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Formation of new pyridyl substituted enamines. Observation of a diaza-Cope rearrangement

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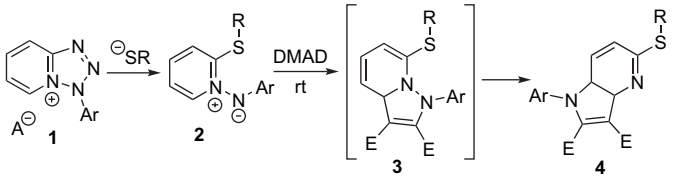
ABSTRACT

Some 2-arylthiopyridinium imides when reacted with dimethyl acetylene dicarboxylate exhibited ambident behaviour: either a 1,3-dipolar cyclization occurred followed by a ring transformation to yield pyrrolopyridines or 5-pyridyl substituted enamines were formed in a different route. Mechanistic considerations revealed that this latter unusual transformation is initiated by a Michael addition of the imide nitrogen atom of the starting pyridinium compound on the reagent, which is followed by a [3,3]-sigmatropic ('diaza-Cope') rearrangement. Ring opening of the pyrrolopyridine compounds by a base also yielded pyridylenamines, which proved to be positional isomers of the sigmatropic rearrangement products. The new pyridyl derivatives seem to be valuable compounds for further transformations. Thus, they can undergo thermal electrocyclization to 7-azaindoles.

1. Introduction

In our earlier study[1,2] we have reported that some sulfur-containing pyridyl mesomeric betaines (**2**)—easily available from tetrazolopyridinium salts (**1**)—readily undergo cycloadditions as 1,3-dipoles. Thus, reaction of **2** with dimethyl acetylene dicarboxylate (DMAD) yielded the pyrrolopyridine compound **4**. Formation of this product was rationalized by a 1,3-dipolar cycloaddition between **2** and DMAD to give a cycloadduct (**3**), which undergoes ring transformation to the fused pyrrole **4** (Scheme 1).

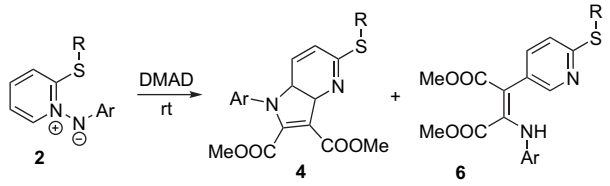


Scheme 1.

Similar transformations were also experienced with other dipolarophiles, e.g., with *N*-phenylmaleinimide and fumaronitrile. The finding that the yield of **4** (17%) was substantially lower than those of the cycloadducts obtained with other dipolarophiles (50–70%) indicated that this reaction pathway might be only a minor route besides an alternative one. Thus, careful analysis of the reaction mixture seemed of high interest.

2. Results and discussion

Thin layer chromatography of the mixture obtained from the reaction of **2** and DMAD indicated that besides **4**, another well-defined component was also present in the mother liquor. Column chromatographic separation allowed the isolation of a new crystalline product, the spectra of which seemed to be in accordance with the structure **6** (Scheme 2).



	Ar	R	**4** (%)	**6** (%)
a	4-Cl-C_6H_4-	4-Cl-C_6H_4-	27	15
b	4-Cl-C_6H_4-	4-CH_3-C_6H_4-	17	36
c	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-	26	20
d	4-CH_3-C_6H_4-	4-Cl-C_6H_4-	21	18
e	4-CH_3-C_6H_4-	C_6H_5-CH_2-	-	24
f	4-Cl-C_6H_4-	C_6H_5-CH_2-	-	24

Scheme 2.

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This structural assignment was also verified by single crystal X-ray diffraction.

There is one molecule in the asymmetric unit of crystal structure of (2*Z*)-2-[6-(benzylsulfanyl)pyridin-3-yl]-3-[(4-methylphenyl)amino] but-2-enedioate (**6e**) (Fig. 1).[3] It crystallizes in the triclinic crystal system, space group *P*-1 (No. 2). The quality of the crystal was good, the measurement was performed at low temperature (117 K), the structure is ordered, it was possible to locate all hydrogen atoms in the difference Fourier maps, and to refine the structure to R=0.0334 for $I>2\sigma$. The unit cell contains no residual solvent accessible void. Packing coefficient is 69.7%.

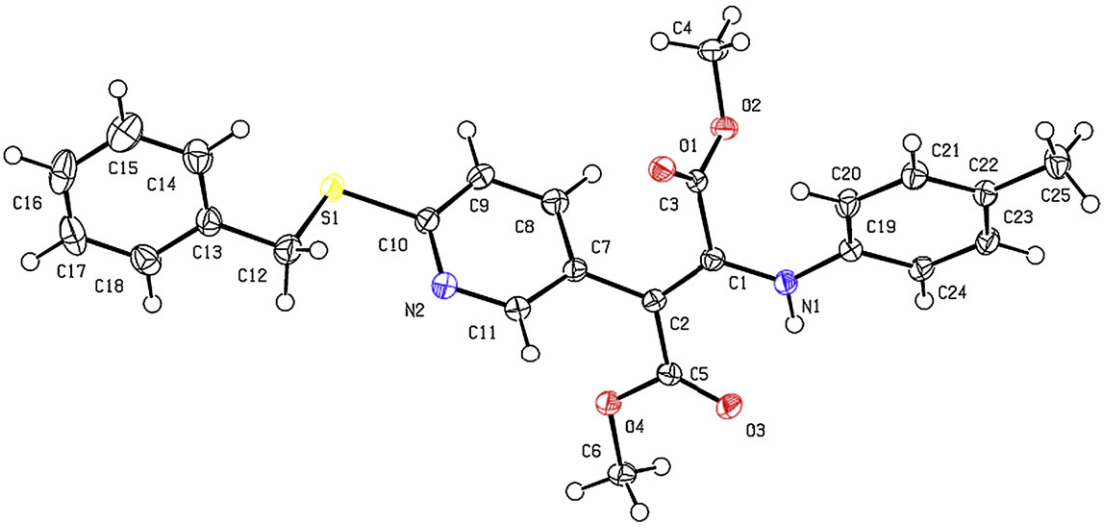


Figure 1. ORTEP diagram[4] of (2*Z*)-2-[6-(benzylsulfanyl)pyridin-3-yl]-3-[(4-methylphenyl)amino]but-2-enedioate (**6e**) represented at 50% probability level, heteroatoms are shaded.

One strong and one weak intramolecular interaction contributes to the stability of the molecular conformation, their graph set descriptors[5] are S6 and S7, respectively: N1–H1···O3 (D–H=0.880 Å, H···A=1.950 Å, D···A=2.6323(15) Å, D–H···A=133°), C20–H20···O1 (D–H=0.950 Å, H···A=2.540 Å, D···A=3.3482(17) Å, D–H···A=143°). With the attractive but weak C–H···O type intermolecular interaction [2−*x*,4−*y*,2−*z*]C23–H23···O3 (D–H=0.950 Å, H···A=2.400 Å, D···A=3.2362(16) Å, D–H···A=147°) repeated by the symmetry centre, two molecules form a dimer. The graph set descriptor[5] of the ring is $R^2_4(14)$ (Fig. 2).

There are no more strong intermolecular interactions in the crystal structure owing to the lack of donors, although several potential acceptors are present. There are no attractive π···π interactions, but two C–H···π interactions are found to the aromatic rings: C4–H4A···ring$_{C13–C18}$ 2.74 Å, 150° [1−*X*,2−*Y*,1−*Z*]; C6–H6C···ring$_{C19–C24}$ 2.54 Å, 155° [−1+*X*,*Y*,*Z*]. There is one oxygen (O3) relatively close to the ring$_{C13–C18}$: 3.869 Å and 94.8° [1+*X*,1+*Y*,1+*Z*].

The fact that the sequence of C and N atoms in the products **4** and **6** is entirely different suggests that these two compounds are formed via different pathways. Furthermore the structural feature of **6**, where the pyridine ring is attached in position 5 to the β-carbon atom of an enamine moiety strongly suggests that a predominant rearrangement has taken place. A likely reaction route can be defined (Scheme 3) by supposing that the observed 1,3-dipolar cycloadditions might proceed, not only in a concerted manner, but also in two steps, of which the first can be a Michael addition to **a**. If the second step is formation of the 4-azaindole derivative **4**, the regular 1,3-cycloaddition product will be formed as shown in Scheme 2. There is, however, a possibility for a [3,3]-sigmatropic rearrangement with participation of the C5–C6–N1–Nα–C1′–C2′ string of atoms having double bonds at each terminal atom pair (see mesomeric structure **b**). As a result of this diaza-Cope rearrangement, the N1–Nα bond is broken and the C5–C2′ bond is established (i.e., **c** is formed, which is also illustrated by its mesomeric structure **d**). Finally, the product can be stabilized by tautomerism to the heteroaromatic **6**. An analogous conversion taking place by a different mechanism has been reported by Sasaki et al.[6]

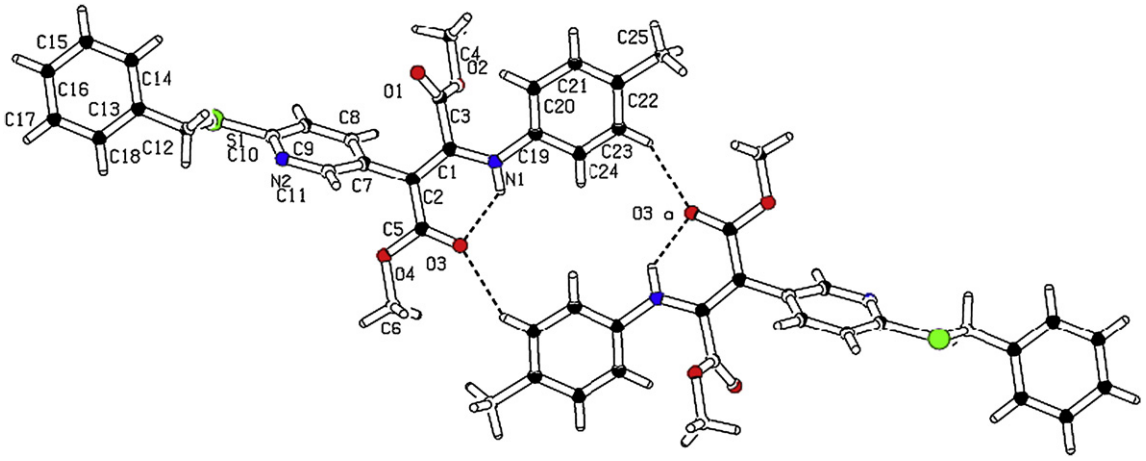
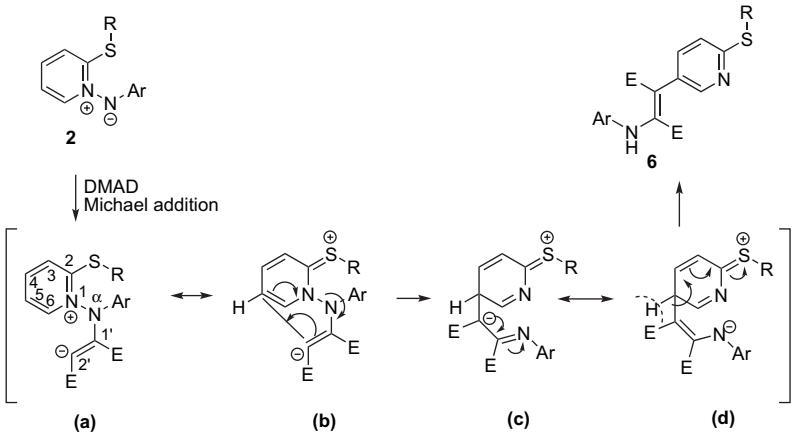
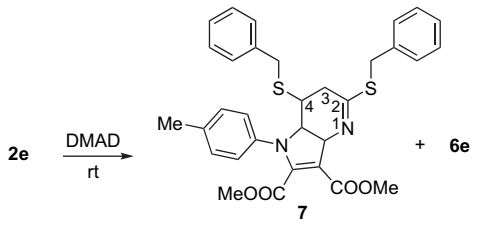


Figure 2. The two molecules of **6e** forming a dimer around the symmetry centre.



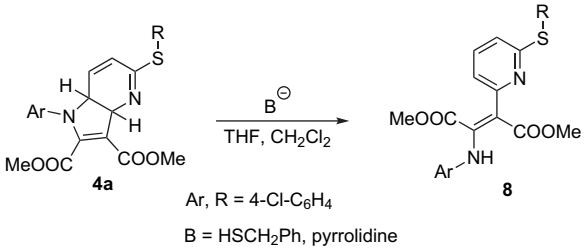
Scheme 3.

In one case, interestingly, the formation of the 4-azaindole (**4a**) from (**2e**) was accompanied by formation of a new type of product (**7**), which can be regarded as an addition product of the expected **4e** and benzylmercaptan (Scheme 4). Such a product can obviously be formed by nucleophilic addition of the thiolate on the pyridine C3–C4 double bond.



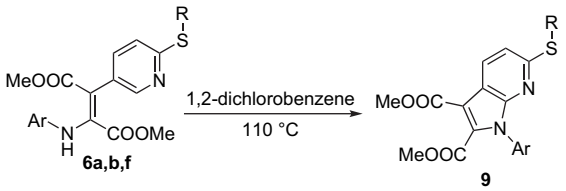
Scheme 4.

In order to support this mechanism, the isolated 4-azaindole **4a** was reacted with benzylthiolate. Formation of a product related to **7** was, unexpectedly, not observed and, instead, the ring opening of the pyrrole moiety was found, and 6-pyridylenamine (**8**) was obtained in very low yield (Scheme 5). The fact that arylthio structural moiety was not incorporated in the structure of this compound revealed that the thiolate anion acted as a base rather than a nucleophile: most probably the C6–H was deprotonated and ring-chain tautomerism of this intermediate lead to formation of the open chained enamine. The driving force of this transformation is clearly formation of the aromatic pyridine moiety. The same conversion can be more conveniently carried out by using pyrrolidine as a base and, thus, the **4**→**8** transformation takes place in acceptable (51%) yield. Comparison of structures **8** and **6** reveals, interestingly, that in these transformations two positionally isomeric derivatives were formed in independent reaction pathways. Our literature search revealed that very few such pyridinyl enamines have been described.[7]



Scheme 5.

The new pyridyleneamines seemed to have structural feature potentially enabling further cyclization reactions. Recently we have described that azinylaldehyde hydrazones can undergo electrocyclization to yield fused pyrazoloazines.[8] Since the difference between the electronic structures of these reported hydrazones and **6** is only the presence of a N or C atom, a similar thermal cyclization with **6** is possible. In order to explore this synthetic possibility, some derivatives of **6** were subjected to heating for prolonged time. As expected, cyclization to fused pyrroles was found and the 7-azaindoles **9a–c** were obtained in medium yield (Scheme 6). The cyclization was found to proceed in a regioselective manner, and the side chain N atom attached to the C6 of the pyridine ring in every case. In contrast to some 7-azaindole syntheses reported in the literature,[9,10] our finding represents a new compilation mode of this ring system. The synthesis and reactivity of this important class of compounds has been recently reviewed.[11]



9	Ar	R
a	4-Cl-C_6H_4	4-Cl-C_6H_4
b	4-Cl-C_6H_4	4-Me-C_6H_4
c	4-Cl-C_6H_4	benzyl

Scheme 6.

3. Conclusion

The above findings reveal that recognition of a side-product in some cycloaddition reactions allowed the discovery of a new rearrangement pathway yielding new enaminopyridine derivatives. These compounds can serve as valuable starting materials for novel ring closure reactions.

4. Experimental part

4.1. General methods

Melting points were determined on a Büchi apparatus and are uncorrected. The IR spectra were recorded on a Thermo Nicolet

Avatar 320 FT-IR spectrometer. NMR measurements were performed on Varian INOVA-200 or Varian INOVA-400 spectrometers equipped with a 5 mm inverse detection *z*-gradient probe. ^{1}H and ^{13}C NMR spectra were measured at room temperature (25 °C) in an appropriate solvent. ^{1}H and ^{13}C chemical shifts are expressed in parts per million (δ) referenced to residual solvent signals. The elemental analysis has been carried out with an Elementar Vario EL III apparatus (at the Analytical Laboratory for Organic Chemistry, Chemical Research Center, Hungarian Academy of Sciences, H-1025 Budapest, Pusztaszeri út 59). Chromatographic separations were carried out on aluminium oxide (activated, neutral, Brockmann I, approx. 150 mesh, Sigma–Aldrich). Reactions were monitored with Merck aluminium oxide 60 F_{254}, neutral, precoated TLC plates (0.25 mm thickness). All the chemicals and solvents were used as supplied.

Syntheses of pyridinium arylimides (**2a**–**f**)[1,2,12] and dimethyl 1-(4-chlorophenyl)-5-[(4-chlorophenyl)sulfanyl]-1*H*-pyrrolo[3,2-*b*]pyridine-2,3-dicarboxylate (**4a**)[2] have been published earlier.

4.2. General procedure for reaction of aryl- and benzylsulfanylpyridinium arylimides with DMAD

A solution of the appropriate pyridinium arylimide (1 mmol) and DMAD (1.35 mmol, 163 μL) in abs dichloromethane (5 mL) was stirred at room temperature, and the progress of the reaction was monitored by TLC. After disappearance of the starting material (1–4 h) the solution was evaporated and treated with diethyl ether to give white precipitate (**4**). The filtrate was then evaporated and subjected to column chromatography on alumina with a mixture of hexane–ethyl acetate (4:1) as eluent. Separation of the main fraction around R_f=0.6 gave the appropriate compound (**6**).

*4.2.1. Dimethyl 1-(4-chlorophenyl)-5-[(4-methylphenyl)sulfanyl]-1H-pyrrolo[3,2-b]pyridine-2,3-dicarboxylate (**4b**)*

Prepared from **2b**, colorless crystals (0.080 g, 17%), mp 94–102 °C. IR (KBr) ν_{max}: 2949, 1733, 1689, 1591, 1495, 1439, 1220, 1065, 1014, 810 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.34 (3H, s, C*H*$_3$′), 3.70+3.78 (6H, s, 2×OC*H*$_3$), 4.68 (1H, dd, *J*=12.4+5.3 Hz, H7a), 5.24 (1H, d, *J*=12.4 Hz, H3a), 5.82 (1H, d, *J*=11.2 Hz, H6), 6.10 (1H, dd, *J*=11.2+5.3 Hz, H7), 7.02 (2H, m, H2″+H6″), 7.15 (2H, m, H3′+H5′), 7.30 (2H, m, H2′+H6′), 7.40 (2H, m, H3″+H5″). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.2, 51.2, 55.9, 56.6, 61.6, 114.7, 122.9, 124.4, 125.0, 125.8, 126.3, 129.4, 129.6, 131.0, 134.6, 136.3, 159.4, 163.0, 164.8, 168.8. Anal. Calcd for $C_{24}H_{21}ClN_2O_4S$ (468.09): C, 61.47; H, 4.51; N, 5.97; S, 6.83. Found: C, 61.25; H, 4.54; N, 5.83; S, 6.96.

*4.2.2. Dimethyl 1-(4-methylphenyl)-5-[(4-methylphenyl)sulfanyl]-1H-pyrrolo[3,2-b]pyridine-2,3-dicarboxylate (**4c**)*

Prepared from **2c**, colorless crystals (0.230 g, 26%), mp 145–149 °C. IR (KBr) ν_{max}: 2951, 2919, 1738, 1698, 1609, 1514, 1438, 1218, 1066, 821, 810, 769 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.31+2.36 (6H, s, C*H*$_3$′+C*H*$_3$″), 3.71+3.76 (6H, s, 2×OC*H*$_3$), 4.70 (1H, dd, *J*=12.6+5.0 Hz, H7a), 5.27 (1H, d, *J*=12.6 Hz, H3a), 5.80 (1H, d, *J*=9.1 Hz, H6), 6.10 (1H, dd, *J*=9.1+5.0 Hz, H7), 6.96 (2H, m, H3″+H5″), 6.98 (2H, m, H2′+H6′), 7.0–7.20 (4H, m, H3′+H5′+H2″+H6″). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.8, 21.1, 51.0, 52.8, 56.9, 61.7, 105.9, 122.5, 124.1, 125.8, 126.3, 129.6, 130.0, 134.5, 135.9, 136.4, 138.8, 159.1, 163.2, 165.0, 170.2. Anal. Calcd for $C_{25}H_{24}N_2O_4S$ (448.15): C, 66.94; H, 5.39; N, 6.25. Found: C, 66.77; H, 5.39; N, 6.24.

*4.2.3. Dimethyl 5-[(4-chlorophenyl)sulfanyl]-1-(4-methylphenyl)-1H-pyrrolo[3,2-b]pyridine-2,3-dicarboxylate (**4d**)*

Prepared from **2d**, colorless crystals (0.100 g, 21%), mp 144–148 °C. IR (KBr) ν_{max}: 2947, 1738, 1689, 1597, 1516, 1437, 1223, 1068, 1013, 819 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.32 (3H, s, C*H*$_3$), 3.70+3.75 (6H, s, 2×OC*H*$_3$), 4.71 (1H, dd, *J*=11.6+4.4 Hz, H7a), 5.26 (1H, d, *J*=11.6 Hz, H3a), 5.83 (1H, d, *J*=9.7 Hz, H6), 6.13 (1H, dd, *J*=9.7+4.4 Hz, H7), 6.98 (2H, m, H3″+H5″), 7.14 (2H, m, H2″+H6″), 7.31 (2H, m, H2′+H6′), 7.47 (2H, m, H3′+H5′). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.9, 51.0, 52.8, 56.9, 61.7, 105.6, 122.8, 124.1, 126.8, 127.7, 128.8, 130.1, 134.8, 135.5, 135.9, 136.6, 157.7, 167.6, 167.7, 170.0. Anal. Calcd for $C_{24}H_{21}ClN_2O_4S$ (468.09): C, 61.47; H, 4.51; N, 5.97. Found: C, 61.33; H, 4.15; N, 5.97.

*4.2.4. Dimethyl (2Z)-2-[(4-chlorophenyl)amino]-3-{6-[(4-chlorophenyl)sulfanyl]pyridin-3-yl}but-2-enedioate (**6a**)*

Prepared from **2a**, colorless crystals (0.076 g, 15%), mp 129–134 °C. IR (KBr) ν_{max}: 3270, 2950, 1736, 1662, 1583, 1220, 1092, 1014, 818, 748 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 3.41 (3H, s, O–C*H*$_3$ (β)), 3.72 (3H, s, O–C*H*$_3$ (α)), 6.82 (1H, d, *J*=8 Hz, H3), 6.95 (2H, m, H2″+H6″), 7.20–7.60 (7H, m, H3″+H5″+H2′+H3′+H5′+H6′+H4), 8.26 (1H, d, *J*=2 Hz, H6), 10.6 (1H, s, N*H*). ^{13}C NMR ($CDCl_3$) δ (ppm): 51.7, 52.5, 98.4, 120.4, 122.9, 127.8, 129.5, 129.6, 129.8, 130.7, 135.3, 136.0, 137.8, 139.4, 149.9, 151.3, 159.0, 163.7, 169.5. Anal. Calcd for $C_{23}H_{18}Cl_2N_2O_4S$ (488.04): C, 56.45; H, 3.71; N, 5.72; S, 6.55. Found: C, 56.52; H, 3.67; N, 5.66; S, 6.67.

*4.2.5. Dimethyl (2Z)-2-[(4-chlorophenyl)amino]-3-{6-[(4-methylphenyl)sulfanyl]pyridin-3-yl}but-2-enedioate (**6b**)*

Prepared from **2b**, colorless crystals (0.170 g, 36%), mp 110–113 °C. IR (KBr) ν_{max}: 2951, 1737, 1664, 1601, 1219, 1023, 814 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.40 (3H, s, C*H*$_3$′), 3.40 (3H, s, O–C*H*$_3$ (β)), 3.68 (3H, s, O–C*H*$_3$ (α)), 6.77 (1H, d, *J*=8 Hz, H3), 6.92 (2H, m, H2″+H6″), 7.18–7.40 (5H, m, H3″+H5″+H3′+H5′+H4), 7.50 (2H, m, H‴+H6′), 8.25 (1H, d, *J*=2 Hz, H6), 10.56 (1H, s, N*H*). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.2, 51.7, 52.5, 98.6, 119.7, 122.8, 127.0, 127.2, 129.4, 130.4, 130.5, 135.2, 137.8, 139.2, 139.4, 149.8, 151.0, 160.8, 163.7, 169.6. Anal. Calcd for $C_{24}H_{21}ClN_2O_4S$ (468.09): C, 61.47; H, 4.51; N, 5.97. Found: C, 61.39; H, 4.68; N, 5.98.

*4.2.6. Dimethyl (2Z)-2-[(4-methylphenyl)amino]-3-{6-[(4-methylphenyl)sulfanyl]pyridin-3-yl}but-2-enedioate (**6c**)*

Prepared from **2c**, colorless crystals (0.180 g, 20%), mp 128–129 °C. IR (KBr) ν_{max}: 3267, 2949, 1737, 1664, 1583, 1218, 1044, 809, 748 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.30 (3H, s, C*H*$_3$″), 2.40 (3H, s, C*H*$_3$′), 3.38 (3H, s,O–C*H*$_3$ (β)), 3.67 (3H, s, O–C*H*$_3$ (α)), 6.77 (1H, d, *J*=8.2 Hz, H3), 6.92 (2H, m, H2″+H6″), 7.09 (2H, m, H3″+H5″), 7.24 (2H, m, H3′+H5′), 7.33 (1H, dd, *J*=8.2+2.3 Hz, H4), 7.50 (2H, m, H2′+H6′), 8.24 (1H, d, *J*=2.3 Hz, H6), 10.58 (1H, s, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.1, 21.5, 51.8, 52.6, 97.2, 120.0, 122.1, 127.6, 127.7, 130.2, 130.7, 135.3, 135.4, 136.9, 139.6, 139.7, 151.1, 151.5, 160.7, 164.2, 170.0. Anal. Calcd for $C_{25}H_{24}N_2O_4S$ (448.15): C, 66.94; H, 5.39; N, 6.25. Found: C, 66.74; H, 5.58; N, 6.21.

*4.2.7. Dimethyl (2Z)-2-{6-[(4-chlorophenyl)sulfanyl]pyridin-3-yl}-3-[(4-methylphenyl)-amino]but-2-enedioate (**6d**)*

Prepared from **2d**, colorless crystals (0.087 g, 18%), mp 140–142 °C. IR (KBr) ν_{max}: 3267, 2949, 1736, 1665, 1590, 1218, 1015, 818 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.32 (3H, s, C*H*$_3$″), 3.40 (3H, s, O–C*H*$_3$ (β)), 3.73 (3H, s, O–C*H*$_3$ (α)), 6.86 (1H, d, *J*=8.5 Hz, H3), 6.91 (2H, m, H2″+H6″), 7.10 (2H, m, H3″+H5″), 7.38 (1H, dd, *J*=8.5+2 Hz, H4), 7.40 (2H, m, H3′+H5′), 7.54 (2H, m, H2′+H6′), 8.26 (1H, d, *J*=2 Hz, H6), 10.58 (1H, s, N*H*). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.8, 51.5, 52.3, 96.7, 120.4, 121.9, 128.2, 129.7, 129.8, 129.9, 135.2, 135.3, 135.9, 136.5, 139.6, 150.9, 151.5, 151.8, 158.6, 169.5. Anal. Calcd for $C_{24}H_{21}ClN_2O_4S$ (468.09): C, 61.47; H, 4.51; N, 5.97; S, 6.84. Found: C, 61.12; H, 4.50; N, 5.91; S, 6.89.

*4.2.8. Dimethyl (2Z)-2-[6-(benzylsulfanyl)pyridin-3-yl]-3-[(4-methylphenyl)amino]but-2-enedioate (**6e**)*

Prepared from **2e**, yellow crystals (0.110 g, 24%), mp 108–110 °C. Besides this product, compound **7** was also separated from the reaction mixture by chromatography as discussed below. IR (KBr)

ν_{max}: 2951, 1744, 1662, 1602, 1215, 1039, 816 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 2.31 (3H, s, CH_3″), 3.33+3.69 (6H, s, 2×OCH_3), 4.43 (2H, s, CH_2), 6.93 (2H, m, H2″+H6″), 7.10 (3H, m, H3″+H5″+H3), 7.20–7.50 (6H, m, H2′+H3′+H4′+H5′+H6′+H4), 8.27 (1H, d, J=2.5 Hz, H6), 10.54 (1H, s, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 20.8, 34.5, 51.5, 52.2, 97.1, 120.9, 121.8, 127.0, 127.4, 128.4, 128.9, 129.9, 135.0, 136.6, 137.9, 138.8, 150.8, 151.0, 157.1, 163.9, 169.7. Anal. Calcd for $C_{25}H_{24}N_2O_4S$ (448.15): C, 66.94; H, 5.39; N, 6.25. Found: C, 66.66; H, 5.37; N, 6.21.

*4.2.9. Dimethyl (2Z)-2-[6-(benzylsulfanyl)pyridin-3-yl]-3-[(4-chlorophenyl)amino]but-2-enedioate (**6f**)*

Prepared from **2f**, yellow crystals (0.110 g, 24%), mp 126–128 °C. IR (KBr) ν_{max}: 2955, 1743, 1666, 1593, 1217, 1112, 1037, 824 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 3.36+3.70 (6H, s, 2×OCH_3), 4.43 (2H, s, CH_2), 6.95 (2H, m, H2″+H6″), 7.10 (3H, m, H3″+H5″+H3), 7.20–7.50 (6H, m, H2′+H3′+H4′+H5′+H6′+H4), 8.27 (1H, d, J=2.5 Hz, H6), 10.57 (1H, s, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 34.6, 51.8, 52.4, 98.8, 120.9, 122.8, 127.0, 128.4, 128.9, 129.4, 130.5, 137.8, 137.9, 138.7, 150.8, 151.2, 157.5, 163.7, 167.7, 169.7. Anal. Calcd for $C_{24}H_{21}ClN_2O_4S$ (468.09): C, 61.47; H, 4.51; N, 5.97. Found: C, 61.32; H, 4.43; N, 5.93.

4.3. Dimethyl 5,7-bis(benzylsulfanyl)-1-(4-methylphenyl)-1*H*-pyrrolo[3,2-*b*]pyridine-2,3-dicarboxylate (7)

The mixture obtained from the reaction of **2e** and DMAD when subjected to chromatography contained two products: the main product was **6e** as described above whereas another component of R_f=0.3 was also isolated as colorless crystals (0.025 g, 6%), mp 116–119 °C. IR (KBr) ν_{max}: 3028, 2950, 1743, 1692, 1604, 1515, 1208, 1123, 702 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 2.15 (1H, ddd, J=17+1.5+1 Hz, H6′), 2.30 (3H, s, CH_3′), 2.55 (1H, ddd, J=17+5+1.5 Hz, H6″), 3.05 (1H, ddd, J=5+3+1 Hz, H7), 3.70+3.90 (6H, s, 2×OCH_3), 3.72 (2H, m, S–CH_2–Ph‴), 4.04+4.38 (2H, d, J=12 Hz, S–CH_2–Ph″), 4.20 (1H, ddd, J=8+3+1.5 Hz, H7a), 5.30 (1H, dd, J=8+1.5 Hz, H3a), 6.67 (2H, m, H2′+H6′), 7.02 (2H, m, H3′+H5′), 7.20 (2H, m, H2‴+H6‴), 7.21 (1H, m, H4″), 7.25 (3H, m, H3‴+H4‴+H5‴), 7.26 (2H, m, H3″+H5″), 7.32 (2H, m, H2″+H6″). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.2, 32.0, 33.3, 35.4, 36.5, 51.4, 53.0, 60.2, 64.3, 107.0, 124.1, 127.1, 128.6, 128.9, 129.0, 129.3, 130.4, 135.6, 136.7, 137.8, 138.6, 152.2, 163.2, 165.2. Anal. Calcd for $C_{32}H_{32}N_2O_4S_2$ (572.18): C, 67.11; H, 5.63; N, 4.89; S, 11.20. Found: C, 67.02; H, 5.93; N, 4.80; S, 11.21.

4.4. Dimethyl (2*Z*)-2-[(4-chlorophenyl)amino]-3-{6-[(4-chlorophenyl)sulfanyl]-pyridin-2-yl}-but-2-enedioate (8)

A 60% suspension of NaH (0.019 g, 0.8 mmol) in THF (1 mL) was cooled down to 10 °C and a solution of pyrrolidine (0.028 g, 0.4 mmol) in THF (1 mL) was added. The mixture was heated at reflux for 15 min, cooled to −40 °C and a solution of **4a** (0.1 g 0.2 mmol) in dichloromethane (4 mL) was added. The reaction mixture was allowed to warm up to room temperature and was stirred for 2 days. The organic solvent was removed by evaporation and the residue was separated by column chromatography on alumina using a mixture of hexane–ethyl acetate (8:2) as eluent. Yellow crystals (0.050 g, 51%), mp 108–118 °C. IR (KBr) ν_{max}: 2950, 1743, 1568, 1497, 1432, 1213, 1094, 1013, 800 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 3.64+3.75 (6H, s, 2×OCH_3), 6.74 (2H, m, H2″+H6″), 6.98 (1H, dd, J=8+2.5 Hz, H5), 7.14 (2H, m, H2′+H6′), 7.22 (2H, m, H3″+H5″), 7.38 (2H, m, H3′+H5′), 7.50 (1H, dd, J=8.5+8 Hz, H4), 7.62 (1H, dd, J=8.5+2.5 Hz, H3), 12.2 (1H, s, NH). ^{13}C NMR ($CDCl_3$) δ (ppm): 51.8, 52.5, 97.4, 108.7, 118.8, 120.6, 124.6, 129.1, 129.3, 129.7, 131.2, 134.9, 135.8, 137.1, 146.5, 149.1, 156.3, 161.5, 165.4. Anal. Calcd for $C_{23}H_{18}Cl_2N_2O_4S$ (488.04): C, 56.45; H, 3.71; N, 5.72. Found: C, 56.49; H, 3.61; N, 5.68.

4.5. General procedure for ring closure of pyridylenamines (6) to pyrrolo[2,3-*b*]pyridines (9)

A solution of the appropriate pyridylenamine **6** (0.6 mmol) in *o*-dichlorobenzene (11 mL) was heated at 110 °C until the starting material disappeared, which was monitored by TLC (typically 168–264 h). The organic solvent was removed in vacuo and the residue was separated by column chromatography on alumina by a mixture of hexane–ethyl acetate (2:1) as eluent.

*4.5.1. Dimethyl 1-(4-chlorophenyl)-6-[(4-chlorophenyl)sulfanyl]-1H-pyrrolo[2,3-b]pyridine-2,3-dicarboxylate (**9a**)*

Prepared from **6a**, white crystals (0.180 g, 60%), mp 127–135 °C. IR (KBr) ν_{max}: 2953, 1735, 1715, 1496, 1226, 1114, 821 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 3.83+3.93 (6H, s, 2×OCH_3), 7.06 (1H, d, J=7.1 Hz, H5), 7.26 (2H, m, H3′+H5′), 7.32 (2H, m, H3″+H5″), 7.39 (2H, m, H2″+H6″), 7.45 (2H, m, H2′+H6′), 8.26 (1H, d, J=7.1 Hz, H4). ^{13}C NMR ($CDCl_3$) δ (ppm): 52.0, 53.5, 107.5, 115.3, 118.1, 128.1, 129.4, 129.6, 131.7, 133.6, 134.4, 134.7, 135.5, 136.7, 147.2, 149.8, 157.2, 162.5, 163.7. Anal. Calcd for $C_{23}H_{16}Cl_2N_2O_4S$ (486.02): C, 56.68; H, 3.31; N, 5.75; S, 6.58. Found: C, 56.55; H, 3.23; N, 5.70; S, 6.74.

*4.5.2. Dimethyl 1-(4-chlorophenyl)-6-[(4-methylphenyl)sulfanyl]-1H-pyrrolo[2,3-b]pyridine-2,3-dicarboxylate (**9b**)*

Prepared from **6b**, white crystals (0.130 g, 46%), mp 124–127 °C. IR (KBr) ν_{max}: 2952, 1739, 1711, 1495, 1227, 1111, 814 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 2.45 (3H, s, CH_3′), 3.83+3.91 (6H, s, 2×OCH_3), 6.97 (1H, d, J=8.6 Hz, H5), 7.19 (2H, m, H3′+H5′), 7.30–7.40 (4H, m, H2″+H3″+H5″+H6″), 7.44 (2H, m, H2′+H6′), 8.21 (1H, d, J=8.6 Hz, H4). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.2, 51.7, 53.2, 107.2, 114.6, 117.4, 127.0, 128.0, 129.1, 130.1, 131.3, 133.5, 134.1, 135.3, 139.3, 147.0, 149.1, 158.7, 162.3, 163.5. Anal. Calcd for $C_{24}H_{19}ClN_2O_4S$ (466.08): C, 61.73; H, 4.10; N, 6.00; S, 6.87. Found: C, 61.41; H, 4.03; N, 5.92; S, 7.01.

*4.5.3. Dimethyl 6-(benzylsulfanyl)-1-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-2,3-dicarboxylate (**9c**)*

Prepared from **6c**, light yellow crystal (0.140 g, 50%), mp 85–93 °C. IR (KBr) ν_{max}: 2952, 1747, 1705, 1496, 1219, 1113, 821 cm^{-1}. ^1H NMR ($CDCl_3$) δ (ppm): 3.83+3.93 (6H, s, 2×OCH_3), 4.26 (2H, s, CH_2), 7.18 (1H, d, J=8.3 Hz, H5), 7.20–7.30 (5H, m, Ph), 7.38 (2H, m, H3″+H5″), 7.58 (2H, m, H2″+H6″), 8.22 (1H, d, J=8.3 Hz, H4). ^{13}C NMR δ (ppm): 34.2, 51.7, 53.1, 107.7, 114.3, 118.4, 126.9, 128.2, 128.5, 128.8, 129.3, 131.0, 133.9, 134.6, 137.9, 138.7, 147.4, 156.3, 162.2, 163.6. Anal. Calcd for $C_{24}H_{19}ClN_2O_4S$ (466.08): C, 61.73; H, 4.10; N, 6.00; S, 6.87. Found: C, 61.53; H, 4.24; N, 5.90; S, 7.06.

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References and notes

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3. The crystals of (2*Z*)-2-[6-(benzylsulfanyl)pyridin-3-yl]-3-[(4-methylphenyl)amino]but-2-enedioate (**6e**) are yellow prisms. The size of the crystal selected for single crystal X-ray diffraction measurement is 0.50×0.35×0.25 mm. Formula is $C_{25}H_{24}N_2O_4S$ and formula weight is 448.52. It crystallizes in the triclinic crystal system, space group *P*-1. The cell dimensions are a=9.0469(17) Å, b=11.532(2) Å, c=12.298(2) Å, α=111.382(8)°, β=97.422(9)°, γ=106.297(8)°, V=1107.5(4) Å^3, Z=2, F(000)=472, D_x=1.345 Mg m^{-3}. A crystal was mounted on a loop in oil. The diffraction measurement was performed at T=117(2) K. Intensity data were collected on a Rigaku R-Axis Rapid diffractometer (graphite monochromator, Mo Kα radiation, λ=0.71073 Å) in the range 3.01≤θ≤27.48°. Cell parameters were determined by least-squares of the setting angles of 48,838

collected reflections in the range $6.03 \leq \theta \leq 55.03^{\circ}$. A total of 52,894 reflections were collected of which 5065 were unique [R(int)=0.021, $R(\sigma)$=0.0094]; 4704 reflections were $>2\sigma(I)$. Completeness to 2θ=0.999. An empirical absorption correction was applied to the data, μ=0.181 mm^{-1}, the minimum and maximum transmission factors were 0.9148 and 0.9561. The structure was solved by direct methods with SHELXS-97.[13] Anisotropic full-matrix least-squares refinement with SHELXL-97[14,15] on F^2 for all non-hydrogen atoms yielded R_1=0.0334 and wR_2=0.0932 for 4704 [$I>2\sigma(I)$], R_1=0.0355 and wR_2=0.0932 for all (5065) intensity data (goodness-of-fit=1.061; the maximum and mean shift/esd 0.002 and 0.000). Number of parameters=292. The maximum and minimum residual electron density in the final difference map was 0.379 and −0.261 e $Å^{-3}$. The weighting scheme applied was $w=1/[\sigma^2(F_o^2)+(0.0536P)^2+0.3678P]$, where $P=(F_o^2+2F_c^2)/3$. Hydrogen atomic positions were located in difference maps. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U(eq) value of the atom they were bonded.[16]

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16. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 691696. Copies of the data can be obtained, free of charge, on application to CCCD, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).