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MICROWAVE-ASSISTED SYNTHESIS OF 3-METHYLISOTHIAZOLO[5,4-*b*]PYRIDINE AND VARIOUS 2-AMINO DERIVATIVES OF THIENO[2,3-*b*]PYRIDINE AND 1-(2-AMINOPYRIDIN-3-YL)ETHANONE

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Abstract – Various 2-amino derivatives of thieno[2,3-*b*]pyridin-2-amine (**3a-g**) were prepared in fair to good yields (30-76%) by subjecting 1-(2-chloro-pyridin-3-yl)ethanone (**1**) and appropriate primary amine (**2a-g**) to microwave heating at 90-120 ˚C for 15-20 min in the presence of elemental sulfur, NaOAc, and DMF. Lower yields (4-15%) of the secondary 2-amino derivatives of 1-(pyridin-3-yl)ethanone product (**4a-g**) were also obtained. However, when the microwave-assisted reactions were carried out on primary (**2b-h**) and secondary amines (**2i-o**) in the absence of elemental S at 100-200 ˚C for 15-20 min, the respective secondary 2-amines (**4b-h**) and tertiary 2-amines (**4i-o**) of 1-(pyridin-3-yl)ethanones were obtained in good to excellent yields (61-98%). Finally, when **1** subjected to microwave heating at 120 ˚C for 15 min in the presence of elemental sulfur, NH_4Cl, NaOAc, and DMF, 3-methyl-isothiazolo[5,4-*b*]pyridine (**5**) was obtained in 79% yield. Possible mechanisms for the formation of compounds **3-5** are presented.

INTRODUCTION

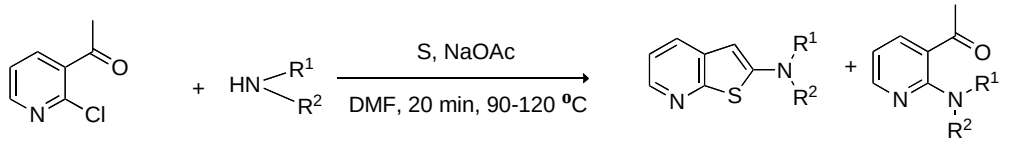
During the course of our investigation of microwave-assisted synthesis of heterocycles,[1] we prepared several 2-amino-5-nitrobenzo[*b*]thiophenes in good to excellent yields by subjecting 1-(2-chloro-5-nitrophenyl)ethanone to microwave heating for 10 min at 90 ˚C in the presence of a mixture of elemental sulfur, a primary amine, NaOAc and DMF.[2] In addition, minor amounts of

2-amino-5-(nitrophenyl)ethanones were obtained. We proposed two parallel S_NAr pathways in which the key step in the synthesis of 2-aminothiophenes involved the intramolecular addition of a thioamine anion to the 2-chloro atom of the benzo ring to give a Meisenheimer complex in which the resulting negative charge is stabilized by the 5-nitro group by resonance. On the other hand, we suggested that the key step in the formation of the 2-aminoethanones involved the intermolecular addition of a primary amine to the same 2-chloro substituted atom to give another Meisenheimer complex in which the negative charge is stabilized by electronic delocalization into the 5-nitro and ethanone carbonyl groups. These complexes then collapsed to the respective products. Support for the former mechanism was obtained by demonstrating that 2-chlorophenylethanone (lacking a 5-nitro group) failed to react under these conditions. Support for the latter mechanism was obtained when the reaction of 2-chloro-5-(nitrophenyl)ethanone was carried in the absence of elemental sulfur, gave amino ethanones in excellent yields.

To extend the scope of this reaction, the microwave-assisted reaction of 1-(2-chloropyridin-3-yl)ethanone (**1**) with various amines (**2**) was studied. Since the pyridine ring is an electron deficient ring and is known to undergo S_NAr reactions, similar products should be obtained. We report herein that the expected products were indeed obtained.

RESULTS AND DISCUSSION

We first established microwave conditions that gave maximum yields of *N*-substituted 2-aminopyrido[*b*]-thiophenes (**3a-g**) from the reaction of 1-(2-chloropyridin-3-yl)ethanone (**1**) with primary amines (**2a-g**). After much experimentation in which microwave temperatures and heating times and solvents were varied, optimum yields of **3a-g** were obtained when elemental sulfur, primary amines (**2a-g**) and NaOAc were heated with microwave radiation for 15-20 min at 90-120 ˚C in DMF (see Scheme 1).



Scheme 1

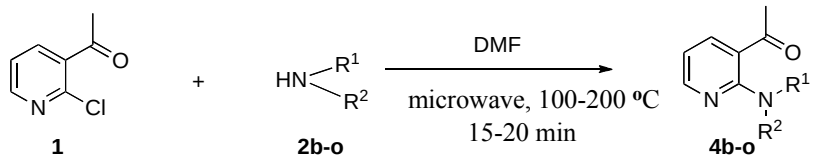
As shown in Table 1, compounds **3a-g** were formed in 30-76% yields. In addition, *N*-substituted 2-amino derivatives of 1-(pyridin-3-yl)ethanone (**4a-g**) were obtained, albeit in significantly lower yields (5-15%). Interestingly, the reaction of **1** with secondary amines (**2i-o**) gave predominately waxy materials that could be neither separated nor identified. However, minor amounts (5-10%) of **4i-o** were obtained. We are currently attempting to identify the waxy materials.

As shown in Scheme 2 and Table 2, we next carried out reactions of **1** with both primary (**2b-h**) and secondary amines (**2i-o**) in the absence of elemental sulfur and NaOAc, and obtained the corresponding *N*-substituted (**4b-h**) and *N,N*-disubstituted (**4i-o**) ethanones in 61-80% and 65-98% yields, respectively.

Table 1. Synthesis of **3a-g** and **4a-g**

entry	R^1	R^2	ratio amine/S/base	temp (°C)	time (min)	**3** yield, (%)	**4** yield, (%)
3a, 4a	Me[a]	H	3/5/3	100	20	30	5
3b, 4b	allyl	H	2/5/0	90	15	66	10
3c, 4c	*i*-Pr	H	3/5/0	90	15	54	8
3d, 4d	Bu	H	3.5/5/2	100	20	49	12
3e, 4e	Bn	H	3.5/5/0	120	15	74	10
3f, 4f	cyclopentyl	H	3/5/0	100	20	73	15
3g, 4g	cyclohexyl	H	3/5/0	100	20	76	10

[a]Used as the hydrochloride salt.



Scheme 2

Also shown in Table 2, the yields of **4k** and **4l** were slightly increased from 75 to 85% and 81 to 87%, respectively when the 2-fluoro derivative of **1** was used. This is indicative of S_NAr pathway vide infra. Given the exorbitant cost of the 2-fluoro derivative, we were unable to carry out further reactions on the 2-fluoro derivative. We previously reported that 2-chloro-5-(nitrophenyl)ethanone when treated with NH_4Cl, elemental sulfur and NaOAc in DMF gave 3-methylbenzo[*b*]isothiazole in 90% yield.[3] Consequently, we carried the reaction with **1** under similar conditions and obtained 3-methyl-isothiazolo[5,4-*b*]pyridine (**5**) in 79% yield (see Scheme 3).

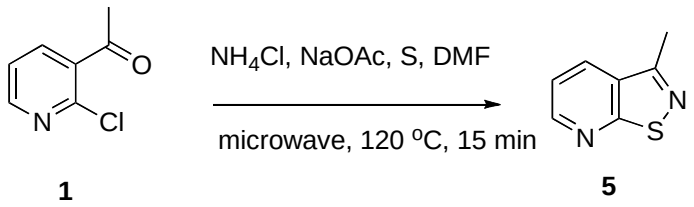
To confirm that the amino group occupied the 2-position in the thiophene ring in **3,** 1D NOE, HBMC, and HMQC NMR techniques were carried out. A correlation was found between the H-3 proton on the thiophene ring and the 4-H proton on the pyridine ring. In addition, the chemical shifts of the H-3 proton in the 2-amino derivatives of **3** were in the range of 5.97-6.1, which is considerably upfield from those reported (8.41-8.43) for H-2 protons in the 3-amino derivatives of thieno[2,3-*b*]pyridine.[4] The structures of **4** were readily confirmed by ^{1}H NMR and ^{13}C NMR.

Possible mechanisms for the formation of compounds **3-5** are shown in Schemes 4 and 5. Thus, two competing parallel pathways are proposed for the synthesis of **3** and **4** in Scheme 4. In the former, ethanone **1** is converted to enamine **6** (the first step of the Willgerodt-Kindler (W-K) mechanism)[5] which reacts with elemental sulfur to give the thioamide **7.** The mechanism for conversion of **6** to **7** is not shown due to conflicting explanations in the literature. Then **7**, with assistance from the lone pair on the amine

Table 2. Synthesis of **4b-o**

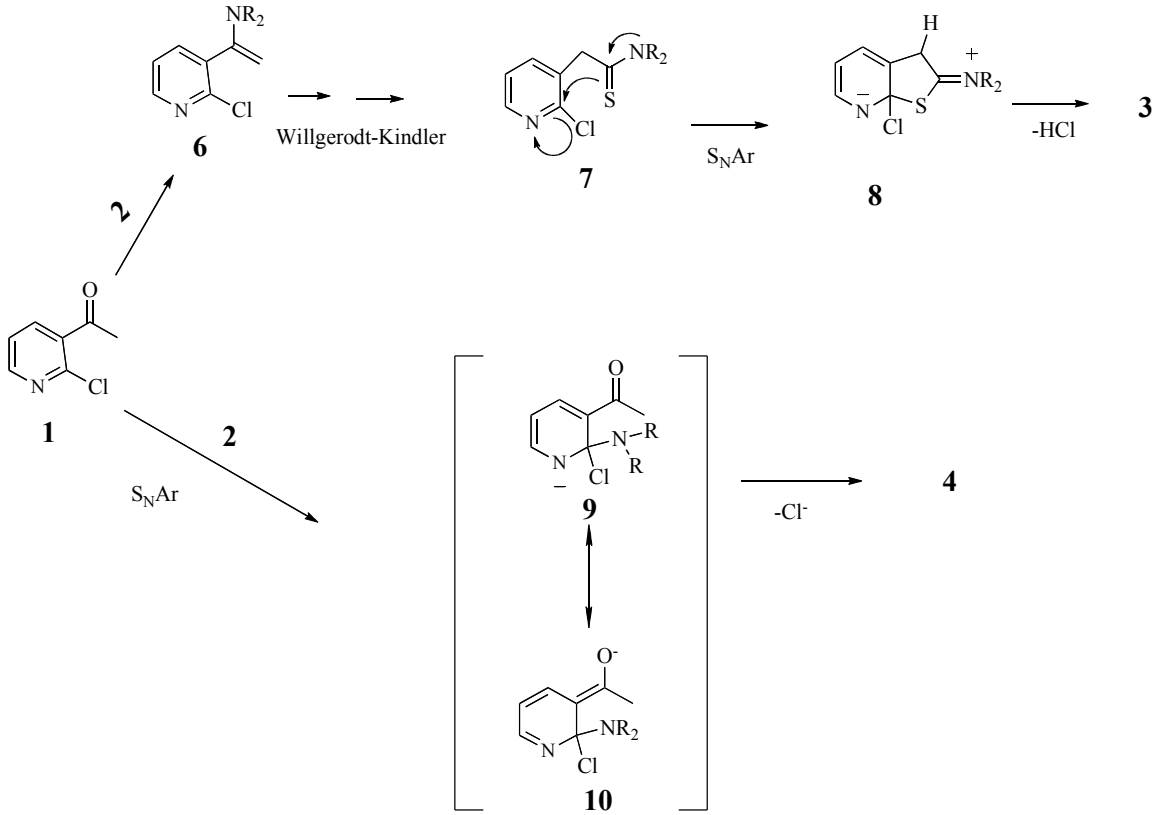
entry	R^1	R^2	temp (°C)	time (min)	yield, (%)
4b	allyl	H	120	20	78
4c	*i*-Pr	H	100	20	65
4d	Bu	H	120	15	62
4e	Bn	H	200	20	85
4f	cyclopentyl	H	150	15	79
4g	cyclohexyl	H	150	15	80
4h	*t*-Bu	H	100	15	61
4i	Me[a]	Me	100	20	65
4j	$-CH_2CH_3$	$-CH_2CH_3$	120	20	71
4k	$-(CH_2)_4-$	-	200	15	75 (85)[b]
4l	$-(CH_2)_5-$	-	200	15	81 (87)[b]
4m	$-CH_2CH_2OCH_2CH_2)-$	-	200	15	79
4n	$-(CH_2CH_2N(Me)CH_2CH_2)-$	-	200	15	89
4o	$-(CH_2CH_2CH(Bn)CH_2CH_2)-$	-	200	15	98

[a]used as the hydrochloride salt. [b]yield using 2-fluoro derivative of **1**.

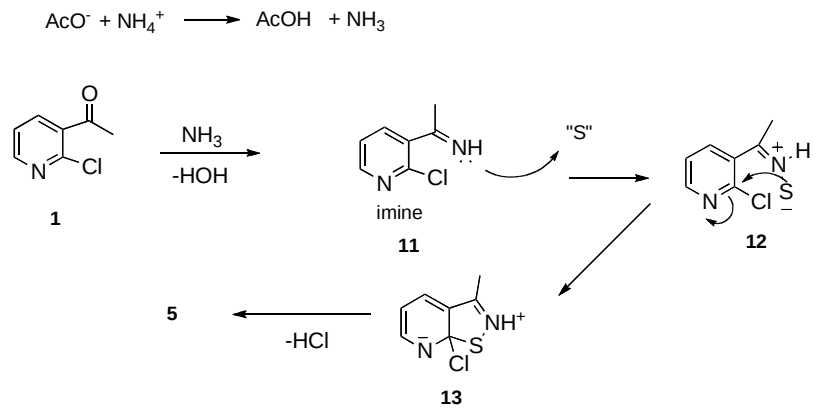


Scheme 3

nitrogen, adds intramolecularly to the 2-position of the pyridine ring to give the Meisenheimer complex[6] in which the negative charge is stabilized by the electronegative nitrogen atom on the pyridine ring. Complex **8** then aromatizes to product **3** with the loss of HCl. On the other hand, **1** undergoes intermolecular addition by amine **2** *via* a typical S_NAr pathway to give Meisenheimer complex in which the negative charge is stabilized by the pyridine nitrogen (**9**) and the carbonyl group of the ethanone moiety (**10**). Collapse of the complex with loss of chloride ion yields **4.** Scheme 5 shows possible mechanism for formation of **5** which involves **1** reacting with NH_3 (formed by the reaction of NaOAc and NH_4Cl) to give imine **11.** Intermediate **11** then reacts with elemental sulfur (abbreviated as "S" for S_8 in Scheme 5) to give the iminium sulfide **12**[7] which adds to the 2-chloro position of the pyridine ring to give the Meisenheimer complex **13** whose anion is stabilized by the nitrogen atom of the pyridine ring. Collapsed of **13** by the loss of HCl gives observed product **5**.



Scheme 4



Scheme 5

In conclusion we have prepared a series of titled compounds **3**-**5** in good to excellent yields by subjecting **1** to microwave heating for 15 to 20 min at temperatures ranging from 90 to 200 ˚C.

EXPERIMENTAL

The mp were taken on a MelTemp apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHZ Brucker and 500 MHz JOEL multi-nuclear NMR spectrometers; chemical shifts were referenced to TMS as internal standard. GC/MS data were recorded on an Agilent G1701DA GC/MS ChemStation. IR spectra were recorded on a Varian 3100 FTIR spectrometer. Microwave experiments were carried out in a CEM-Driver Discover model using a 300W, 250 psi microwave oven. All starting materials and reagents were purchased from Sigma Aldrich Chemicals, and were used without further purification. Elemental analyses were carried out by the SMU Analytical Services.

Procedure for the preparation of 1-(2-Chloropyridin-3-yl)ethanone (1). Prepared according to literature procedure.[8]

General Procedure for the Synthesis of 2-Aminopyrido[*b*]thiophenes (3a-g). Into a microwave test tube, a solution of 1-(2-chloropyridin-3-yl)ethanone (155 mg, 1 mmol), the corresponding amine (2-3.5 equiv), DMF (4 mL), elemental sulfur (5 equiv) and NaOAc (3 equiv) was added. The tube was then capped and charged into a CEM microwave instrument where the mixture was irradiated with 250 psi pressure at 90-120 ˚C for 15-20 min. After cooling, the reaction mixture was concentrated under reduced pressure and the mixture was diluted with EtOAc and washed with water and finally with brine. The organic layer was dried over sodium sulphate then concentrated under reduced pressure to give the crude product which was purified by column chromatography (20% EtOAc: hexane) affording the corresponding 2-aminopyrido[*b*]thiophene.

General Procedure for the Synthesis of 2-(Aminopyridin-3-yl)ethanones (4b-o). Into a microwave test tube, a solution of 1-(2-choropyridin-3-yl)ethanone (155 mg, 1 mmol), the corresponding amine (2-3

equiv) and DMF (4 mL) was added. The reaction tube was then capped, charged into a CEM microwave instrument, and the mixture was irradiated with 250 psi pressure and at 100-200 ˚C for 15-20 min. After cooling, the reaction mixture was first concentrated under reduced pressure then was diluted with EtOAc. The resulting solution was washed with water and then with brine. The organic layer was dried over sodium sulphate and then concentrated under reduced pressure to give the crude product which was purified by column chromatography (15% EtOAc: hexane) affording the corresponding 2-(aminopyridin-3-yl)ethanone.

Procedure for the Synthesis of 3-methylisothiazolo[5,4-*b*]pyridine (5). In a microwave test tube, a solution of 1-(2-chloropyridin-3-yl)ethanone (155 mg, 1 mmol), NH_4Cl (160 mg, 3.0 mmol), NaOAc (246 mg, 3.0 mmol), elemental S (160 mg, 5.0 mmol) and DMF (4 mL) was added. The tube was then capped and charged into a CEM microwave instrument, the mixture was irradiated with 250 psi pressure at 120 ˚C for 15 min. After cooling, the reaction mixture was concentrated under reduced pressure and the mixture was diluted with EtOAc and washed with water and finally with brine. The organic layer was dried over sodium sulphate, then concentrated under reduced pressure to give the crude product which was purified by column chromatography (20% EtOAc: hexane) to give the white solid product **5** in 79% yield.

Physical properties and spectral and elemental analyses for compounds (3-5)

***N*-Methylthieno[2,3-*b*]pyridine-2-amine (3a)** was obtained as a light yellow solid, mp 79.8-82.9 ^{o}C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.97 (s, 3H), 4.10 (br, 1H, NH), 6.10 (s, 1H), 7.25 (dd, *J* = 8.05, 2.85 Hz, 1H), 7.82 (dd, *J* = 7.05, 1.75 Hz, 1H), 8.55 (dd, *J* = 8.0, 1.75 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.0 (CH_3), 94.7 (CH), 118.4 (CH), 126.8 (C), 127.1 (CH), 138.2 (C), 147.0 (CH), 161.1 (C); GC/MS 164 [M+]; IR (neat) 3944, 3423, 3054, 2986, 2685, 2305, 1640, 1421, 1265, 896, 745, 705 cm^{-1}; Anal. Calcd for $C_8H_8N_2S$: C, 58.51; H, 4.91; N, 17.06. Found: C, 58.72; H, 5.01; N, 17.12.

***N*-Allylthieno[2,3-*b*]pyridine-2-amine (3b)** was obtained as a light yellow solid, mp 98.5-101.1 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (d, *J* = 7.45 Hz, 2H), 4.0 (br, 1H, NH), 5.23 (dd, *J* = 10.2, 1.40 Hz, 1H), 5.36 (dd, *J* = 17.15, 1.40 Hz, 1H), 5.99-6.05 (m, 1H), 6.12 (s, 1H), 7.23 (dd, *J* = 8.0, 2.85 Hz, 1H), 7.85 (dd, *J* = 6.85, 1.75 Hz, 1H), 8.54 (dd, *J* = 7.50, 1.75 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 48.0 (CH_2), 95.7 (CH), 117.1 (CH_2), 118.4 (CH), 126.5 (C), 127.3 (CH), 134.9 (CH), 138.6 (C), 146.9 (CH), 161.0 (C); GC/MS 190 [M^+]; IR (neat) 3944, 3423, 3054, 2986, 2685, 2305, 1641, 1421, 1265, 895, 737, 705 cm^{-1}; Anal. Calcd for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30; N, 14.72. Found: C, 63.27; H, 5.39; N, 14.71.

***N*-Isopropylthieno[2,3-*b*]pyridine-2-amine (3c)** was obtained as a light yellow solid, mp 81.3-84.8 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, *J* = 7.85 Hz, 6H), 3.52-3.57 (m, 1H), 4.30 (br, 1H, NH), 5.97 (s, 1H), 7.15 (dd, *J* = 7.5, 2.30 Hz, 1H), 7.74 (dd, *J* = 5.40, 1.80 Hz, 1H), 8.46 (dd, *J* = 8.0, 1.80 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (CH_3), 46.2 (CH), 95.2 (CH), 118.6 (CH), 127.1 (C), 127.6 (CH), 138.2

(C), 147.1 (CH), 161.2 (C); GC/MS 192 [M^+]; IR (neat) 3943, 3054, 2985, 2685, 2305, 1654, 1575, 1421, 1379, 1265, 1129, 896, 738, 705 cm^{-1}; Anal. Calcd for $C_{10}H_{12}N_2S$: C, 62.46; H, 6.29; N, 14.57. Found: C, 62.29; H, 6.33; N, 14.71.

***N*-Butylthieno[2,3-*b*]pyridine-2-amine (3d**) was obtained as a light yellow solid, mp 153.9-154.5 ˚C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.45 Hz, 3H), 1.45-1.50 (m, 2H), 1.68-1.71 (m, 2H), 3.20 (t, *J* = 6.85 Hz, 2H), 4.0 (br, 1H, NH), 6.07 (s, 1H), 7.24 (dd, *J* = 7.45, 2.80 Hz, 1H), 7.83 (dd, *J* = 8.05, 1.75 Hz, 1H), 8.53 (dd, *J* = 6.70, 1.75 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (CH_3), 20.4 (CH_2), 31.5 (CH_2), 45.1 (CH_2), 94.6 (CH), 118.4 (CH), 126.9 (C), 127.2 (CH), 139.2 (C), 146.9 (CH), 161.2 (C); GC/MS 206 [M^+]; IR (neat) 3944, 3422, 3054, 2986, 2685, 2410, 2305, 1646, 1585, 1535, 1421, 1265, 1217, 1136, 896, 737, 706 cm^{-1}; Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 64.04, H, 6.89, N, 13.71.

***N*-Benzylthieno[2,3-*b*]pyridine-2-amine (3e)** was obtained as a light green solid, mp 78.3-81.5 ˚C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (br, 3H), 6.12 (s, 1H), 7.27-7.49 (m, 5H), 7.86 (dd, *J* = 7.45, 1.75 Hz, 1H), 8.79 (dd, *J* = 8.5, 1.75 Hz, 1H), 9.23 (dd, *J* = 5.20, 1.75 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 49.8 (CH_2), 95.8 (CH), 118.4 (CH), 120.8 (CH), 127.3 (C), 127.7 (CH), 127.9 (CH), 135.6 (CH), 138.8 (C), 147.0 (CH), 151.8 (CH), 160.6 (C), 161.0 (C); GC/MS 240 [M^+]; IR (neat) 3944, 3054, 2986, 2685, 2305, 1675, 1529, 1421, 1265, 896, 738, 705 cm^{-1}; Anal. Calcd for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66. Found: C, 70.14; H, 5.10; N, 11.56.

***N*-Cyclopentylthieno[2,3-*b*]pyridine-2-amine (3f)** was obtained as a light yellow solid, mp 102.1-103.9 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.59-1.74 (m, 6H), 2.03-2.06 (m, 2H), 3.81-3.83 (m, 1H), 4.01 (br, 1H, NH), 6.06 (s, 1H), 7.24 (dd, *J* = 8.0, 2.85 Hz, 1H), 7.80 (dd, *J* = 6.55, 1.75 Hz, 1H), 8.52 (dd, *J* = 7.0, 1.75 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4 (CH_2), 33.5 (CH_2), 56.1 (CH), 95.3 (CH), 118.3 (CH), 126.7 (C), 127.3 (CH), 138.6 (C), 146.8 (CH), 161.1 (C); GC/MS 218 [M^+]; IR (neat) 3944, 3405, 2986, 2872, 2685, 2410, 2305, 1654, 1563, 1517, 1421, 1394, 1265, 1156, 896, 735, 706 cm^{-1}; Anal. Calcd for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83. Found: C, 66.22; H, 6.49; N, 12.70.

***N*-Cyclohexylthieno[2,3-*b*]pyridine-2-amine (3g)** was obtained as a light orange solid, mp 83.1-84.5 ^{o}C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23-1.42 (m, 5H), 1.65-1.69 (m, 1H), 1.78-1.80 (m, 2H), 2.13-2.15 (m, 2H), 3.25-3.29 (m, 1H), 4.01 (br, 1H, NH), 6.06 (s, 1H), 7.24 (dd, *J* = 6.85, 2.85 Hz, 1H), 7.81 (dd, *J* = 8.0, 1.75 Hz, 1H), 8.53 (dd, *J* = 6.85, 1.75 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.0 (CH_2), 26.0 (CH_2), 33.3 (CH_2), 53.5 (CH), 94.7 (CH), 118.3 (CH), 126.8 (C), 127.2 (CH), 137.6 (C), 146.9 (CH), 161.0 (C); GC/MS 232 [M^+]; IR (neat) 3943, 3054, 2988, 2937, 2685, 2305, 1654, 1421, 1265, 895, 738, 705 cm^{-1}; Anal. Calcd for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06. Found: C, 67.30; H, 6.87; N, 12.18.

1-[2-(Allylamino)pyridin-3-yl]ethanone (4b) was obtained as a light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.54 (s, 3H), 4.17 (t, *J* = 5.45 Hz, 2H), 5.12 (d, *J* = 10.3 Hz, 1H), 5.24 (d, *J* = 12.0 Hz, 1H),

5.96-6.01 (m, 1H), 6.53 (dd, *J* = 4.60, 2.85 Hz, 1H), 7.95 (dd, *J* = 6.55, 1.55 Hz, 1H), 8.28 (dd, *J* = 4.60, 1.70 Hz, 1H), 9.04 (br, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.2 (CH_3), 43.0 (CH_2), 110.7 (CH), 113.1 (C), 115.4 (CH_2), 135.0 (CH), 140.7 (CH), 154.4 (CH), 157.9 (C), 199.7 (CO); GC/MS 176 [M^+]; IR (neat) 3945, 3322, 3053, 2983, 2926, 2305, 1646, 1594, 1576, 1515, 1459, 1422, 1390, 1360, 1293, 1265, 1248, 1118, 1090, 1021, 955, 919, 896, 770, 738, 704 cm^{-1}; Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.22; H, 6.90; N, 15.83.

1-[2-(Isopropylamino)pyridin-3-yl]ethanone (4c) was obtained as a light red liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.30 Hz, 6H), 2.52 (s, 3H), 4.31-4.37 (m, 1H), 6.48 (dd, *J* = 8.0, 2.75 Hz, 1H), 7.94 (dd, *J* = 4.60, 1.75 Hz, 1H), 8.27 (dd, *J* = 4.60, 1.75 Hz, 1H), 8.88 (br, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.9 (CH_3), 27.2 (CH_3), 42.0 (CH), 110.1 (CH), 112.6 (C), 140.8 (CH), 154.3 (CH), 157.4 (C), 199.6 (CO); GC/MS 178 [M^+]; IR (neat) 3944, 3424, 3054, 2983, 2685, 2305, 1644, 1593, 1575, 1514, 1422, 1392, 1364, 1265, 1170, 1118, 1033, 954, 896, 738, 705 cm^{-1}; Anal: Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.50; H, 7.82; N, 15.81.

1-[2-(Butylamino)pyridin-3-yl)]ethanone (4d) was obtained as a light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, *J* = 1.70 Hz, 3H), 1.38-1.44 (m, 2H), 1.58-1.63 (m, 2H), 2.51 (s, 3H), 3.47-3.50 (m, 2H), 6.47 (dd, *J* = 8.0, 4.55 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.70 Hz, 1H), 8.25 (dd, *J* = 4.55, 1.70 Hz, 1H), 8.94 (br, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (CH_3), 20.4 (CH_2), 27.1 (CH_3), 31.6 (CH_2), 40.6 (CH_2), 110.2 (CH), 112.8 (C), 140.7 (CH), 154.4 (CH), 158.2 (C), 199.6 (CO); GC/MS 192 [M^+]; IR (neat) 3945, 3318, 3050, 2958, 2930, 2872, 2685, 2306, 1931, 1644, 1595, 1577, 1517, 1465, 1435, 1391, 1371, 1296, 1247, 1186, 1146, 1115, 1091, 1033, 954, 896, 768, 737, 703 cm^{-1}; Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.63; H, 8.48; N, 14.71.

1-[2-(Benzylamino)pyridin-3-yl]ethanone (4e) was obtained as a light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 (s, 3H), 4.77 (d, J = 5.15 Hz, 2H), 6.56 (dd, *J* = 4.55, 2.85 Hz, 1H), 7.24-7.34 (m, 5H), 7.97 (dd, *J* = 8.0, 1.75 Hz, 1H), 8.30 (dd, *J* = 4.60, 1.75 Hz, 1H), 9.31 (br, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.2 (CH_3), 44.7 (CH_2), 110.9 (CH), 113.1 (C), 127.1 (CH), 127.5 (CH), 128.6 (CH), 139.3 (C), 140.8 (CH), 154.4 (CH), 157.9 (C), 199.7 (CO); GC/MS 226 [M^+]; IR (neat) 3943, 3662, 3320, 3053, 2985, 2926, 2684, 2305, 1698, 1645, 1576, 1515, 1451, 1391, 1363, 1327, 1265, 1186, 1134, 1093, 1027, 956, 896, 736, 703 cm^{-1}; Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.42; H, 6.29; N, 12.48.

1-[2-(Cyclopentyl)aminopyridin-3-yl]ethanone (4f) was obtained as a light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47-1.74 (m, 6H), 1.99-2.04 (m, 2H), 2.49 (s, 3H), 4.40-4.45 (m, 1H), 6.45 (dd, *J* = 4.60, 2.85 Hz, 1H), 7.89 (dd, *J* = 6.55, 1.55 Hz, 1H), 8.25 (dd, *J* = 4.60, 1.70 Hz, 1H), 9.01 (br, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.8 (CH_2), 27.1 (CH_3), 33.4 (CH_2), 52.2 (CH), 110.1 (CH), 112.7 (C), 140.7 (CH), 154.9 (CH), 157.8 (C), 199.5 (CO); GC/MS 204 [M+]; IR (neat) 3945, 3310, 3051, 2955,

2872, 2685, 2304, 1640, 1595, 1571, 1510, 1465, 1424, 1394, 1361, 1341, 1248, 1179, 1127, 1091, 1057, 955, 895, 823, 763, 737, 704 cm^{-1}; Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found 70.59; H, 7.99; N, 13.69.

1-[2-(Cyclohexylamino)pyridin-3-yl]ethanone (4g) was obtained as a light yellow liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 1.21-1.45 (m, 5H), 1.56-1.60 (m, 1H), 1.68-1.73 (m, 2H), 1.95-1.99 (m, 2H), 2.50 (s, 3H), 4.05-4.10 (m, 1H), 6.44 (dd, *J* = 8.0, 4.60 Hz, 1H), 7.91 (dd, *J* = 8.0, 1.70 Hz, 1H), 8.23 (dd, *J* = 4.60, 1.70 Hz, 1H), 9.0 (br, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7 (CH_2), 25.9 (CH_2), 27.2 (CH_3), 48.6 (CH_2), 110.0 (CH), 112.5 (C), 140.9 (CH), 154.5 (CH), 157.4 (C), 199.5 (CO); GC/MS 218 [M+]; IR (neat) 3945, 3305, 3052, 2931, 2854, 2686, 2305, 1643, 1595, 1576 1512, 1465, 1450, 1395, 1365, 1264, 1245, 1151, 1127, 1096, 1033, 954, 890, 768, 738, 704 cm^{-1}; Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.70; H, 8.25; N, 12.94.

1-[2-(*tert*-Butylamino)pyridin-3-yl]ethanone (4h) was obtained as a light yellow liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.51 (s, 3H), 6.45 (dd, J = 8.05, 4.55 Hz, 1H), 7.90 (dd, J = 8.05, 1.75 Hz, 1H), 8.24 (dd, J = 4.60, 1.75 Hz, 1H), 9.10 (br, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.3 (CH_3), 29.2 (CH_3), 51.4 (C), 109.8 (CH), 112.8 (C), 140.7 (CH), 153.8 (CH), 158.0 (C), 199.7 (CO); GC/MS 192 [M^+]; IR (neat) 3944, 3685, 3303, 3053, 2965, 2685, 2305, 1642, 1581, 1518, 1450, 1394, 1360, 1265, 1216, 1127, 1089, 971, 951, 896, 738, 705 cm^{-1}; Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.83; H, 8.33; N, 14.71.

1-[2-(Dimethylamino)pyridin-3-yl]ethanone (4i) was obtained as a light yellow liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.93 (s, 6H), 6.64 (dd, *J* = 4.55, 2.80 Hz, 1H), 7.71 (dd, *J* = 7.50, 1.70 Hz, 1H), 8.20 (dd, *J* = 4.60, 1.70 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0 (CH_3), 41.5 (NCH_3), 112.7 (CH), 121.3 (C), 138.6 (CH), 150.0 (CH), 158.8 (C), 200.1 (CO); GC/MS 164 [M^+]; IR (neat) 3944, 3510, 2930, 2800, 2685, 2304, 1919, 1673, 1584, 1544, 1512, 1444, 1402, 1354, 1285, 1242, 1203, 1177, 1118, 1083, 1064, 1039, 965, 806, 771, 734, 703 cm^{-1}; Anal. Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.88; H, 7.43; N, 17.10.

1-[2-(Diethylamino)pyridin-3-yl]ethanone (4j) was obtained as light yellow liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (t, *J* = 7.50, 1.70 Hz, 6H), 2.50 (s, 3H), 3.32-3.36 (m, 4H), 6.71 (dd, *J* = 5.0, 2.75 Hz, 1H), 7.64 (dd, *J* = 7.60, 1.70 Hz, 1H), 8.23 (dd, *J* = 5.0, 1.70 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5 (CH_3), 27.9 (CH_3), 45.2 (NCH_2), 114.1 (CH), 124.7 (C), 138.1 (CH), 149.7 (CH), 158.6 (C), 201.8 (CO); GC/MS 192 [M^+]; IR (neat) 3945, 3053, 2982, 2932, 2684, 2305, 1676, 1581, 1554, 1431, 1378, 1355, 1265, 1179, 1108, 1083, 1015, 954, 896, 737, 703 cm^{-1}; Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.84; H, 8.32; N, 14.67.

1-[2-(Pyrrolidin-1-yl)pyridin-3-yl]ethanone (4k) was obtained as a light yellow liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 1.88-1.91 (m, 4H), 2.52 (s, 3H), 3.24-3.28 (m, 4H), 6.58 (dd, *J* = 4.60, 2.80 Hz, 1H), 7.77

(dd, *J* = 7.10, 1.70 Hz, 1H), 8.22 (dd, *J* = 4.55, 1.70 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.6 (CH_2), 28.6 (CH_3), 50.3 (CH_2), 110.7 (CH), 119.7 (C), 138.0 (CH), 150.6 (CH), 155.2 (C), 198.9 (CO); GC/MS 190 [M^+]; IR (neat) 3944, 3441, 2969, 2871, 2684, 2306, 1667, 1584, 1541, 1475, 1455, 1381, 1353, 1327, 1285, 1245, 1221, 1114, 1088, 1036, 950, 866, 787, 767, 734, 701 cm^{-1}; Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.61; H, 7.36; N, 14.79.

1-[2-(Piperidin-1-yl)pyridin-3-yl]ethanone (4l) was obtained as a light orange liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60-1.66 (m, 6H), 2.54 (s, 3H), 3.27 (t, *J* = 5.70 Hz, 4H), 6.76 (dd, *J* = 4.55, 2.85 Hz, 1H), 7.68 (dd, *J* = 7.45, 1.70 Hz, 1H), 8.24 (dd, *J* = 4.60, 1.70 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4 (CH_2), 25.8 (CH_2), 27.6 (CH_3), 51.6 (NCH_2), 114.9 (CH), 124.9 (C), 138.5 (CH), 149.9 (CH), 160.1 (C), 202.1 (CO); GC/MS 204 [M^+]; IR (neat) 3941, 3424, 2935, 2853, 2684, 2306, 1678, 1579, 15555, 1470, 1434, 1373, 1285, 1236, 1199, 1103, 1026, 933, 866, 773, 735, 703 cm^{-1}; Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.71; H, 7.85; N, 13.67.

1-(2-Morpholinopyridin-3-yl)ethanone (4m) was obtained as a light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.51 (s, 3H), 3.26 (t, *J* = 4.60 Hz, 4H), 3.74 (t, *J* = 4.60 Hz, 4H), 6.79 (dd, *J* = 4.60, 2.85 Hz, 1H), 7.67 (dd, *J* = 7.45, 1.70 Hz, 1H), 8.23 (dd, *J* = 4.55, 1.70 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.0 (CH_3), 50.6 (NCH_2), 66.7 (OCH_2), 115.7 (CH), 124.6 (C), 138.7 (CH), 150.1 (CH), 159.1 (C), 201.4 (CO); GC/MS 206 [M^+]; IR (neat) 3946, 3500, 3054, 2971, 2930, 2857, 2685, 2306, 1681, 1580, 1557, 1434, 1366, 1287, 1265, 1118, 1069, 1046, 943, 896, 749, 704 cm^{-1}; Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 66.46; H, 6.84; N, 13.58. Found: C, 66.60; H, 6.78; N, 13.62.

1-[2-(4-Methylpiperazin-yl)pyridin-3-yl]ethanone (4n) was obtained as a light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.44 (t, *J* = 5.15 Hz, 4H), 2.48 (s, 3H), 3.29 (t, *J* = 5.15 Hz, 4H), 6.74 (dd, *J* = 7.45, 4.60 Hz, 1H), 7.62 (dd, *J* = 7.20, 2.55 Hz, 1H), 8.20 (dd, *J* = 4.55, 2.55 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.9 (CH_3), 46.1 (CH_3), 50.1 (CH_2), 54.8 (CH_2), 115.4 (CH), 124.7 (C), 138.6 (CH), 149.9 (CH), 159.2 (C), 201.7 (CO); GC/MS 219 [M^+]; IR (neat) 3943, 3658, 3415, 3053, 2985, 2942, 2848, 2800, 2685, 2305, 1677, 1580, 1557, 1434, 1368, 1434, 1368, 1291, 1265, 1239, 1143, 1109, 1008, 942, 896, 797, 738, 704 cm^{-1}; Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.75; H, 7.89; N, 19.24.

1-[2-(4-Benzylpiperidin-1-yl)pyridin-3-yl]ethanone (4o) was obtained as a light yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34-1.37 (m, 2H), 1.68-1.70 (m, 3H), 2.52 (s, 3H), 2.55 (d, *J* = 6.85 Hz, 2H), 2.83-2.90 (m, 2H), 3.67-3.69 (m, 2H), 6.75 (dd, *J* = 4.60, 2.85 Hz, 1H), 7.12-7.18 (m, 3H), 7.24-7.27 (m, 2H), 7.67 (dd, *J* = 7.50, 2.20 Hz, 1H), 8.24 (dd, *J* = 4.60, 2.20 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.7 (CH_3), 32.1 (CH_2), 38.1 (CH), 43.2 (CH_2), 50.8 (CH_2), 114.9 (CH), 124.7 (C), 126.0 (CH), 128.3 (CH), 129.2 (CH), 138.6 (CH), 140.3 (C), 150.0 (CH), 159.7 (C), 201.7 (CO); GC/MS 294 [M^+]; IR (neat) 3943, 3432, 3053, 2984, 2929, 2847, 2684, 2306, 1676, 1581, 1555, 1477, 1437, 1374, 1287, 1265,

1236, 1105, 1057, 935, 894, 737, 702 cm^{-1}; Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.64; H, 7.59; N, 9.59.

3-Methylisothiazolo[5,4-*b*]pyridine (5) was obtained as a white solid, mp 83.1-84.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.74 (s, 3H), 7.37 (dd, *J* = 8.25, 4.60 Hz, 1H), 8.20 (dd, *J* = 8.0, 1.75 Hz, 1H), 8.75 (dd, *J* = 4.60, 1.75 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.9 (CH_3), 119.3 (CH), 122.9 (C), 127.7 (C), 131.6 (CH), 150.1 (CH), 161.8 (C); GC/MS 150 [M^+]; IR (neat) 3943, 3423, 3054, 2986, 2685, 2305, 1580, 1421, 1367, 1265, 1139, 896, 741, 705 cm^{-1}; Anal. Calcd for $C_7H_6N_2S$: C, 55.97; H, 4.03; N, 18.65. Found: C, 56.05; H, 4.08; N, 18.77.

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REFERENCES

1. See, for example: (a) S. Kamila and E. R. Biehl, *J. Heterocycl. Chem*., 2007, **44**, 407; (b) S. Kamila and E. R. Biehl, *J. Heterocycl. Chem.,* 2006, **43,** 1; (c) S. Kamila, B. Koh, O. Khan, and E. R. Biehl, *J. Heterocycl. Chem*., 2006, **43**, 1641; (d) S. Kamila, H. Zhang, and E. R. Biehl, *Heterocycles,* 2005, **65**, 2493.
2. A. Rais, H. Ankati, and E. R. Biehl, *J. Heterocycl. Chem.*, 2009, **46**, 599.
3. A. Rais, H. Ankati, and E. R. Biehl, *Trends in Heterocycl. Chem*., 2009, in press.
4. R. H. Bahekar, M. R. Jain, P. A. Jadav, V. M. Prajapati, D. N. Patel, A. A. Gupta, A. Sharma, R. Tom, D. Bandyopadhya, H. Modi, and P. R. Patel, *J. Bioorg. Med. Chem.,* 2007, **15**, 6782.
5. M. Carmack, *J. Heterocycl. Chem.*, 1989, **26,** 1319.
6. M. R. Crampton, 'Organic Reaction Mechanisms: Nucleophilic Aromatic Substitution in Heterocyclic Systems', ed. by A. C. Knipe and W. E. Watts, John Wiley & Sons, Vol. 32, 1986, pp. 147-162.
7. Y. Sasaki and F. P. Olsen, *Can. J. Chem*., 1971, **49**, 283.
8. M. Gilligan, H. A. Charles, and L. Tamara, *PCT Int. Appl.* 2004, WO 2004101518.