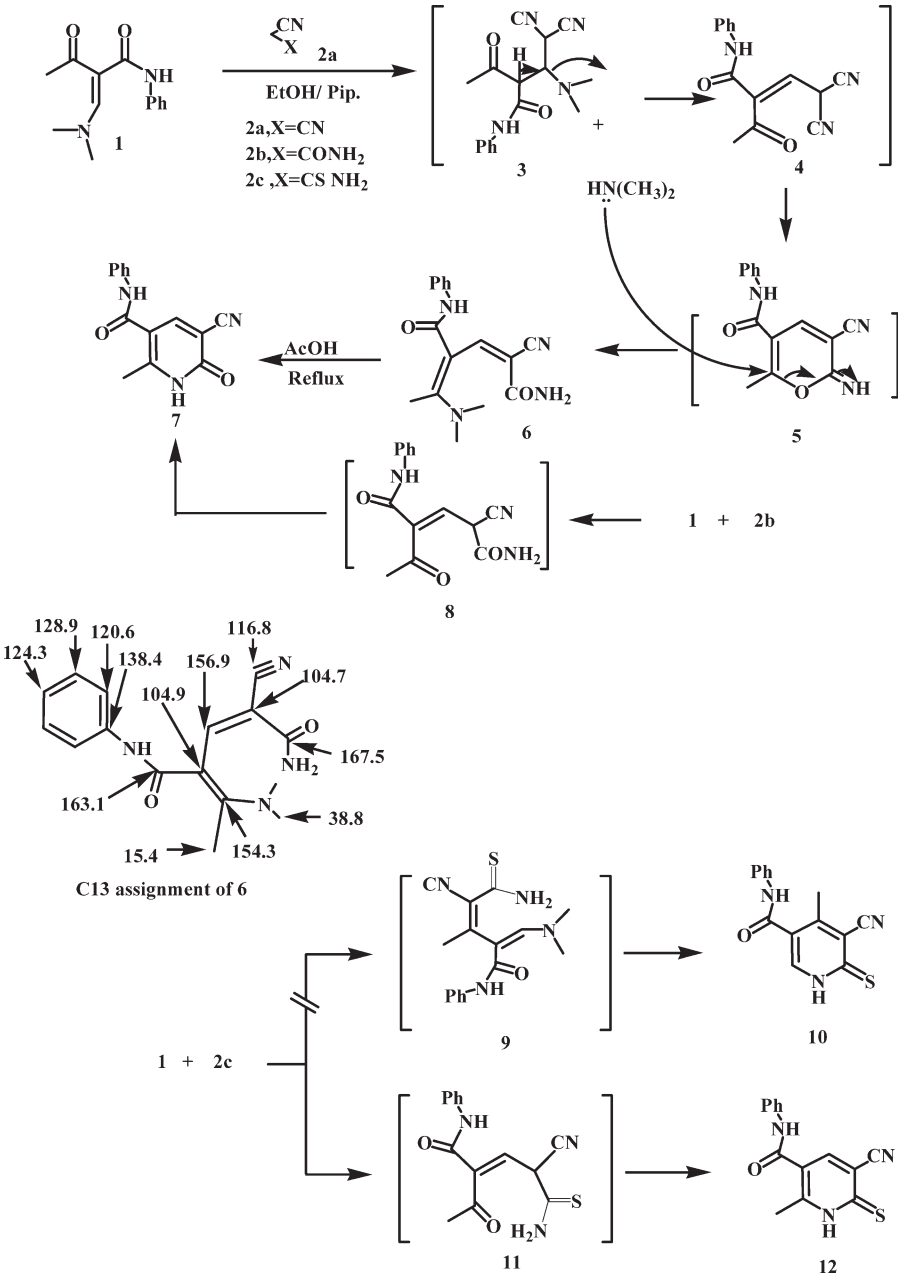
INTRODUCTION

In the past 2 decades, we have been involved in a program aiming to develop new simple routes for the synthesis of heterocyclic compounds of biological interest to be evaluated as biodegradable agrochemicals [1–5]. Some functionally substituted pyridine and pyridone derivatives posses marked pharmaceutical activities such as anti HIV-1 reverse transcriptase agents, calcium channel blockers, anticongestive heart failure agents, and antagonists of P2 receptors for neurotransmitters [6–12]. The reaction of enaminones with active methylene nitriles represents one of the strategies for the preparation of 2-1*H*-pyridone [13–15]. Thus, some functionally substituted 2-1*H*-pyridone derivatives were required for biological activity studies. 2-Dimethylaminomethylene-3-oxo-*N*-phenylbutyramide (obtained from the reaction of acetoacetanilide with DMFDMA according to the literature method [16]) seemed a suitable synthone for the synthesis of the required 2-1*H*–pyridone derivatives through its reaction with active methylene reagents.

RESULTS AND DISCUSSION

Thus, the enaminone compound **1** was prepared and allowed to react with the active methylene compounds **2a-c** (Scheme 1) according to the method reported earlier by us [17]. The reaction of **1** with malononitrile **2a** afforded a yellow crystalline solid of mp.197°C. The IR spectrum of this product showed absorption bands at υ_{max} = 2217, 1665, and 1656 cm^{-1} corresponding to a cyano and two amide carbonyl functions. The mass spectrum of this product showed a molecular ion peak

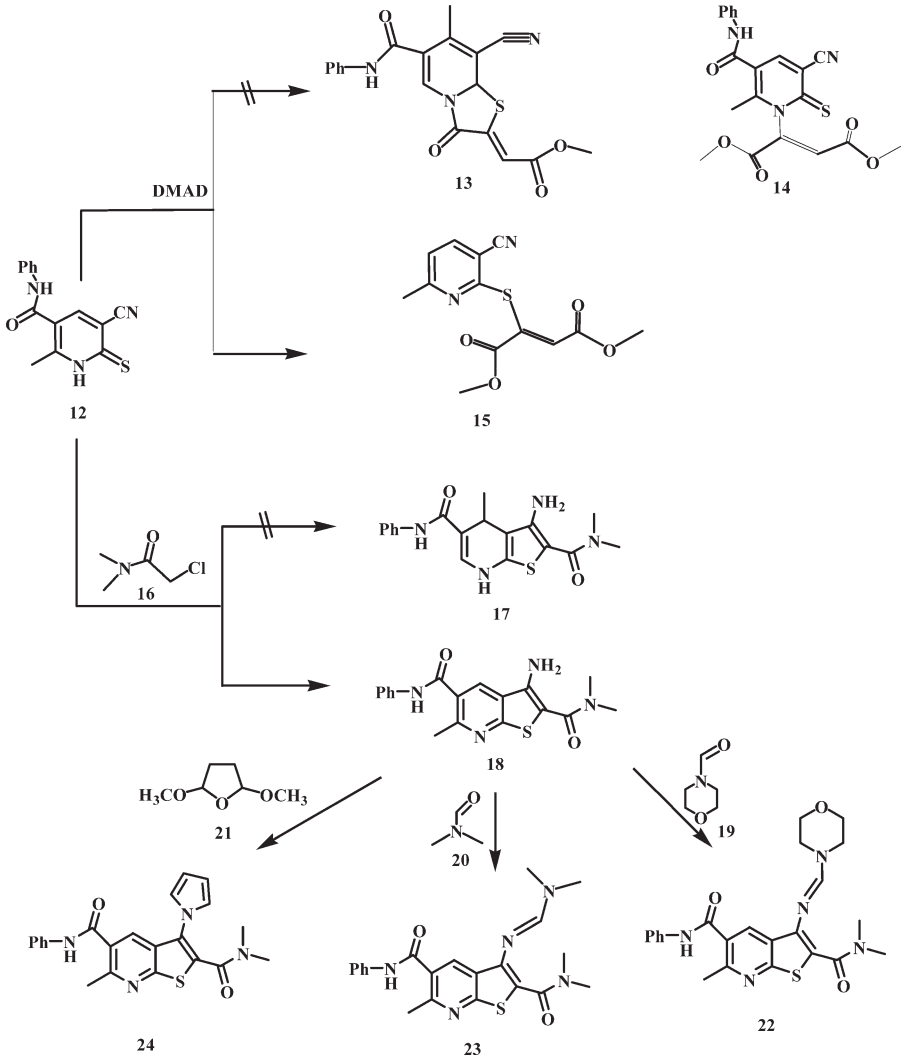
Scheme 1. Preparation of compounds **6**, **7**, and **12**.



at $m/z = 298$, which corresponds to the molecular formula $C_{16}H_{18}N_4O_2$ (M. Wt. 298.34). The ^{1}H NMR spectrum of this product revealed a singlet (3H) at 1.69 corresponding to a methyl group, a singlet (6H) at 2.75 corresponding to the N(CH_3)$_2$ groups, a singlet (1H) at 7.15 due to the =C*H* proton, a D_2O exchangeable singlet at 8.35 (1H) attributable to an NH, beside an aromatic multiplet at 7.24–7.55 (7H, Ph+NH_2). Based on these data and on the analogy with our previous reported work [17], the 2-Cyano-4-(1-dimethylamino-ethylidene)-pent-2-enedioic acid 1-amide 5-phenylamide **6** was assigned to this product.

The formation of **6** from the reaction of **1** with **2a** is assumed to take place *via* the sequence shown in Scheme 1. The active methylene of malononitrile undergoes addition to the double bond of **1** to afford the intermediate **3**, followed by elimination of dimethyl amine to afford 2-acetyl-4,4-dicyanobut-2-enoic acid phenylamide **4** that directly undergoes ring closure *via* its enolized form to afford the iminopyran intermediate **5**. This newly formed iminopyran is attacked by the dimethyl amine (still present in the reaction medium) and undergoes ring opening to afford **6**. The ring opening of iminopyran under the effect ammonia and amines is well

Scheme 2. Preparation of compounds **15**, **18**, **22**, **23**, and **24**.



established in the literature [14,17]. The ^{13}C NMR data of this product are in complete agreement with structure **6** (*cf*. Scheme 1 and Experimental).

Compound **6** could be readily cyclized *via* elimination of dimethyl amine upon reflux in acetic acid to afford yellow crystals of mp. 217–219°C.

The ^{1}H NMR spectrum of **7** revealed the disappearance of the NMe_2 signal and the presence of a singlet integrated for 1H at $\delta = 8.65$, which is attributed to the C4-H, beside the other signals as expected (*cf*. Experimental). The 2-1*H*-pyridinone derivative structure **7** was assigned to this product based on the analytical and spectral data, and compound **7** has been previously described in the literature from other route, mp. 216–218°C [18].

The reaction of **1** with cyanoacetamide **2b** afforded the same 2-1*H*-pyridinone **7**. It is assumed that **2b** followed the same addition elimination sequence to afford the intermediate **8** (analogous to **4** in the above sequence) that undergoes directly the cyclization *via* elimination of water without passing through the iminopyran step, as the amide group is already present. The identity of the products obtained from the reactions of **1** with either **2a** or **2b** was deduced from the typical melting points and spectral data. A similar result has been previously observed [17].

The reaction of compound **1** with cyanothioacetamide **2c** was reported earlier to afford the pyridinthione **10** (No. **3** in the original article [19]) *via* the intermediate **9** (Number **2** in the original article). The author of ref. 19 incorrectly assumed that the reaction proceeds *via* a Knoevenagel condensation between the carbonyl group of **1** and the active methylene of **2c** to afford **9** (his **2**). On the basis of our aforementioned results, we have reinvestigated this reaction. This reaction of **1** and **2c** was found to follow the same pathway as that of **1** with **2b** to afford the intermediate **11** (analogous to **8**; Scheme 1) *via* the addition–elimination sequence, which

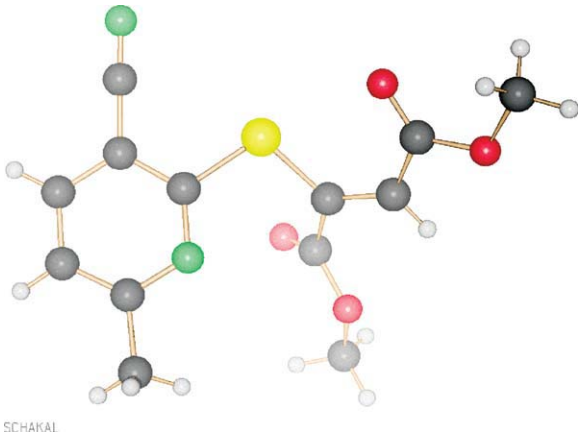


Figure 1. X-ray crystallographic structure of **15**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

then undergoes cyclization *via* loss of water to afford the pyridinethione **12**. The melting point, analytical, and spectral data of our product are the same as those reported in [19]; however, the ^{13}C NMR data reported in [19] are wrong; the phenyl carbons should appear as four signals and not six as reported, and the whole spectrum showed only 12 signals.(*cf.* experimental).

The incorrect assignment in [19] leads to the pyridinethione **10** (his **3**) with the methyl group in the 4-position, whereas the correct structure is **12** carrying the methyl group in the 6-position. This has serious consequences for some other reactions described in this article. For example, all the reactions depicted in his Scheme 2 are all based on the imaginary presence of the methyl group in position-4 and are all vagaries.

The reaction of this pyridinethione **12** with dimethyl acetylenedicarboxylate was claimed to afford the thiazolopyridine derivative **13** (Scheme 2) (number **9** in the original article [19]). The formation of this thiazolopyridine seemed doubtful as the pyridinethione has only one proton on its nitrogen, so how the thiazole ring is formed while still retaining one hydrogen on C-2. Furthermore, the ^{13}C NMR data given to **13** (his **9**) cited only 10 carbons (excluding the repeated values for the aromatic carbons), while it should reveal 17 carbons. Based on all these discrepancies, we decided to reinvestigate this reaction.

Compound **12** was allowed to react with dimethyl acetylenedicarboxylate (DMAD) in chloroform (the same reaction conditions reported in [19]) to afford after recrystallization and purification on column with silica gel using pentane/ethyl acetate (3:1) as eluent a white crystalline product of mp. 126°C (Lit. mp. of compound **13** in Scheme 2 (his **9**); >300°C [19]). The mass spectrum of this product showed $m/z = 292$ [M^+]. From this molecular mass and the elemental analysis data (*cf.* experimental), we could calculate a molecular formula $C_{13}H_{12}N_2O_4S$ for this product, which is not applicable to **13** (old **9**) or **14** (assuming that the NH adds to the C≡C in DMAD). The IR spectrum of this product showed two carbonyl absorption at $\upsilon_{max} = 1712$ and 1710 assignable to two ester CO, a cyano absorption band at 2220 cm^{-1} and no bands that could be assigned to the amide CO. The ^1H and ^{13}C NMR showed a pattern that could not be justified to either of the structures **13** (reported **9** [19]) or **14** (*cf.* experimental). From the presence of two ester carbonyl absorption bands and the presence of two methyl signals in the ^1H and C^{13} NMR spectra, we got the impression that a Michael addition took place from either the NH in the pyridinethione or the SH in the tautomer mercapto pyridine to the activated C≡C of DMAD, and from the absence of the amide carbonyl absorption band in the IR spectrum and the presence of two doublets at $\delta = 7.36$ and 8.22 ppm with $j = 8.56$ Hz in the ^1H NMR spectrum, we got the impression that the amide group was eliminated either in the form of phenyl isocyanate or *via* hydrolysis of the amide linkage followed by decarboxylation. Thus, structure **15** was suggested to this product. This structure actually fulfills all the requirements of all the available data. However, it was mandatory to have an X-ray crystallographic picture for this compound. Fortunately, the X-ray picture [20,21] came exactly in complete agreement with our imagination; (see Fig. 1 and the experimental). It shows clearly the attachment of S to the DMAD, the absence of the anilide group, and also shows the methyl group at the 6-position of the pyridine ring (the *p*-position to the cyano group) which is a further proof to our suggested mechanism (*cf.* Scheme 1).

Compound **12** reacts also with *N,N*-dimethyl chloroacetamide **16** under the same reaction conditions described in ref. 19 to afford the fully aromatic thieno[2,3-*b*]pyridine derivative **18** rather than the claimed dihydro-derivative **17** (his **11** [19]). It should be stated that the ^1H NMR data reported for compound **17** (old **11**) are completely applicable to our compound **18** (*cf.* experimental part).

Compound **18** was allowed to react with morpholine-4-carboxaldehyde **19**, *N,N*-diemthylformamide **20**, and 2,5-dimethoxy-tetrahydrofuran **21** under the same reaction conditions described in ref. 19 to afford products very similar to those described (his numbers **15**, **16**, and **17** in his Scheme 4); however, the obtained products were found to be the fully aromatic thieno[2,3-*b*]pyridine derivatives **22**, **23**, and **24**, respectively (*cf.* Scheme 2). It should be stated also that the ^1H NMR data reported in reference [19] for compounds **22**, **23**, and **24** (Scheme 2; numbers **15**, **16**, and **17** in his Scheme 4) are completely not applicable to their assigned structures.

EXPERIMENTAL

Melting points were measured on an Electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as

KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in DMSO-d_6 using TMS as internal standard and chemical shifts are expressed in δ ppm values. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 ev). Elemental analyses were carried out at the Micro-analytical Center at Cairo University. X-ray data [20] were collected using a Bruker Nonius 5622 diffractometer and were corrected by SADABS factors and emperical absorption. The structure was solved by direct methods and expanded using Fourier technique. SCHAKAL 99 program system was used in the graphic representation of the structure [21]. The nonhydrogen atoms are refined anisotropically and the hydrogen atoms were refined according to theoretical models. X-ray crystallography, elemental and spectral data of compound **15** were made in the Institute of Organic Chemistry, TU-Dresden, Germany.

2-Cyano-4-(1-dimethylamino-ethylidene)-pent-2-enedioic acid 1-amide 5-phenylamide 6. To a mixture of 2-dimethylaminomethylene-3-oxo-*N*-phenylbutyramide **1** (2.32 g; 10 mmol) and malononitrile **2a** (0.66 g; 10 mmol) in ethanol (15 mL) was added few drops of piperidine as catalyst. The reaction mixture was refluxed for 2 h and then left to cool to room temperature. The solid product thus precipitated was collected by filtration and recrystallized from dioxan to give yellow crystals, yield (2.23 g, 75%); mp 197–198°C (Dioxan); υ_{max} = 3435–3284 (NH_2 and NH), 2217 (CN), 1665, and 1656 cm^{-1} (2 CO); MS: *m*/*z* = 298 [M$^+$]; δ_H = 1.69 (s, 3H, CH_3), 2.75 (s, 6H, $2CH_3$), 7.15 (s, 1H, CH), 7.10–7.65 (m, 7H, Ph+NH_2), 8.35 (s, 1H, NH). δ_C = 15.4 (q), 38.8 (q), 104,7 (s), 104,9 (s), 116,8 (s), 120.6 (d), 124.3 (d), 128.9 (d), 138.4 (s), 154.3 (s), 156.9 (d), 163.1 (s), 167.5 (s).

Anal. Calcd. for $C_{14}H_{18}N_4O_2$: (298.34): C, 64.41; H, 6.08; N, 18.78. Found: C, 64.45; H, 6.10; N, 18.90.

Synthesis of 5-cyano-2-methyl-6-oxo-1,6-dihydro-pyridine-3-carboxylic acid phenyl amide 7. ***Method A: Cyclization of compound 6.*** Compounds **6** (2.98 g, 10 mmol) was refluxed in ethanolic sodium ethoxide (15 mL) for 30 min. The solvent was reduced to one third of its volume under reduced pressure and left to cool overnight. The solid precipitate that appeared was collected by filtration and crystallized from ethanol to afford **7** as yellow crystals, yield (2.15 g, 85%), mp. 219–220°C.

Method B: The reaction of 2-dimethylaminomethylene-3-oxo-N-phenylbutyramide 1 with cyanoacetamide 2b. To a mixture of **1** (2.32 g, 10 mmol) and cyanoacetamide **2b** (0.84 g, 10 mmol) in ethanol (20 mL) was added a catalytic amount of piperidine (5 drops). The reaction mixture was refluxed for 6 h and then left to cool to room temperature. The contents of the flask were poured onto ice-cold water and acidified with few drops of conc. HCl till just neutral (pH paper). The precipitated solid product was filtered off, washed thoroughly with cold water, dried, and recrystallized from ethanol/DMF (4:1) to give **7** as yellow crystals, yield (1.97 g, 78%); mp. 217–219°C (Lit. mp. 216–218°C [18]); υ_{max} = 3382, 3275 (NH), 2235 (CN), and 1657 and 1638 cm^{-1} (2CO); MS: *m*/*z* = 253 [M$^+$]; δ_H = 2.63 (s, 3H, CH_3), 7.12–7.68 (m, 5H, Ph), 7.82 (br.s., 1H, NH), 8.65 (s, 1H, H-4), 10.60 (br.s., 1H, NH). δ_C = 16.48 (q), 104.66 (s), 112.65 (s), 116.15 (s), 121.05 (d), 124.57 (d), 128.65 (d), 138.45 (s), 145.6 (s), 153.95 (d), 159.86 (s), 164.55 (s).

Anal. Calcd. *for* $C_{14}H_{11}N_3O_2$: (253.26): C, 66.40; H, 4.38; N, 16.59. Found: C, 66.45; H, 4.47; N, 16.70.

5-Cyano-2-methyl-6-thioxo-1,6-dihydro-pyridine-3-carboxylic acid phenylamide 12. A mixture of compound **1** (2.32 g, 10 mmol) and cyanothioacetamide **2c** (1.0 g, 10 mmol) in ethanol (25 mL) with sodium ethoxide catalyst was refluxed for 30 min. After cooling down, the reaction mixture was poured onto cold water and acidified with dil. HCl. The precipitated solid product thus formed was collected by filtration and recrystallized from ethanol to afford **12** as yellow crystals, Yield (1.94 g, 72%), mp. 225–227°C (lit. 235°C [19]), υ_{max} = 3345, 3228 (NH), 2215 (CN), and 1658 cm^{-1} (CO); MS: *m*/*z* = 269 [M$^+$]; δ_H = 1.74 (s, 3H, CH_3), 7.05–7.68 (m, 5H, Ph), 8.15 (s, 1H, H-4), 9.25 (br.s., 1H, NH), 13.92 (br.s., 1H, NH). δ_C = 185.65 (s), 167.46 (d), 163.85 (s), 143.15 (s), 135.26 (s), 128.66 (d), 124.25 (d), 120.38 (d), 116.24 (s), 116.58 (s), 107.47 (s), 15.42 (q).

Anal. Calcd for $C_{14}H_{11}N_3OS$: (269.32): C, 62.43; H, 4.12; N, 15.60. Found: C, 62.45; H, 4.18; N, 15.70.

2-(3-Cyano-6-methylpyridin-2-ylsulfanyl)-but-2-enedioic acid dimethyl ester 15. To a suspension of **12** (2.69 g, 10 mmol) in 15 mL of chloroform was added (2.13 g, 15 mmol) dimethyl acetylenedicarboxylate (DMAD) and a catalytic amount of triethylamine. The reaction mixture was stirred at room temperature for 3h. The precipitated solid formed after evaporation of the solvent was collected and recrystallized from methanol and then purified by flash chromatography using a column with silica gel (10 cm height with 2 cm^2 diameter) using pentane/ethyl acetate (3:1) as eluent to afford compound **15** as yellow crystals, yield (2.29 g, 65%), mp. 125–126°C (lit. >300°C [19]), υ_{max} = 2220 (CN), 1712 and 1710 (2 ester CO); MS: *m*/*z* = 292 [M$^+$]; δ_H = 2.47 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 6.98 (s, 1H, olefin H), 7.36 (d, 1H, *j* = 8.65 Hz, H-5); 8.22 (d, 1H, *j* = 8.56 Hz, H-4). δ_C = 24.04 (q), 52.00 (q), 52.50 (q), 104.46 (s), 115.57 (s), 121.24 (d), 127.82 (d), 139.63 (s), 142.16 (d), 157.74 (s), 162.85 (s), 163.85 (s), 163.93 (s).

X-ray crystallographic data: Colourless crystals, $C_{13}H_{12}N_2O_4S$ (M_r = 292.31 g mol^{-1}), monoclinic, space group $P2_1/c$ (No. 14), *a* = 8.950(2) Å, *b* = 21.930(4) Å, *c* = 7.337(2) Å, α[^{O}] = 90.00, β[^{O}] = 104.48 (3), γ[^{O}] = 90.00; *V*[Å^3] = 1394.3 (6), *Z* = 4, $D_{calc.}$ = 1.392 g cm^{-3}, *F*(000) = 608e, μ(M_o K_α) = 0.246 nm^{-1}; the final difference Fourier ρ = 0.29 (−0.21) e Å^{-3}.crystal dimensions = 0.33 × 0.17 × 0.08 mm. Max. resolution [sin θ/λ]$_{max}$ = 0.64 Å^{-1}/ 99.8%. Data were collected using a Bruker Nonius area detector at T[°C] = −75 (2), with graphite monochromator with Mo Kα radiation (λ = 0.71073 Å) using the CCD data collection and SADABS absorption correction method; min 90.5%; max 98.1%. No. of independent reflections are 3043 were counted with observed reflections 2415. R_{av} = 0.071. The final *R* and R_W^2 = 0.040 and 0.098, respectively.

Anal. Calcd for $C_{13}H_{12}N_2O_4S$: (292.31): C, 53.42; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.01; H, 3.86; N, 9.73; S, 10.88.

3-Amino-6-methyl-thieno[2,3-b]pyridine-2,5-dicarboxylic acid 2-dimethylamide 5-phenylamide 18. To a solution of **12** (2.69 g, 10 mmol) in methanol (25 mL) was added *N*,*N*-dimethyl chloroacetamide **16** (1.22 g, 10 mmol) followed by few drops of sodium methoxide. The reaction mixture was refluxed for 1 h and then left to cool to room temperature. The mixture was then poured onto ice-cold water and acidified by few drops of dil. HCl till just neutral. The precipitated solid product was filtered off and recrystallized from methanol to afford

compound **18** as yellow crystals, yield (2.4 g, 68%), mp. 221–222°C (lit. 220°C [19]), υ_{max} = 3445, 3328 (NH_2 and NH), 1680 and 1668 (2CO) cm^{-1}; MS: *m*/*z* = 354 [M^+]; δ_H = 2.32 (s, 3H, CH_3), 3.54 (s, 6H, $2CH_3$), 7.05–7.80 (m, 7H, Ph+NH_2), 8.22 (s, 1H, H-4), 9.35 (br.s., 1H, NH).

Anal. Calcd for $C_{18}H_{18}N_4O_2S$: (354.43): C, 61.00; H, 5.12; N, 15.81; S, 9.05. Found: C, 60.92; H, 5.15; N, 15.87; S, 9.25.

The reaction of compound 18 with morpholine-4-carboxaldehyde 19, *N*,*N*-diemthylformamide 20, and 2,5-dimethoxy-tetrahydrofuran 21 (general procedure). To a solution of **18** (3.54 g; 10 mmol) in 20 mL of phosphorus oxychloride was added each of **19**, **20**, or **21**. The reaction mixture was refluxed for 2 h in each case, left to cool to room temperature, and then poured onto ice-cold water and neutralized with ammonia. The precipitated solids thus formed were filtered off and recrystallized from the proper solvent to afford **22**, **23**, and **24**, respectively.

6-Methyl-3-[(morpholin-4-ylmethylene)-amino]-thieno[2,3-b]pyridine-2,5-dicarboxylic acid 2-dimethylamide 5-phenylamide 22. Yellow crystals, Yield (3.16 g; 70%), mp. 279–281°C (EtOH/DMF) (lit. 280°C [19]), υ_{max} = 3385, 3258 (NH), 1675 and 1668 cm^{-1} (2CO); MS: *m*/*z* = 451 [M^+]; d_H = 2.25 (s, 3H, CH_3), 3.05 (t, 4H, $2CH_2$), 3.29 (s, 6H, $2CH_3$), 3.72 (t, 4H, $2CH_2$), 7.05–7.60 (m, 6H, Ph + olefin H), 8.22 (s, 1H, H-4), 9.34 (br.s., 1H, NH).

Anal. Calcd. for $C_{23}H_{25}N_5O_3S$: (451.54): C, 61.18; H, 5.58; N, 15.51; S, 7.10. Found: C, 61.25; H, 5.68; N, 15.57; S, 7.23.

3-(Dimethylamino-methyleneamino)-6-methyl-thieno[2,3-b]pyridine-2,5-dicarboxylic acid 2-dimethylamide 5-phenylamide 23. Coffee brown crystals, yield (2.66 g; 65%), mp. 272–273°C (dioxan) (lit. 275°C [19]), υ_{max} = 3442, 3328 (NH), 1678, and 1669 cm^{-1} (2CO); MS: *m*/*z* = 409 [M^+]; d_H = 2.23 (s, 3H, CH_3), 2.55 (s, 6H, $2CH_3$), 3.15 (s, 6H, $2CH_3$), 7.05–7.55 (m, 6H, Ph + olefin H), 8.28 (s, 1H, H-4), 9.31 (br.s., 1H, NH).

Anal. Calcd for $C_{21}H_{23}N_5O_2S$: (409.50): C, 61.59; H, 5.66; N, 17.10; S, 7.83. Found: C, 61.72; H, 5.73; N, 17.25; S, 7.98.

6-Methyl-3-pyrrol-1-yl-thieno[2,3-b]pyridine-2,5-dicarboxylic acid 2-dimethylamide 5-phenylamide 24. Yellow crystals, Yield (2.9 g; 72%), mp. 312–313°C (EtOH/DMF) (lit. >300°C [19]), υ_{max} = 3435, 3329 (NH), 1676, and 1667 cm^{-1} (2CO); MS: *m*/*z* = 404 [M^+]; d_H = 2.24 (s, 3H, CH_3), 3.05 (s, 6H, $2CH_3$), 6.12–7.68 (m, 9H, Ph + pyrrole H), 8.25 (s, 1H, H-4), 9.33 (br.s., 1H, NH).

Anal. Calcd for $C_{22}H_{20}N_4O_2S$: (404.48): C, 65.33; H, 4.98; N, 13.85; S, 7.93. Found: C, 65.37; H, 4.85; N, 13.72; S, 8.13.

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[20] Crystallographic data (excluding structure factors) for the structure **15** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 746861. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) + 44 1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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