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Synthesis of Aryl- and Pyridinyl-substituted 2-Amino-6-thioxopyridine-3-carbonitrile Derivatives by Tandem *Michael* Addition and Cyclization Reactions

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Summary. The tandem *Michael* addition and cyclization of 2-, 3-, and (4-pyridinylcarbonyl) thioacetanilides with arylidenemalononitriles yielded polysubstituted pyridines and bipyridines. Tetrahydro-6-thioxopyridine-3-carbonitrile was dehydrogenated to its dihydro derivative by means of HgO or *DBU*. The reaction of enamines of 3-, and (4-pyridinylcarbonyl)thioacetanilides with malononitrile furnished 3,4′- and 4,4′-bipyridines.

Keywords. *Michael* addition; (Pyridinylcarbonyl)thioacetanilides; Enamines; Pyridines; Bipyridines.

Introduction

The chemistry of pyridine and oligopyridines has been the subject of increasing interest. The synthesis of polyfunctionalized pyridines is important because of their widespread occurrence in nature and biological activity [1–3]. The pyridine ring is a basic unit of numerous biological active alkaloids and pharmaceutical products [1, 4, 5]. Oligopyridines and their complexes with metal ions have been extensively studied because of their application in coordination and supramolecular chemistry [6]. For example, ligands bearing 2,2′-bipyridine are versatile building blocks for the construction of metallo-supramolecular systems [7]. Some bipyridine derivatives are applied in the area of catalysis [8], molecular electronics [9], photoactivated species [10], and as optoelectronic devices [11].

Continuing our study of the synthesis of potential biologically active compounds, we were interested in the construction of the pyridine skeleton using an efficient synthesis route. In previous experiments we synthesized polyfunctionalized

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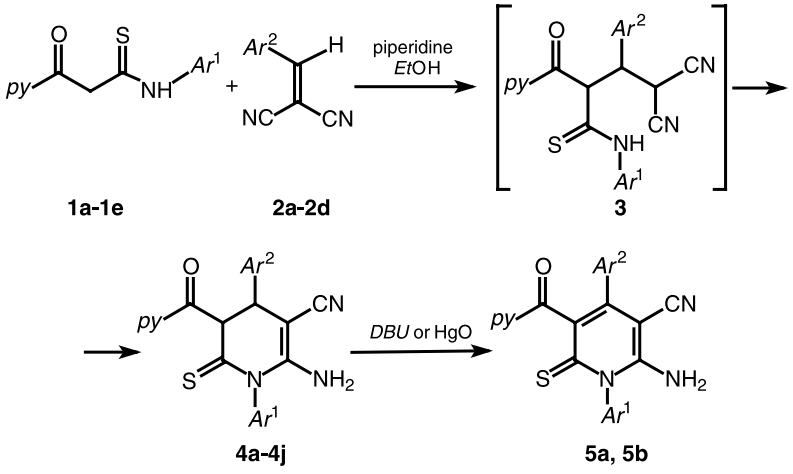
pyridines based on conjugate addition of (benzoyl)thioacetanilides [12], cyclic 3-oxoacid thioanilides [13, 14], and (2-thienylcarbonyl)thioacetanilides [15] to α,β-unsaturated nitriles. *Sharanin et al.* [16] and *Litvinov et al.* [17] applied a similar strategy for the synthesis of some natural oligopyridines, *e.g.* nicotelline, consisting in the addition of cyanothioacetamide to 1,3-dipyridin-3-yl-propene. In this paper we report an application of (pyridinylcarbonyl)thioacetanilides **1** and their enamine derivatives **8** in the synthesis of molecules containing two and three pyridine rings.

Results and Discussion

The reaction of (3-pyridinylcarbonyl)thioacetanilide (**1a**) with benzylidenemalononitrile (**2a**) carried out in ethanolic solution in the presence of piperidine yields **4a** (Scheme 1). The structure of **4a** was established on the basis of analytical and spectroscopic data. *E.g.* the IR spectrum revealed a carbonyl band at 1646 cm^{-1}, the band at 2187 cm^{-1} for the cyano group, and four bands in the range of 3376–3239 cm^{-1} for the amino group. In the ^1H NMR spectrum of **4a** two doublets at $\delta = 4.21$ ppm



				py	Ar^1	Ar^2				py	Ar^1	Ar^2
1a	**2a**	**4a**	**5a**	3-*py*	C_6H_5	C_6H_5	**1e**	**2a**	**4g**	4-*py*	C_6H_5	C_6H_5
1a	**2b**	**4b**		3-*py*	C_6H_5	4-Cl-C_6H_4	**1e**	**2b**	**4h**	4-*py*	C_6H_5	4-Cl-C_6H_4
1b	**2a**	**4c**		3-*py*	4-Cl-C_6H_4	C_6H_5	**1f**	**2a**	**4i**	4-*py*	4-Cl-C_6H_4	C_6H_5
1c	**2a**	**4d**		2-*py*	C_6H_5	C_6H_5	**1a**	**2c**	**4j**	3-*py*	C_6H_5	3-*py*
1c	**2b**	**4e**		2-*py*	C_6H_5	4-Cl-C_6H_4	**1e**	**2d**	**- 5b**	4-*py*	C_6H_5	4-*py*
1d	**2a**	**4f**		2-*py*	4-Cl-C_6H_4	C_6H_5						

Scheme 1

($J = 6.5$ Hz) and 5.70 ppm ($J = 6.5$ Hz) corresponding to two vicinal protons were observed. The protons of the amino group appeared as a broad signal at $\delta = 5.96$ ppm and the aromatic protons appeared in the range of 7.24–7.70 ppm. Protons of the 3-pyridinyl moiety resonated as a multiplet at $\delta = 8.39$ ppm, a doublet of doublet at $\delta = 8.80$ ppm ($J = 5.0$, 1.5 Hz), and a doublet at $\delta = 9.17$ ppm ($J = 2.0$ Hz). The 6-thioxopyridine structure of **4a** was confirmed by the ^{13}C NMR spectrum because it revealed a signal at $\delta = 199$ ppm assigned to the carbon atom of the C=S group and a signal at $\delta = 194$ ppm of the carbon atom of the C=O group.

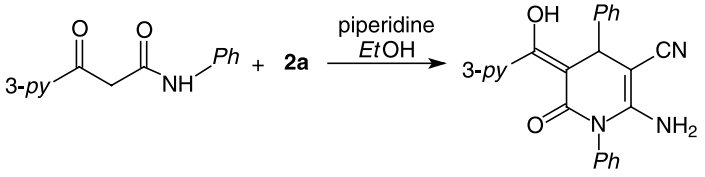
The reaction of **1b**–**1e** with **2a**–**2d** carried out under similar conditions afforded compounds **4b**–**4j** in good yields (44–65%). Their spectral features were similar to those of compound **4a**. Exceptionally the ^{1}H NMR spectrum of **4g** showed two singlets $\delta = 4.55$ and $\delta = 10.85$ ppm. The first one was assigned to the 4-CH proton of the formed pyridine ring, whereas the second one to the OH proton of enolic form of the pyridinylcarbonyl moiety.

The above reactions of **1** with **2** are assumed to proceed as a conjugate addition of the anion of the thioanilides **1** generated in basic medium to **2** involving the *Michael* adducts **3**, which underwent spontaneous cyclization to pyridine skeleton **4** (Scheme 1).

In order to prepare the target bipiridine molecules we used thioanilides **1a** and **1e** and 3- and 4-pyridinylidenemalononitriles **2c** and **2d**. The reaction of **1a** with **2c** carried out in ethanolic solution in the presence of piperidine yielded the 3,3′-bipyridine **4j** (Scheme 1). However, the product of the reaction of **1e** with **2d** possessing a 4-pyridinyl group underwent spontaneous dehydrogenation yielding **5b**. Its structure was confirmed by MS and its ^{1}H NMR spectrum showed signals only in the range of aromatic protons.

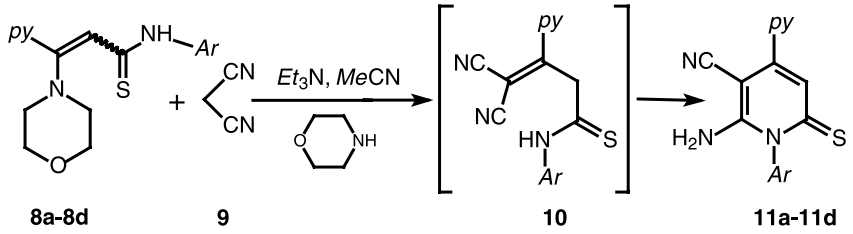
In the following experiments the reaction of **4** with HgO was studied. On the basis of previous findings [12] we expected the replacement of the sulfur atom of C=S group by oxygen as well as dehydrogenation of the tetrahydropyridine ring. However, the reaction of **4a** with HgO in glacial acetic acid afforded only the product of dehydrogenation, **5a** (Scheme 1). Its structure was consistent with analytical and spectral data. Using an excess of HgO in the reaction with **4a** led only to **5a**. Reaction of **4d** and **4g** with HgO in acetic acid gave a complex mixture difficult to separate. Compound **5a** was also obtained from **4a** in boiling ethanol in the presence of a catalytic amount of *DBU* (Scheme 1).

6-Oxopyridine **7a** was synthesized in the reaction of (3-pyridinylcarbonyl)acetanilide (**6a**) with **2a** in ethanol with a catalytic amount of piperidine. Compound **7a** was obtained as colourless prisms in 56% yield (Scheme 2). The analytical and



6a **7a**

Scheme 2



8a-8d **9** **10** **11a-11d**

		py	*Ar*			*py*	*Ar*
8a	**11a**	3-*py*	C_6H_5	**8c**	**11c**	4-*py*	C_6H_5
8b	**11b**	3-*py*	4-Cl-C_6H_4	**8d**	**11d**	4-*py*	4-Cl-C_6H_4

Scheme 3

spectroscopic data of **7a** were in agreement with the expected structure. The ^{1}H NMR spectrum suggested the enol form in *DMSO*-d_6 solution, because it exhibited a singlet at $\delta = 9.85$ ppm of the enol OH proton and the singlet of 4-CH at $\delta = 4.59$ ppm.

To synthesize functionalized bipyridines, we studied the reaction of (pyridinylcarbonyl)thioanilides **1** with malononitrile (**9**). Since compounds **1** were found to be nonreactive towards **9** we used the enamine procedure reported earlier [18]. It consisted in the reaction of appropriate enamines of 3-oxoacid thioanilides with **9**. Among the methods for the preparation of the enamines of 2-, 3-, and 4-acetylpyridine, only the reaction involving the morpholine-$TiCl_4$ complex proved to be effective [19, 20]. Morpholine enamines of 3- and (4-pyridinylcarbonyl)thioacetanilides **8a**–**8d** were obtained from the morpholine enamine of 3- and 4-acetylpyridine and arylisothiocyanates [21]. Reaction of morpholine enamine of 2-acetylpyridine and phenylisothiocyanate in chloroform solution gave a dark brown complex mixture difficult to separate. The reactions of **8a**–**8d** with **9** carried out in acetonitrile solution in the presence of a catalytic amount of triethylamine provided bipyridines **11a**–**11d** in good yields (Scheme 3).

Analytical and spectroscopic data of the bipyridines **11a**–**11d** were consistent with the proposed structure. The above reactions were assumed to proceed *via* a tandem *Michael* addition-elimination mechanism. The resulting intermediate **10** underwent *in situ* cyclization to the pyridine skeleton (Scheme 3).

In conclusion, we demonstrated an efficient synthesis route to polysubstituted pyridines using conjugated addition of 2-, 3-, (4-pyridinylcarbonyl)thioacetanilides to α,β-unsaturated nitriles. We showed that the reaction of the enamines of 3- and (4-pyridinylcarbonyl)thioacetanilides with malononitrile (**9**) leads to substituted bipyridines. Our investigations provide an entry into a variety of pyridine derivatives.

Experimental

Melting points were determined on a *Boetius* hot stage apparatus. IR spectra: Bruker IFS 48 in KBr pellets. NMR spectra: Bruker AMX 500 (^{1}H: 500.14 MHz, ^{13}C: 125.76 MHz) in *DMSO*-d_6 with

TMS as an internal standard. Mass spectra: Finningan Mat 95 (EI, 70 eV). Microanalyses were performed with a Euro EA 3000 Elemental Analyzer at the Department of Organic Chemistry of the Jagiellonian University; their results were found to be in good agreement (±0.2%) with the calculated values.

Compounds **1a**–**1e** were prepared from 2-, 3-, and 4-acetylpyridine and the appropriate arylisothiocyanates according to the procedure described in Ref. [19].

*General Procedure for the Preparation of **4a–4j***

An equimolar mixture of thioanilides **1a**–**1e** (5 mmol), arylidenemalononitriles **2a**–**2d** (5 mmol), and a catalytic amount of piperidine was heated under reflux in 50 cm^3 ethanol for 2 h. After cooling the precipitate was filtered off. Recrystallization from acetonitrile afforded yellow crystals.

2-Amino-1,4-diphenyl-5-(3-pyridinylcarbonyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**4a**, $C_{24}H_{18}N_4OS$)

Yellow needles; mp 248–250°C; yield 65%; IR (KBr): $\bar{\nu} = 3376$, 3239 (NH), 2187 (CN), 1646 (C=O) cm^{-1}; ^{1}H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 4.21$ (d, $J = 6.5$ Hz, H-4), 5.70 (m, $J = 6.5$ Hz, H-5) 5.96 (bs, NH_2), 7.24–7.70 (m, 10 CHarom, 1 CHpy), 8.39 (m, 1 CHpy), 8.80 (dd, $J = 5.0$, 1.5 Hz, 1 CHpy), 9.17 (d, $J = 2.0$ Hz, 1 CHpy), ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 59.3$ (C-4), 64.2 (C-5), 119.9 (CN), 122.7, 126.7, 127.4, 128.5, 128.9, 129.3, 129.9, 138.2, 138.6, 140.6, 149.5, 150.4, 152.7 (Carom), 194.5 (C=O), 199.6 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 410 (7) $[M]^{+\bullet}$, 304 (100), 106 (26).

2-Amino-4-(4-chlorophenyl)-1-phenyl-5-(3-pyridinylcarbonyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**4b**, $C_{24}H_{17}ClN_4OS$)

Yellow needles; mp 271–273°C; yield 58%; IR (KBr): $\bar{\nu} = 3318$, 3238, 3186 (NH), 2186 (CN), 1642 (C=O) cm^{-1}; ^{1}H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 4.27$ (d, $J = 7.1$ Hz, H-4), 5.71 (d, $J = 7.1$ Hz, H-5), 6.01 (bs, NH_2), 7.27–7.60 (m, 9 CHarom), 8.38 (m, 1 CHpy), 8.81 (m, 1 CHpy), 8.88 (m, 1 CHpy) 9.18 (m, 1 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 58.9$ (C-4), 69.9 (C-5), 119.5 (CN), 123.6, 128.1, 128.7, 128.9, 129.1, 130.0, 132.4, 135.9, 137.4, 139.7, 149.4, 150.1, 152.6 (Carom), 194.3 (C=O), 200.0 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 446 (8) $[M+2]^{+\bullet}$, 444 (30) $[M]^{+\bullet}$, 413 (35), 334 (100), 106 (60).

2-Amino-1-(4-chlorophenyl)-4-phenyl-5-(3-pyridinylcarbonyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**4c**, $C_{24}H_{17}ClN_4OS$)

Yellow needles; mp 273–275°C; yield 49%; IR (KBr): $\bar{\nu} = 3386$, 3293, 3156 (NH), 2184 (CN), 1649 (C=O) cm^{-1}; ^{1}H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 4.20$ (d, $J = 6.8$ Hz, H-4), 5.68 (d, $J = 6.8$ Hz, H-5), 6.17 (bs, NH_2), 7.25–7.65 (m, 9 CHarom), 8.37 (m, 1 CHpy), 8.80 (m, 1 CHpy), 8.95 (m, 1 CHpy) 9.17 (m, 1 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 61.5$ (C-4), 69.9 (C-5), 119.5 (CN), 123.6, 127.4, 128.1, 128.7, 129.0, 130.0, 131.1, 135.9, 137.3, 139.7, 148.7, 149.4, 150.1, 152.6 (Carom), 194.3 (C=O), 200.0 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 446 (10) $[M+2]^{+\bullet}$, 444 (35) $[M]^{+\bullet}$, 338 (100), 106 (15).

2-Amino-1,4-diphenyl-5-(2-pyridinylcarbonyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**4d**, $C_{24}H_{18}N_4OS$)

Yellow needles; mp 178–180°C; yield 44%; IR (KBr): $\bar{\nu} = 3461$, 3365 (NH), 2187 (CN), 1641 (C=O) cm^{-1}; ^{1}H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 4.18$ (d, $J = 3.2$ Hz H-4), 6.04 (m, 3H, H-5, NH_2), 7.32–7.59 (m, 10 CHarom), 7.78 (m, 1 CHpy), 8.12 (m, 2 CHpy), 8.90 (m, 1 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 59.3$ (C-4), 64.2(C-5), 119.9 (CN), 122.7, 126.7, 127.4, 128.5, 128.9, 129.3, 129.9, 138.2, 138.6, 140.6, 149.5, 150.4, 152.7 (Carom, C=C), 194.5 (C=O), 199.3 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 410 (20) $[M]^{+\bullet}$, 304 (68), 106 (10), 78 (100).

2-Amino-4-(4-chlorophenyl)-1-phenyl-5-(2-pirydinylcarbonyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**4e**, $C_{24}H_{17}ClN_4OS$)
Yellow needles; mp 208–210°C; yield 58%; IR (KBr): $\bar{\nu} = 3466$, 3369 (NH), 2185 (CN), 1637 (C=O) cm^{-1}; ^1H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 4.24$ (d, $J = 3.7$ Hz, H-4), 5.99 (d, $J = 3.7$ Hz, H-5), 6.10 (bs, NH_2), 7.24 (d, 2 CHarom), 7.34–7.78 (m, 7 CHarom), 7.88 (m, 1 CHpy), 8.11 (m, 2 CHpy), 8.88 (m, 1 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 58.9$ (C-4), 69.9 (C-5), 119.7 (CN), 122.7, 128.5, 128.7, 128.9, 129.3, 129.9, 131.9, 138.2, 138.5, 139.6, 149.5, 150.4, 152.8 (Carom, C=C), 194.3 (C=O), 199.5 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 444 (5) $[M]^{+\bullet}$, 338 (10), 106 (8), 78 (100).

2-Amino-4-(1-chlorophenyl)-4-phenyl-5-(2-pyridinylcarbonyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**4f**, $C_{24}H_{17}ClN_4OS$)
Yellow needles; mp 212–214°C; yield 53%; IR (KBr): $\bar{\nu} = 3432$, 3311 (NH), 2191 (CN), 1697 (C=O) cm^{-1}; ^1H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 4.18$ (d, $J = 3.0$ Hz, H-4), 6.02 (d, $J = 3.0$ Hz, H-5), 6.27 (bs, NH_2), 7.31–7.62 (m, 9 CHarom, 1 CHpy) 8.11 (m, 2 CHpy), 8.89 (m, 1 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 59.6$ (C-4), 64.7 (C-5), 120.4 (CN), 123.3, 127.3, 127.9, 129.1, 129.5, 130.6, 134.4, 138.0, 138.8, 141.2, 150.1, 150.9, 153.1 (Carom, C=C), 195.0 (C=O), 200.6 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 444 (2) $[M]^{+\bullet}$, 411 (3), 338 (100), 106 (11).

2-Amino-1,4-diphenyl-5-(4-pyridinylcarbonyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**4g**, $C_{24}H_{18}N_4OS$)
Yellow needles; mp 163–165°C; yield 65%; IR (KBr): $\bar{\nu} = 3437$, 3249 (NH), 2189 (CN), 1692 (C=O) cm^{-1}; ^1H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 4.55$ (s, CH), 6.98–7.09 (m, 3 CHarom, NH_2) 7.23–7.37 (m, 7 CHarom, 2 CHpy), 8.49 (dd, $J = 4.4$, 1.4 Hz, 2 CHpy), 10.85 (s, OH enol) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 110.2$ (C-5), 119.9 (CN), 121.4, 122.1, 124.9, 127.1, 127.0, 128.3, 128.8, 129.0, 129.6, 139.8 (Carom), 143.1 (C=C), 147.7, 149.9, 153.3, 154.5 (Carom) 190.8 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 410 (9) $[M]^{+\bullet}$, 338 (8), 304 (100).

2-Amino-4-(4-chlorophenyl)-1-phenyl-5-(4-pyridinylcarbonyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**4h**, $C_{24}H_{17}ClN_4OS$)
Yellow needles; mp 248–250°C; yield 64%; IR (KBr): $\bar{\nu} = 3428$, 3287 (NH), 2181 (CN), 1679 (C=O) cm^{-1}; ^1H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 4.26$ (d, $J = 7.2$ Hz H-4), 5.72 (d, $J = 7.2$ Hz, H-5), 6.07 (bs, NH_2), 7.28–7.73 (m, 9 CHarom), 7.91 (dd, $J = 4.6$, 1.4 Hz, 2 CHpy), 8.82 (dd, $J = 4.6$, 1.4 Hz, 2 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 61.8$ (C-4), 69.6 (C-5), 116.3 (CN), 122.1, 128.4, 128.9, 129.0, 130.3, 131.0, 133.8, 137.5, 138.5, 139.6, 148.2, 151.1, 152.8 (Carom, C=C), 195.5 (C=O), 200.0 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 444 (16) $[M]^{+\bullet}$, 413 (100), 338 (42), 337 (99), 106 (13).

2-Amino-4-(1-chlorophenyl)-1-phenyl-5-(4-pyridinylcarbonyl)-6-thioxo-1,4,5,6-tetrahydropyridine-3-carbonitrile (**4i**, $C_{24}H_{17}ClN_4OS$)
Yellow needles; mp 244–246°C; yield 58%; IR (KBr): $\bar{\nu} = 3310$, 3246 (NH), 2190 (CN), 1642 (C=O) cm^{-1}; ^1H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 4.19$ (d, $J = 7.0$ Hz, H-4), 5.68 (d, $J = 7.0$ Hz, H-5), 6.21 (bs, NH_2), 7.26–7.61 (m, 9 CHarom), 7.89 (d, $J = 4.7$ Hz, 2 CHpy), 8.82 (d, $J = 4.7$ Hz, 2 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 61.9$ (C-4), 64.3 (C-5), 119.9 (CN), 121.9, 128.0, 129.3, 130.6, 131.1, 131.2, 134.4, 137.8, 140.0, 142.3, 151.4, 152.7 (Carom, C=C), 195.5 (C=O), 200.4 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 444 (12) $[M]^{+\bullet}$, 338 (21), 106 (100).

2′-Amino-1′-phenyl-5′-(3-pyridinylcarbonyl)-6′-thioxo-1′,4′,5′,6′-tetrahydro-3,4′-bipyridine-3′-carbonitrile (**4j**, $C_{23}H_{17}N_5OS$)
Yellow needles; mp 274–276°C; yield 59%; IR (KBr): $\bar{\nu} = 3367$, 3274 (NH), 2180 (CN), 1666 (C=O) cm^{-1}; ^1H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 4.36$ (d, $J = 7.7$ Hz, H-4), 5.81 (d, $J = 7.7$ Hz, H-5), 6.06

(bs, NH_2), 7.37–7.58 (m, 5 CHarom, 2 CHpy), 7.84 (dt, $J = 8.0$, 2.9 Hz 1 CHpy), 8.38 (dt, $J = 8.0$, 2.9 Hz 1 CHpy), 8.46 (m, 1 CHpy) 8.63 (d, $J = 2.2$ Hz, 1 CHpy), 8.78 (dd, $J = 4.6$, 1.6 Hz, 1 CHpy), 9.18 (d, $J = 2.2$ Hz, 1 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 61.8$ (C-4′), 63.4 (C-5′), 119.9 (CN), 123,6 124.8, 128.8, 129.3, 129.2, 131.0, 131.2, 133.0, 137.6, 150.6, 153.3, 156.4 (Carom, C=C), 194.7 (C=O), 200.2 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 409 (48) $[M]^{+\bullet}$, 380 (100), 331 (7), 106 (11).

2-Amino-1,4-diphenyl-5-(3-pyridinylcarbonyl)-6-thioxo-1,6-dihydropyridine-3-carbonitrile (**5a**, $C_{24}H_{16}N_4OS$)

To 1.0 g **4a** (2.5 mmol) dissolved in 50 cm^3 boiling glacial acetic acid 0.54 g HgO (2.5 mmol) were added in small portions. The reaction mixture was refluxed for 4 h. After cooling the precipitate was filtered off. Recrystallization from acetonitrile afforded 0.66 g (65%) **5a**. Compound **5a** was also obtained by refluxing of 1.0 g **4a** (2.5 mmol) in 30 cm^3 CH_3CN with a catalytic amount *DBU* (yield 49%). Yellow needles; mp 360–362°C; IR (KBr): $\bar{\nu} = 3360$, 3334 (NH), 2189 (CN), 1678 (C=O) cm^{-1}; ^{1}H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 7.25$ (bs, NH_2), 7.33–7.61 (m, 10 CHarom, 1 CHpy), 8.12 (m, 1 CHpy), 8.64 (dd, $J = 4.8$, 1.75 Hz, 1 CHpy), 8.95 (d, $J = 1.75$ Hz, 1 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 119.9$ (CN), 124.2, 128.7, 128.9, 129.5, 130.2, 130.9, 133.0, 135.0, 136.4, 137.8, 148.9, 150.6, 153.7, 156.4 (Carom), 179.1 (C=O), 191.2 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 408 (54) $[M]^{+\bullet}$, 379 (100), 106 (90).

2-Amino-1-phenyl-5-(4-pyridinylcarbonyl)-6-thioxo-1,6-dihydro-4,4′-bipyridine-3-carbonitrile (**5b**, $C_{23}H_{15}N_5OS$)

A mixture 1.4 g thioanilide **1e** (5 mmol), 0.8 g **2d** (5 mmol), and a catalytic amount of piperidine was refluxed in 50 cm^3 ethanol for 2 h. After cooling the precipitate was filtered off. Recrystallization from acetonitrile afforded 1.1 g (54%) **5b**. Yellow needles; mp 368–370°C; IR (KBr): $\bar{\nu} = 3210$, 3146 (NH), 2198 (CN), 1676 (C=O) cm^{-1}; ^{1}H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 7.28$ (d, $J = 5.5$ Hz, 2 CHarom) 7.38 (d, $J = 8.0$ Hz, 2 CHarom), 7.53 (t, $J = 7.4$ Hz, 1 CHarom), 7.60 (m, NH_2, 2 CHpy), 7.75 (dd, $J = 4.4$, 1.6 Hz, 2 CHpy), 8.58 (d, $J = 5.5$ Hz, 2 CHpy), 8.68 (dd, $J = 4.4$, 1.6 Hz, 2 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 80.9$ (C-4), 115.9 (C-5), 122.1 (CN), 123.0, 127.9, 128.8, 130.3, 137.4, 142.9, 143.8, 150.2, 151.1, 156.5 (Carom, C=C), 179.6 (C=O), 191.1 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 409 (41) $[M]^{+\bullet}$, 381 (24), 380 (100), 106 (3).

2-Amino-5-(hydroxypyridin-3-ylmethylene)-6-oxo-1,4-diphenyl-1,4,5,6-tetrahydropyridine-3-carbonitrile (**7a**, $C_{24}H_{18}N_4O_2$)

Compound **7a** was obtained in a similar way as **4a**–**4j** from 1.28 g anilide **6a** (5 mmol) and 0.77 g benzylidenemalononitrile (**2a**, 5 mmol). Recrystallization from CH_3CN afforded 1.10 g **7a** as colourless prisms. Mp 238–240°C; yield 56%; IR (KBr): $\bar{\nu} = 3361$, 3336 (NH) 3138 (OH), 2190 (CN), 1678 (C=O) cm^{-1}; ^{1}H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 4.59$ (s, CH), 6.99–7.43 (m, 10 CHarom, 1 CHpy, NH_2), 7.90 (dt, $J = 8.0$, 1.8 Hz, 1 CHpy), 8.56 (dd, $J = 4.8$, 1.6 Hz, 1 CHpy), 8.73 (d, $J = 1.4$ Hz, 1 CHpy) 9.85 (s, OH enol) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 114.7$ (C-5), 119.6 (CN), 123.0, 123.7, 127.0, 127.7, 128.3, 128.6, 135.2, 138.1, 144.5 (Carom), 148.2 (C=C), 150.3, 159.4, 153.3 (Carom), 193.4 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 395 (3) $[M]^{+\bullet}$, 233 (90), 105 (50), 93 (100).

General Procedure for the Synthesis of Enamines of Pyridinylcarbonyl (thioacetanilides) ***8a–8d***

Compounds **8a**–**8d** were prepared from morpholine enamines of 3- and 4-acetylpyridine [20, 21] and the appropriate arylisothiocyanates according to the procedure described previously in Ref. [22]. Recrystallization from *Me*OH afforded yellow prisms.

3-(4-Morpholinyl)-N-phenyl-3-(3-pyridinyl)-2-propenethioamide (**8a**, $C_{18}H_{19}N_3OS$)
Yellow crystals; mp 170–173°C; yield 64%; IR (KBr): $\bar{\nu} = 3172–3116$ (NH), 1577 (C=C) cm^{-1}; ^1H NMR (500.14 MHz, $CDCl_3$): $\delta = 2.94$ (t, $J = 4.6$ Hz, 2 NCH_2), 3.73 (t, $J = 4.6$ Hz, 2 OCH_2), 5.77 (s, =CH), 7.02–7.24 (m, 5 CHarom, 3 CHpy), 8.14 (bs, NH), 8.63 (d, $J = 2.2$ Hz, 1 CHpy), ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 48.9$ (NCH_2), 66.4 (OCH_2), 123.0, 123.6, 126.1, 128.8, 130.9, 137.3, 138.8, 150.2, 150.6 (Carom, C=C), 194.1 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 325 (18) $[M]^{+\bullet}$, 292 (100) 189 (18).

N-(4-Chlorophenyl)-3-(4-morpholinyl)-3-(3-pyridinyl)-propenethioamide
(**8b**, $C_{18}H_{18}ClN_3OS$)
Yellow crystals; mp 190–192°C; yield 73%; IR (KBr): $\bar{\nu} = 3453$, 3230–3157 (NH), 1576 (C=C) cm^{-1}; ^1H NMR (500.14 MHz, $CDCl_3$): $\delta = 2.95$ (t, $J = 4.4$ Hz, 2 NCH_2), 3.66 (t, $J = 4.4$ Hz, 2 OCH_2), 5.78 (s, =CH), 7.23–7.38 (m, 4 CHarom, 3 CHpy), 8.35 (s, NH), 8.40 (d, $J = 3.7$ Hz, 1 CHpy) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 49.1$ (NCH_2), 66.2 (OCH_2), 123.3, 123.7 125.3, 128.6, 131.6, 137.6, 140.4, 150.4 (Carom, C=C), 194.1 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 359 (17) $[M]^{+\bullet}$, 326 (100), 217 (75), 189 (38), 169 (28).

3-(4-Morpholinyl)-N-phenyl-3-(4-pyridinyl)-propenethioamide (**8c**, $C_{18}H_{19}N_3OS$)
Yellow crystals; mp 177–179°C; yield 67%; IR (KBr): $\bar{\nu} = 3437$, 3159–3113 (NH), 1567 (C=C) cm^{-1}; ^1H NMR (500.14 MHz, $CDCl_3$): $\delta = 3.08$ (t, $J = 4.7$ Hz, 2 NCH_2), 3.83 (t, $J = 4.7$ Hz, 2 OCH_2), 5.93 (s, =CH), 7.18–7.41 (m, 5 CHarom, 2 CHpy), 8.37 (s, NH), 8.73 (d, $J = 4.6$ Hz, 2 CHpy) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 48.8$ (NCH_2), 66.3 (OCH_2), 122.7, 124.0, 126.0, 128.8, 138.7, 143.0, 150.5 (Carom, C=C), 194.8 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 325 (15) $[M]^{+\bullet}$, 292 (100).

N-(4-Chlorophenyl)-3-(4-morpholinyl)-3-(4-pyridinyl)propenethioamid (**8d**, $C_{18}H_{18}ClN_3OS$)
Yellow crystals; mp 202–204°C; yield 74%; IR (KBr): $\bar{\nu} = 3438$, 3141–3051 (NH), 1579 (C=C) cm^{-1}; ^1H NMR (500.14 MHz, $CDCl_3$): $\delta = 3.00$ (t, $J = 4.6$ Hz, 2 NCH_2), 3.74 (t, $J = 4.60$ Hz, 2 OCH_2), 5.85 (s, =CH), 7.04 (d, $J = 8.6$ Hz, 2 CHarom), 7.20 (d, $J = 8.6$ Hz, 2 CHarom), 7.33 (d, $J = 5.3$ Hz, 2 CHpy), 7.95 (s, NH), 8.68 (d, $J = 5.3$ Hz, 2 CHpy) ppm; ^{13}C NMR (125.76 MHz, $CDCl_3$): $\delta = 48.8$ (NCH_2), 66.3 (OCH_2), 123.8, 123.9, 128.9, 129.5, 139.1, 145.2, 151.4 (Carom, C=C), 194.2 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 359 (12) $[M]^{+\bullet}$, 326 (86), 189 (100).

*General Procedure for the Preparation of Bipyridines **11a–11d***
A mixture of enaminothioanilide **8a–8d** (5 mmol), malonodinitrile **9** (0.05 g, 7.5 mmol), and a catalytic amount of triethylamine was heated under reflux in 50 cm^3 acetonitrile for 2 h. After cooling the orange precipitate was filtered off. Compounds **11a–11c** were purified by crystallization from CH_3CN.

2′-Amino-1′-phenyl-6′-thioxo-1′,6′-dihydro-3,4′-bipyridine-3′-carbonitrile (**11a**, $C_{17}H_{12}N_4S$)
Orange crystals; mp 322–325°C; yield 68%; IR (KBr): $\bar{\nu} = 3344–3292$ (NH), 2206 (CN) cm^{-1}; ^1H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 6.03$ (s, H-5′), 7.20 (bs, NH_2), 7.29 (d, $J = 7.2$ Hz, 2 CHarom), 7.45–7.62 (m, 3 CHarom, 2 CHpy) 8.72 (dd, $J = 4.8$, 1.4 Hz, 1 CHpy), 8.80 (d, $J = 2.2$ Hz, 1 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 78.1$ (C-3′), 116.9 (CN), 120.9 (C-5′), 124.0, 130.8, 131.1, 132.5, 134.6, 136.1, 137.7, 145.6, 148.5, 151.1 (Carom), 156.9 (C-2′), 182.7 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 304 (100) $[M]^{+\bullet}$, 303 (97).

2′-Amino-1′-(4-chlorophenyl)-6′-thioxo-1′,6′-dihydro-3,4′-bipyridine-3′-carbonitrile
(**11b**, $C_{17}H_{11}ClN_4S$)
Orange crystals; mp 335–337°C; yield 64%; IR (KBr): $\bar{\nu} = 3374–3284$ (NH), 2205 (CN) cm^{-1}; ^1H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 6.88$ (s, H-5′), 7.33 (dd, $J = 8.6$, 2.5 Hz, 2 CHarom), 7.44 (bs, NH_2), 7.57 (dd, $J = 7.8$, 4.8 Hz, 1 CHpy), 7.64 (dd, $J = 8.6$, 2.5 Hz, 2 CHarom), 8.04 (dd, $J = 7.8$, 2.5 Hz, 1 CHpy), 8.72 (dd, $J = 4.8$, 1.6 Hz, 1 CHpy), 8.79 (dd, $J = 2.3$, 0.7 Hz, 1 CHpy) ppm; ^{13}C NMR

(125.76 MHz, *DMSO*-d_6): $\delta = 77.6$ (C-3′), 116.4 (CN), 120.4 (C-5′), 123.5, 130.3, 130.6, 131.9, 134.1, 135.5, 137.2 45.1, 147.1, 150.5 (Carom), 156.5 (C-2′), 182.2 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 341 (8) $[M+2]^{+\bullet}$, 338 (24) $[M]^{+\bullet}$, 334 (25), 168 (100).

2-Amino-1-phenyl-6-thioxo-1,6-dihydro-4,4′-bipyridine-3-carbonitrile (**11c**, $C_{17}H_{12}N_4S$)
Orange crystals; mp 272–274°C; yield 67%; IR (KBr): $\bar{\nu} = 3344$–3292 (NH), 2206 (CN) cm^{-1}; ^1H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 6.02$ (s, H-5), 6.88 (dd, $J = 8.3$, 1.2 Hz, 2 CHarom), 7.13 (t, $J = 7.6$ Hz, 1 CHarom), 7.41 (dd, $J = 8.3$, 7.6 Hz, 2 CHarom), 7.51 (dd, $J = 4.4$, 1.6 Hz, 2 CHpy), 8.33 (bs, NH_2), 8.68 (dd, $J = 4.4$, 1.6 Hz, 2 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 74.15$ (C-3), 116.2 (CN), 119.3 (C-5), 122.4, 124.3, 129.8, 146.1, 145.6, 146.3, 149.7, 151.5 (Carom), 163.3 (C-2), 183.3 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 304 (22) $[M]^{+\bullet}$, 201 (100).

2-Amino-1-(4-chlorophenyl)-6-thioxo-1,6-dihydro-4,4′-bipyridine-3-carbonitrile
(**11d**, $C_{17}H_{11}ClN_4S$)
Orange crystals; mp 293–295°C; yield 61%; IR (KBr): $\bar{\nu} = 3423$–3324 (NH), 2200 (CN) cm^{-1}; ^1H NMR (500.14 MHz, *DMSO*-d_6): $\delta = 6.03$ (s, H-5) 6.91 (m, 2 CHarom), 7.48 (m, 2 CHarom, 2 CHpy), 8.42 (bs, NH_2), 8.69 (dd, $J = 4.4$, 1.8 Hz, 2 CHpy) ppm; ^{13}C NMR (125.76 MHz, *DMSO*-d_6): $\delta = 74.15$ (C-3′), 116.2 (CN), 119.3 (C-5′), 122.4, 124.3, 129.8, 146.1, 145.6, 146.3, 149.7 151.5 (Carom), 163.3 (C-2′), 182.7 (C=S) ppm; MS (EI, 70 eV): m/z (%) = 341 (6) $[M+2]^{+\bullet}$, 338 (18) $[M]^{+\bullet}$, 168 (100).

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