A Facile One-Pot Synthesis of Substituted Thieno[2,3-*b*]pyridines from Enaminones

Baochang Gao,[a,b] Dewen Dong,[b] Jie Zhang,[a] Changjiang Ding,*[a] Chunming Dong,[b] Yongjiu Liang,[b] Rui Zhang*[b]

[a] Department of Chemistry, Jilin University, Changchun 130012, P. R. of China
Fax +86(431)85262676; E-mail: ariel@ciac.jl.cn; E-mail: dcjiang@163.com

[b] Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, P. R. of China

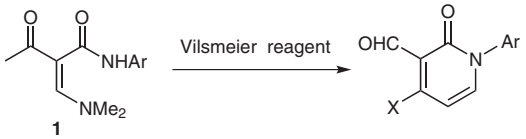
Received 7 September 2011; revised 14 November 2011

Abstract: A facile and efficient one-pot synthesis of substituted thieno[2,3-*b*]pyridines has been developed. Treatment of enaminones, such as 2-acetyl-3-(dimethylamino)propenamides and -propenoates, with 2-cyanothioacetamide in the presence of potassium carbonate in *N*,*N*-dimethylformamide at 80 °C followed by addition of methylene-active bromides at room temperature provided, via intramolecular cyclization, 2,3,5,6-tetrasubstituted thieno[2,3-*b*]pyridines in yields of 78–90%. This protocol, which combines construction and modification of the thieno[2,3-*b*]pyridine ring, increases the structural diversity of the final products from readily available materials.

Key words: enaminones, cyclization, heterocycles, pyridine-2(1*H*)-thiones, thieno[2,3-*b*]pyridines

Pyridines and their benzo/hetero-fused analogues have emerged as an important class of aza-heterocycles due to their presence in numerous natural products and synthetic organic compounds that have diverse biophysio- and pharmacological activity.[1,2] These scaffolds are also of widespread interest in supramolecular and coordination chemistry, as well as for materials science.[3] As representatives of such heterocycles, thieno[2,3-*b*]pyridines have received considerable attention since they show a wide variety of bioactivity, for example antiviral,[4] antidiabetic,[5] antimicrobial,[6] antitumor,[7] antiparasitic,[8] and neurotropic activities.[9] Actually, the key unit of thieno[2,3-*b*]pyridines is found as the central fragment in many clinical pharmaceuticals.[10] The pharmacological importance of thieno[2,3-*b*]pyridines has directed considerable research activity towards the construction of the skeleton of such heterocycles. Many synthetic approaches to thieno[2,3-*b*]pyridines have been developed involving multistep procedures from either a thiophene or a pyridine ring and further ring closure. The condensation reaction of 2-chloropyridine-3-carbonitriles,[11] 2-(alkylthio)pyridine-3-carbonitriles,[9,12] or 2-aminothiophene-3-carbonitriles[13] with alkyl mercaptoacetates, alkyl chloroacetates, or ketones, respectively, is one of the most general synthetic procedure for this heterocyclic-fused system. Additionally, the synthesis of thieno[2,3-*b*]pyridines from acyclic substrates such as 2-cyanothioacetamides via a multistep procedure has also been reported.[14]

During the course of our studies on the chemistry of enaminones, we have developed efficient syntheses of substituted pyridin-2(1*H*)-ones,[15,16] pyrimidin-4(3*H*)-ones,[17] dihydrofurans,[18] and pyrrolin-4-ones[19] from a variety of enaminones. Recently, we achieved the synthesis of functionalized pyridin-2(1*H*)-ones bearing formyl and halo substituents at the 3- and 4-positions, respectively, via the Vilsmeier–Haack reaction of enaminones **1** (Scheme 1).[15] In connection with this previous work and following on from our research on the synthesis of highly valuable heterocycles through enaminones, we became interested in the synthetic potential of the readily available enaminones **1**, and designed the reaction of **1** with 2-cyanothioacetamide (**2**) and methylene-active bromides **4**. As a result of these studies, we have provided a facile and convenient one-pot synthesis of thieno[2,3-*b*]pyridines. Herein, we wish to report our experimental results.

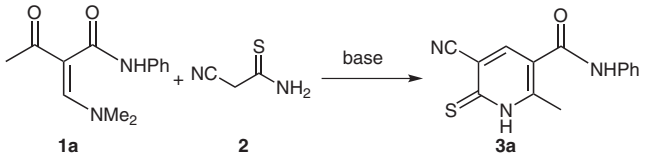


Scheme 1 Vilsmeier reaction of enaminones **1**

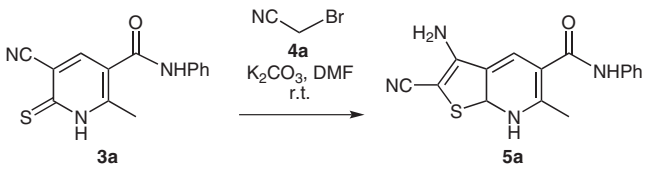
The substrates, enaminones **1**, were prepared according to our previously reported procedure from commercially available β-oxo amides and *N*,*N*-dimethylformamide dimethyl acetal.[15] With substrates **1** in hand, we selected **1a** as a model compound to examine its reaction with 2-cyanothioacetamide (**2**) under basic conditions. Thus, the reaction of **1a** and **2** was first attempted in the presence of potassium carbonate in *N*,*N*-dimethylformamide at room temperature for 8.0 hours, however, no reaction was observed as monitored by TLC. When the mixture was heat to 60 °C, the reaction proceeded and furnished a yellow solid after workup and subsequent purification by column chromatography. The product was characterized as 5-cyano-2-methyl-*N*-phenyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (**3a**, 68% yield) on the basis of its spectral and analytical data (Scheme 2).

The optimization of the reaction conditions, including base, reaction temperature, solvent, and the ratio of 2-cyanothioacetamide (**2**) to **1a** was then investigated. It was found that the reaction could proceed in the presence of sodium alkoxide, sodium hydroxide, or potassium car-

SYNTHESIS 2012, 44, 201–206
Advanced online publication: 05.12.2011
DOI: 10.1055/s-0031-1289633; Art ID: H87411SS



Scheme 2 Reaction of enaminone **1a** with 2-cyanothioacetamide (**2**)

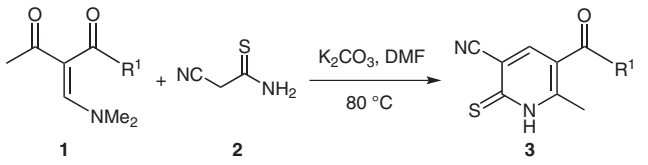


Scheme 3 Reaction of pyridine-2(1*H*)-thione **3a** with bromoacetonitrile (**4a**)

bonate. A series of experiments revealed that 1.1 equivalents of 2-cyanothioacetamide (**2**) was effective for the synthesis of **3a**, and the yield of **3a** reached 90% when the reaction of **1a** and **2** (1.1 equiv) was performed in the presence of potassium carbonate (2.0 equiv) in *N*,*N*-dimethylformamide at 80 °C for 6.0 hours (Table 1, entry 1).

Under the optimal reaction conditions, a series of reactions of enaminones **1b–h** and **2** were conducted, and the results are summarized in Table 1. The corresponding substituted pyridine-2(1*H*)-thiones **3b–h** were obtained in good yields (entries 2–8). Next, we envisaged further synthetic transformation of the available pyridine-2(1*H*)-thiones **3**. Thus, the reaction of **3a** and bromoacetonitrile (**4a**) was attempted in the presence of potassium carbonate (2.0 equiv) in *N*,*N*-dimethylformamide at room temperature. In this case, substituted thieno[2,3-*b*]pyridine **5a** was synthesized in 93% yield (Scheme 3).

Table 1 Synthesis of Substituted Pyridine-2(1*H*)-thiones



Entry	Substrate	R^1	Product	Yield[a] (%)
1	**1a**	PhNH	**3a**	90
2	**1b**	4-ClC_6H_4NH	**3b**	87
3	**1c**	4-MeC_6H_4NH	**3c**	85
4	**1d**	4-$MeOC_6H_4NH$	**3d**	82
5	**1e**	2,4-$Me_2C_6H_3NH$	**3e**	89
6	**1f**	2-$MeOC_6H_4NH$	**3f**	81
7	**1g**	4-Cl-2,5-$(MeO)_2C_6H_2NH$	**3g**	84
8	**1h**	5-Cl-2-$MeOC_6H_3NH$	**3h**	86

[a] Isolated yield.

The results encouraged us to explore the one-pot synthesis of thieno[2,3-*b*]pyridines **5** from enaminones **1**. In a representative experiment, **1a** and 2-cyanothioacetamide (**2**, 1.1 equiv) were treated with potassium carbonate (3.5 equiv) in *N*,*N*-dimethylformamide under 80 °C. After **1a** had been consumed (TLC monitoring), the reaction mixture was cooled to room temperature, and bromoacetonitrile (**4a**, 1.1 equiv) was added with stirring. The reaction furnished **5a** in 90% overall yield (Table 2, entry 1). In the same fashion, a series of reactions of enaminones **1**, 2-cyanothioacetamide (**2**) and methylene-active bromides **4** were carried out. As shown in Table 2, all the reactions proceeded smoothly and afforded the corresponding thieno[2,3-*b*]pyridines **5b–m** in good yields (entries 2–13). To expand the scope of the reaction, we then examined the reaction of 3-[(dimethylamino)methylene]pentane-2,4-dione (**1i**) under identical conditions, and the desired product **5n** was obtained (entry 14). It should be noted that the richness of the functionality, e.g. amino, ester, and amide groups, on the thieno[2,3-*b*]pyridines **5** may render them extremely versatile as synthons in further synthetic transformations.[20] Therefore, we provide an alternative one-pot synthesis of substituted thieno[2,3-*b*]pyridine of types **5**.

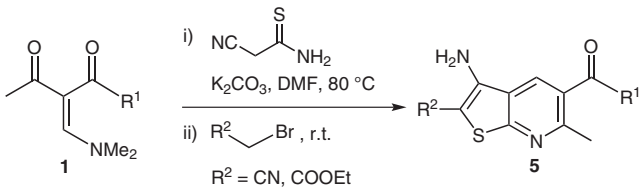
In summary, we have developed a facile and efficient one-pot synthesis of substituted thieno[2,3-*b*]pyridines by treatment of enaminones with potassium carbonate in *N*,*N*-dimethylformamide followed by stepwise addition of 2-cyanothioacetamide and methylene-active bromides. This protocol, which combines construction and modification of the thieno[2,3-*b*]pyridine ring, increases the structural diversity of the final products from readily available materials. The use of easily available starting materials, mild reaction conditions, simple execution, good yields, and wide synthetic potential of the products, make this new strategy attractive for academic research and practical applications.

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^1H and ^{13}C NMR spectra were recorded at 400 MHz (or 300 MHz) and 100 MHz, respectively, with TMS as internal standard at 25 °C on a Varian Inova-400 (or Bruker-300) spectrometer. IR spectra (KBr) were recorded on a Magna-560 FTIR spectrophotometer in the range of 400–4000 cm^{-1}. Petroleum ether (PE) used was the fraction boiling in the range 30–60 °C.

3-Amino-2-cyano-6-methyl-*N*-phenylthieno[2,3-*b*]pyridine-5-carboxamide (5a); Typical Procedure

To a solution of **1a** (1.0 mmol) and K_2CO_3 (3.5 equiv) in DMF (15 mL) was added cyanothioacetamide (**2**, 1.1 mmol) in one portion. The mixture was heated and stirred at 80 °C for 6.0 h. When consumption of **1a** was complete (TLC), the mixture was cooled to r.t., then bromoacetonitrile (**4a**, 1.1 mmol) was added. The mixture was stirred for a further 1.5 h, and then poured into sat. aq NaCl (30 mL) with stirring, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (3 × 15 mL), dried (anhyd

Table 2 One-Pot Synthesis of Substituted Thieno[2,3-*b*]pyridines



Entry	Substrate	R^1	R^2	Product	Yield[a] (%)
1	**1a**	PhNH	CN	**5a**	90
2	**1b**	4-ClC_6H_4NH	CN	**5b**	85
3	**1c**	4-MeC_6H_4NH	CN	**5c**	82
4	**1d**	4-$MeOC_6H_4NH$	CN	**5d**	78
5	**1e**	2,4-$Me_2C_6H_3NH$	CN	**5e**	88
6	**1f**	2-$MeOC_6H_4NH$	CN	**5f**	81
7	**1g**	4-Cl-2,5-$(MeO)_2C_6H_2NH$	CN	**5g**	82
8	**1h**	5-Cl-2-$MeOC_6H_3NH$	CN	**5h**	85
9	**1i**	PhNH	COOEt	**5i**	89
10	**1a**	4-ClC_6H_4NH	COOEt	**5j**	83
11	**1b**	4-MeC_6H_4NH	COOEt	**5k**	81
12	**1c**	2-$MeOC_6H_4NH$	COOEt	**5l**	80
13	**1f**	4-Cl-2,5-$(MeO)_2C_6H_2NH$	COOEt	**5m**	79
14	**1i**	Me	COOEt	**5n**	51

[a] Isolated yield.

$MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, PE–Et_2O, 10:1) to give **5a** (0.277 g, 90%) as a white solid.

5-Cyano-2-methyl-*N*-phenyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (3a)
Yield: 242 mg (90%); yellow solid; mp 264–265 °C.

IR (KBr): 3313, 2239, 1682, 1595, 1541, 1321, 1192, 750, 692 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.58 (s, 3 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 2 H), 8.32 (s, 1 H), 10.37 (s, 1 H), 14.29 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.1, 113.0, 116.7, 119.9, 120.3, 124.0, 128.7, 138.7, 143.6, 155.2, 162.5, 178.3.

Anal. Calcd for $C_{14}H_{11}N_3OS$: C, 62.43; H, 4.12; N, 15.60. Found: C, 62.15; H, 4.16; N, 15.57.

***N*-(4-Chlorophenyl)-5-cyano-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (3b)**
Yield: 263 mg (87%); yellow solid; mp 308–309 °C.

IR (KBr): 3360, 2980, 2230, 1672, 1599, 1527, 1493, 1312, 1178, 825 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.58 (s, 3 H), 7.42 (d, *J* = 8.5 Hz, 2 H), 7.70 (d, *J* = 9.0 Hz, 2 H), 8.33 (s, 1 H), 10.43 (s, 1 H), 14.30 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.1, 113.0, 116.6, 119.8, 121.4, 127.6, 128.6, 137.6, 143.5, 155.5, 162.5, 178.4.

Anal. Calcd for $C_{14}H_{10}ClN_3OS$: C, 55.35; H, 3.32; N, 13.83. Found: C, 55.14; H, 3.27; N, 13.91.

5-Cyano-2-methyl-6-thioxo-*N*-(*p*-tolyl)-1,6-dihydropyridine-3-carboxamide (3c)
Yield: 241 mg (85%); yellow solid; mp 266–267 °C.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.27 (s, 3 H), 2.57 (s, 3 H), 7.15 (d, *J* = 8.0 Hz, 2 H), 7.54 (d, *J* = 8.0 Hz, 2 H), 8.30 (s, 1 H), 10.23 (s, 1 H), 14.28 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.1, 20.5, 113.0, 116.7, 119.9, 120.3, 129.1, 133.0, 136.2, 143.5, 155.2, 162.3, 178.3.

Anal. Calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.72; H, 4.65; N, 14.77.

5-Cyano-*N*-(4-methoxyphenyl)-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (3d)
Yield: 245 mg (82%); yellow solid; mp 269–270 °C.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.57 (s, 3 H), 3.74 (s, 3 H), 6.93 (d, *J* = 8.0 Hz, 2 H), 7.57 (d, *J* = 8.0 Hz, 2 H), 8.30 (s, 1 H), 10.19 (s, 1 H), 14.27 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.1, 55.2, 113.0, 113.9, 116.7, 120.3, 121.4, 131.8, 143.5, 155.2, 155.8, 162.0, 178.2.

Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04. Found: C, 59.97; H, 4.31; N, 14.15.

5-Cyano-*N*-(2,4-dimethylphenyl)-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (3e)

Yield: 265 mg (89%); yellow solid; mp 271–272 °C.

IR (KBr): 3302, 3018, 2976, 2231, 1690, 1603, 1506, 1298, 1194, 887, 812 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.20 (s, 3 H), 2.27 (s, 3 H), 2.59 (s, 3 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 7.06 (s, 1 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 8.32 (s, 1 H), 9.86 (s, 1 H), 14.28 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.9, 18.1, 20.5, 113.1, 116.7, 120.3, 125.8, 126.5, 130.9, 132.8, 133.1, 135.1, 143.6, 155.0, 162.7, 178.3.

Anal. Calcd for $C_{16}H_{15}N_3OS$: C, 64.62; H, 5.08; N, 14.13. Found: C, 64.69; H, 5.03; N, 14.05.

5-Cyano-*N*-(2-methoxyphenyl)-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (3f)
Yield: 242 mg (81%); yellow solid; mp 258–259 °C.

IR (KBr): 3362, 3283, 2230, 1672, 1645, 1601, 1537, 1263, 1192, 735 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.56 (s, 3 H), 3.82 (s, 3 H), 6.95 (t, *J* = 7.5 Hz, 1 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 7.17 (t, *J* = 7.5 Hz, 1 H), 7.79 (d, *J* = 7.5 Hz, 1 H), 8.22 (s, 1 H), 9.66 (s, 1 H), 14.24 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.0, 55.7, 111.5, 116.7, 120.2, 120.7, 123.7, 125.8, 126.4, 140.6, 143.7, 151.0, 154.7, 162.7, 178.2.

Anal. Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04. Found: C, 60.49; H, 4.41; N, 14.12.

***N*-(4-Chloro-2,5-dimethoxyphenyl)-5-cyano-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (3g)**
Yield: 305 mg (84%); yellow solid; mp 261–262 °C.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.56 (s, 3 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 7.19 (s, 1 H), 7.76 (s, 1 H), 8.23 (s, 1 H), 9.76 (s, 1 H), 14.26 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.1, 56.5, 56.6, 108.5, 113.0, 113.5, 116.7, 120.3, 126.1, 143.8, 145.0, 148.0, 154.9, 162.9, 178.4.

Anal. Calcd for $C_{16}H_{14}ClN_3O_3S$: C, 52.82; H, 3.88; N, 11.55. Found: C, 52.57; H, 3.86; N, 11.67.

***N*-(5-Chloro-2-methoxyphenyl)-5-cyano-2-methyl-6-thioxo-1,6-dihydropyridine-3-carboxamide (3h)**
Yield: 287 mg (86%); yellow solid; mp 245–246 °C.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.55 (s, 3 H), 3.84 (s, 3 H), 7.10 (d, *J* = 9.0 Hz, 1 H), 7.21 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1 H), 7.97 (s, 1 H), 8.22 (s, 1 H), 9.80 (s, 1 H), 14.26 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 18.1, 56.1, 112.8, 116.7, 120.2, 122.5, 123.7, 124.8, 127.8, 143.7, 149.5, 154.8, 163.0, 178.4.

Anal. Calcd for $C_{15}H_{12}ClN_3O_2S$: C, 53.97; H, 3.62; N, 12.59. Found: C, 54.04; H, 3.57; N, 12.52.

3-Amino-2-cyano-6-methyl-*N*-phenylthieno[2,3-*b*]pyridine-5-carboxamide (5a)
Yield: 277 mg (90%); white solid; mp 283–284 °C.

IR (KBr): 3350, 3248, 2201, 1663, 1556, 1445, 1325, 754, 690 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.66 (s, 3 H), 7.12 (t, *J* = 7.0 Hz, 1 H), 7.35–7.39 (m, 4 H), 7.71 (d, *J* = 8.0 Hz, 2 H), 8.66 (s, 1 H), 10.60 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.9, 71.3, 115.6, 119.6, 121.7, 124.0, 128.9, 129.1, 130.5, 138.9, 150.4, 157.5, 159.5, 166.1.

Anal. Calcd for $C_{16}H_{12}N_4OS$: C, 62.32; H, 3.92; N, 18.17. Found: C, 62.21; H, 3.96; N, 18.08.

3-Amino-*N*-(4-chlorophenyl)-2-cyano-6-methylthieno[2,3-*b*]pyridine-5-carboxamide (5b)
Yield: 291 mg (85%); white solid; mp 291–292 °C.

IR (KBr): 3227, 3229, 2208, 1647, 1560, 1524, 1493, 1400, 1310, 1094, 827, 812 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.65 (s, 3 H), 7.35 (s, 2 H), 7.43 (d, *J* = 9.0 Hz, 2 H), 7.74 (d, *J* = 9.0 Hz, 2 H), 8.66 (s, 1 H), 10.74 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.9, 71.3, 115.6, 121.1, 121.7, 127.6, 128.8, 130.5, 137.8, 150.3, 157.5, 159.6, 166.2.

Anal. Calcd for $C_{16}H_{11}ClN_4OS$: C, 56.06; H, 3.23; N, 16.34. Found: C, 56.31; H, 3.21; N, 16.28.

3-Amino-2-cyano-6-methyl-*N*-(*p*-tolyl)thieno[2,3-*b*]pyridine-5-carboxamide (5c)
Yield: 263 mg (82%); white solid; mp 321–322 °C.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.26 (s, 3 H), 2.64 (s, 3 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 7.34 (s, 2 H), 7.59 (d, *J* = 8.0 Hz, 2 H), 8.64 (s, 1 H), 10.50 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.5, 22.9, 71.2, 115.6, 119.6, 121.7, 129.2, 130.4, 133.0, 136.4, 150.4, 157.5, 159.4, 165.9.

Anal. Calcd for $C_{17}H_{14}N_4OS$: C, 63.33; H, 4.38; N, 17.38. Found: C, 63.42; H, 4.44; N, 17.42.

3-Amino-2-cyano-*N*-(4-methoxyphenyl)-6-methylthieno[2,3-*b*]pyridine-5-carboxamide (5d)
Yield: 264 mg (78%); white solid; mp 295–296 °C.

IR (KBr): 3333, 3153, 2193, 1645, 1547, 1510, 1250, 876, 827 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.65 (s, 3 H), 3.73 (s, 3 H), 6.94 (d, *J* = 9.0 Hz, 2 H), 7.34 (s, 2 H), 7.63 (d, *J* = 9.0 Hz, 2 H), 8.64 (s, 1 H), 10.46 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.9, 55.2, 71.2, 114.0, 115.6, 121.1, 121.7, 129.3, 130.4, 132.0, 150.4, 155.7, 157.5, 159.3, 165.6.

Anal. Calcd for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56. Found: C, 60.57; H, 4.26; N, 16.49.

3-Amino-2-cyano-*N*-(2,4-dimethylphenyl)-6-methylthieno[2,3-*b*]pyridine-5-carboxamide (5e)
Yield: 295 mg (88%); white solid; mp 313–314 °C.

IR (KBr): 3348, 3232, 2197, 1643, 1526, 1429, 1302, 876 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.25 (s, 3 H), 2.27 (s, 3 H), 2.68 (s, 3 H), 7.03 (d, *J* = 7.5 Hz, 1 H), 7.08 (s, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 7.38 (s, 2 H), 8.64 (s, 1 H), 9.96 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 17.9, 20.5, 22.9, 71.1, 115.7, 121.7, 125.6, 126.6, 129.4, 130.4, 131.0, 132.7, 133.2, 135.2, 150.4, 157.4, 159.3, 166.3.

Anal. Calcd for $C_{18}H_{16}N_4OS$: C, 64.26; H, 4.79; N, 16.65. Found: C, 63.97; H, 4.81; N, 16.70.

3-Amino-2-cyano-*N*-(2-methoxyphenyl)-6-methylthieno[2,3-*b*]pyridine-5-carboxamide (5f)
Yield: 273 mg (81%); white solid; mp 237–238 °C.

^1H NMR (300 MHz, DMSO-d_6): δ = 2.66 (s, 3 H), 3.80 (s, 3 H), 6.97 (t, *J* = 7.5 Hz, 1 H), 7.08 (d, *J* = 8.0 Hz, 1 H), 7.17 (t, *J* = 7.5 Hz, 1 H), 7.34 (s, 2 H), 7.88 (d, *J* = 7.0 Hz, 1 H), 8.60 (s, 1 H), 9.80 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 22.9, 55.7, 71.0, 111.6, 115.7, 120.3, 121.6, 123.4, 125.8, 126.6, 129.4, 130.3, 150.4, 151.0, 157.4, 159.3, 166.3.

Anal. Calcd for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56. Found: C, 60.59; H, 4.14; N, 16.52.

3-Amino-*N*-(4-chloro-2,5-dimethoxyphenyl)-2-cyano-6-methylthieno[2,3-*b*]pyridine-5-carboxamide (5g)
Yield: 329 mg (82%); white solid; mp 143–144 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.66 (s, 3 H), 3.78 (s, 3 H), 3.80 (s, 3 H), 7.19 (s, 1 H), 7.34 (s, 2 H), 7.86 (s, 1 H), 8.63 (s, 1 H), 9.92 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.1, 56.5, 56.7, 71.1, 108.0, 113.6, 115.7, 116.6, 121.7, 126.5, 129.0, 130.6, 144.9, 148.1, 150.5, 157.5, 159.4, 166.5.

Anal. Calcd for $C_{18}H_{15}ClN_4O_3S$: C, 53.67; H, 3.75; N, 13.91. Found: C, 53.82; H, 3.73; N, 13.84.

3-Amino-*N*-(5-chloro-2-methoxyphenyl)-2-cyano-6-methylthieno[2,3-*b*]pyridine-5-carboxamide (5h)
Yield: 317 mg (85%); white solid; mp 245–246 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.65 (s, 3 H), 3.82 (s, 3 H), 7.11 (d, J = 9.0 Hz, 1 H), 7.22 (dd, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1 H), 7.34 (s, 2 H), 8.07 (s, 1 H), 8.59 (s, 1 H), 9.98 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.0, 56.1, 71.1, 112.9, 115.7, 121.6, 122.0, 123.8, 124.8, 128.0, 129.0, 130.5, 149.4, 150.4, 157.4, 159.5, 166.6.

Anal. Calcd for $C_{17}H_{13}ClN_4O_2S$: C, 54.77; H, 3.51; N, 15.03. Found: C, 54.67; H, 3.49; N, 15.01.

Ethyl 3-Amino-6-methyl-5-(phenylcarbamoyl)thieno[2,3-*b*]pyridine-2-carboxylate (5i)
Yield: 317 mg (89%); white solid; mp 264–266 °C.

IR (KBr): 3456, 3267, 1680, 1650, 1620, 1529, 1259, 1128, 1063, 748, 690 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.26 (t, J = 7.0 Hz, 3 H), 2.65 (s, 3 H), 4.25 (q, J = 7.0 Hz, 2 H), 7.09 (t, J = 7.0 Hz, 1 H), 7.34 (s, 2 H), 7.36 (s, 1 H), 7.73 (d, J = 7.5 Hz, 1 H), 8.75 (s, 1 H), 10.62 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.5, 23.0, 60.1, 93.4, 119.7, 123.0, 123.9, 128.6, 128.8, 130.8, 139.0, 147.9, 157.3, 159.7, 164.4, 166.4.

Anal. Calcd for $C_{18}H_{17}N_3O_3S$: C, 60.83; H, 4.82; N, 11.82. Found: C, 61.09; H, 4.76; N, 11.89.

Ethyl 3-Amino-5-[(4-chlorophenyl)carbamoyl]-6-methylthieno[2,3-*b*]pyridine-2-carboxylate (5j)
Yield: 323 mg (83%); white solid; mp 295–297 °C.

IR (KBr): 3256, 1682, 1647, 1612, 1493, 1292, 1258, 1094, 825, 814 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.26 (t, J = 7.0 Hz, 3 H), 2.63 (s, 3 H), 4.24 (q, J = 7.0 Hz, 2 H), 7.34 (s, 2 H), 7.39 (d, J = 9.0 Hz, 2 H), 7.78 (d, J = 9.0 Hz, 2 H), 8.79 (s, 1 H), 10.86 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 15.0, 23.5, 60.6, 93.9, 121.7, 123.5, 128.1, 128.8, 129.3, 131.3, 138.5, 148.3, 157.8, 160.3, 164.9, 167.0.

Anal. Calcd for $C_{18}H_{16}ClN_3O_3S$: C, 55.45; H, 4.14; N, 10.78. Found: C, 55.71; H, 4.19; N, 10.76.

Ethyl 3-Amino-6-methyl-5-(*p*-tolylcarbamoyl)thieno[2,3-*b*]pyridine-2-carboxylate (5k)
Yield: 298 mg (81%); white solid; mp 287–289 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.26 (t, J = 7.0 Hz, 3 H), 2.24 (s, 3 H), 2.63 (s, 3 H), 4.24 (q, J = 7.0 Hz, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 7.32 (s, 2 H), 7.60 (d, J = 8.0 Hz, 2 H), 8.70 (s, 1 H), 10.51 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.4, 20.5, 22.9, 60.0, 93.4, 119.6, 123.0, 128.7, 129.2, 130.6, 132.9, 136.5, 147.8, 157.2, 159.6, 164.4, 166.1.

Anal. Calcd for $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.66; H, 5.21; N, 11.43.

Ethyl 3-Amino-5-[(2-methoxyphenyl)carbamoyl]-6-methylthieno[2,3-*b*]pyridine-2-carboxylate (5l)
Yield: 309 mg (80%); white solid; mp 126–128 °C.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.27 (t, J = 7.0 Hz, 3 H), 2.66 (s, 3 H), 3.79 (s, 3 H), 4.24 (q, J = 7.0 Hz, 2 H), 6.96 (t, J = 7.5 Hz, 1 H), 7.06 (d, J = 7.5 Hz, 1 H), 7.13–7.18 (m, 1 H), 7.33 (s, 2 H), 7.89 (d, J = 7.5 Hz, 1 H), 8.65 (s, 1 H), 9.77 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 14.4, 23.0, 55.7, 60.0, 93.3, 111.5, 120.3, 122.9, 123.4, 125.7, 126.7, 128.9, 130.5, 147.9, 151.0, 157.2, 159.5, 164.4, 166.6.

Anal. Calcd for $C_{19}H_{19}N_3O_4S$: C, 59.21; H, 4.97; N, 10.90. Found: C, 58.97; H, 4.91; N, 10.96.

Ethyl 3-Amino-5-[(4-chloro-2,5-dimethoxyphenyl)carbamoyl]-6-methylthieno[2,3-*b*]pyridine-2-carboxylate (5m)
Yield: 353 mg (79%); white solid; mp 147–149 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (t, J = 7.0 Hz, 3 H), 2.84 (s, 3 H), 3.84 (s, 3 H), 3.92 (s, 3 H), 4.37 (q, J = 7.0 Hz, 2 H), 6.04 (s, 2 H), 6.91 (s, 1 H), 8.10 (s, 1 H), 8.21 (s, 1 H), 8.31 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4, 23.8, 56.3, 56.7, 60.8, 98.8, 104.8, 112.2, 116.5, 122.8, 126.4, 127.6, 128.3, 142.0, 146.0, 149.0, 157.5, 161.5, 165.3, 166.1.

Anal. Calcd for $C_{20}H_{20}ClN_3O_5S$: C, 53.39; H, 4.48; N, 9. 34. Found: C, 53.18; H, 4.45; N, 9.40.

Ethyl 3-Amino-5-acetyl-6-methylthieno[2,3-*b*]pyridine-2-carboxylate (5n)
Yield: 117 mg (51%). Compound **5n** is a known compound; its analytical data are in good agreement with those reported in the literature.[21]

Acknowledgement

Financial support of this research by the National Natural Science Foundation of China (21172211 and 20872136) is greatly acknowledged.

References

(1) (a) Gibson, V. C.; Redshaw, C.; Solan, G. A. *Chem. Rev.* **2007**, *107*, 1745. (b) Ma, X. Q.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752. (c) Vidaillac, C.; Guillon, J.; Arpin, C.; Forfar-Bares, I.; Ba, B. B.; Grellet, J.; Moreau, S.; Caignard, D. H.; Jarry, C.; Quentin, C. *Antimicrob. Agents Chemother.* **2007**, *51*, 831.
(2) (a) Temple, C.; Rener, G. A.; Waud, W. R.; Noker, P. E. *J. Med. Chem.* **1992**, *35*, 3686. (b) Mahata, P. K.; Venkatesh, C.; Kumar, U. K. S.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2003**, *68*, 3966.
(3) Balasubramanian, M.; Keay, J. G. In *Comprehensive Heterocyclic Chemistry II*, Vol. 5; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, **1996**, 245–300.

(4) (a) Schnute, M. E.; Anderson, D. J.; Brideau, R. J.; Ciske, F. L.; Collier, S. A.; Cudahy, M. M.; Eggen, M.; Genin, M. J.; Hopkins, T. A.; Judge, T. M.; Kim, E. J.; Knechtel, M. L.; Nair, S. K.; Nieman, J. A.; Oien, N. L.; Scott, A.; Tanis, S. P.; Vaillancourt, V. A.; Wathen, M. W.; Wieber, J. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3349. (b) Schnute, M. E.; Cudahy, M. M.; Brideau, R. J.; Homa, F. L.; Hopkins, T. A.; Knechtel, M. L.; Oien, N. L.; Pitts, T. W.; Poorman, R. A.; Wathen, M. W.; Wieber, J. L. *J. Med. Chem.* **2005**, *48*, 5794.
(5) Bahekar, R. H.; Jain, M. R.; Jadav, P. A.; Prajapati, V. M.; Patel, D. N.; Gupta, A. A.; Sharma, A.; Tom, R.; Bandyopadhya, D.; Modi, H.; Patel, P. R. *Bioorg. Med. Chem.* **2007**, *15*, 6782.
(6) (a) Abdel-Rahman, A. E.; Bakhite, E. A.; Al-Taifi, E. A. *Pharmazie* **2003**, *58*, 372. (b) Eldin, S. M. *Z. Naturforsch., B: Chem. Sci.* **1999**, *54b*, 674. (c) Hussin, A. M.; Abu-Shanab, F. A.; Ishak, E. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *159*, 55.
(7) Hayakawa, I.; Shioya, R.; Agatsuma, T.; Furukawa, H.; Sugano, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3411.
(8) Bernardino, A. M. R.; Pinheiro, L. C. da S..; Rodrigues, C. R.; Loureiro, N. I.; Castro, H. C.; Lanfredi-Rangel, A.; Sabtini-Lopes, J.; Borges, J. C.; Carvalho, J. M.; Romeiro, G. A.; Ferreira, V. F.; Fruguphetti, I. C. P. P.; Vannier-Santos, M. A. *Bioorg. Med. Chem.* **2006**, *14*, 5765.
(9) Krauze, A.; Germame, S.; Eberlins, O.; Sturms, I.; Klusa, V.; Duburs, G. *Eur. J. Med. Chem.* **1999**, *34*, 301.
(10) (a) Buchstaller, H. P.; Siebert, C. D.; Steinmetz, R.; Frank, I.; Berger, M. L.; Gottschlich, R.; Leibrock, J.; Krug, M.; Steinhilber, D.; Noe, C. R. *J. Med. Chem.* **2006**, *49*, 864. (b) May, B. C. H.; Zorn, J. A.; Witkop, J.; Sherrill, J.; Wallace, A. C.; Legname, G.; Prusiner, S. B.; Cohen, F. E. *J. Med. Chem.* **2007**, *50*, 65.
(11) Suarez, M.; Ochoa, E.; Pita, B.; Espinosa, R.; Gonzalez, L.; Martin, N.; Quinteiro, M.; Seoane, C.; Soto, J. L. *J. Heterocycl. Chem.* **1997**, *34*, 931.
(12) (a) Elneairy, M. A. A.; Gad-Elkareem, M. A. M.; Abdel-Fattah, A. M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2006**, *181*, 1451. (b) Abdelhamid, A. O.; Ismail, Z. H.; Abdel-Gawad, S. M.; Ghorab, M. M.; Abdel-Aziem, A. *Phosphorus, Sulfur Silicon Relat. Elem.* **2009**, *184*, 58. (c) Aitken, R. A.; Garnett, A. N. *New J. Chem.* **2009**, *33*, 2402.
(13) Song, Y. H.; Seo, J. M. *J. Heterocycl. Chem.* **2007**, *44*, 1439.
(14) (a) Gad-Elkareem, M. A. M.; Elneairy, M. A. A.; Taha, A. M. *Heteroat. Chem.* **2007**, *18*, 405. (b) Song, Y. H.; Seo, J. M. *J. Heterocycl. Chem.* **2007**, *44*, 1439. (c) Abu-Shanab, F. A.; Elkholy, Y. M.; Elnagdi, M. H. *Synth. Commun.* **2002**, *32*, 3493.
(15) Zhang, R.; Zhang, D. Y.; Guo, Y. L.; Zhou, G. Y.; Jiang, Z. J.; Dong, D. W. *J. Org. Chem.* **2008**, *73*, 9504.
(16) Xiang, D.; Yang, Y.; Zhang, R.; Liang, Y.; Pan, W.; Huang, J.; Dong, D. *J. Org. Chem.* **2007**, *72*, 8593.
(17) Zhang, R.; Zhang, D.; Liang, Y.; Zhou, G.; Dong, D. *J. Org. Chem.* **2011**, *76*, 2880.
(18) Zhang, R.; Liang, Y. J.; Zhou, G. Y.; Wang, K. W.; Dong, D. W. *J. Org. Chem.* **2008**, *73*, 8089.
(19) Huang, J.; Liang, Y.; Pan, W.; Yang, Y.; Dong, D. *Org. Lett.* **2007**, *9*, 5345.
(20) (a) El-Saghier, A. *Molecules* **2002**, *7*, 756. (b) Mohareb, R. M.; Shams, H. Z.; Elkholy, Y. M.; Azam, R. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *155*, 215.
(21) Yakunin, Y. Y.; Dyachenko, V. D.; Litvinov, V. P. *Chem. Heterocycl. Compd. (Engl. Transl.)* **2001**, *37*, 581.

