DOI 10.1007/s10593-016-1883-x

Chemistry of Heterocyclic Compounds **2016**, *52*(5), 326–330

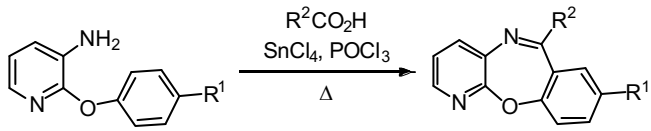
Synthesis of pyrido[2,3-*b*][1,4]benzoxazepines *via* a Friedel–Crafts cyclization

Sigen Guo[1], Xinran Zhong[1], Bowen Gong[1], Hongming Cui[1], Jinbao Xiang[1]*

[1] *Center for Combinatorial Chemistry and Drug Discovery, School of Pharmaceutical Sciences Jilin University, 1266 Fujin Road, Changchun, Jilin 130021, P. R. China e-mail: jbxiang@jlu.edu.cn*

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2016, *52*(5), 326–330

Submitted March 25, 2016
Accepted May 12, 2016



An efficient and practical method has been developed for the synthesis of 6-aryl-substituted pyrido[2,3-*b*][1,4]benzoxazepines *via* a Friedel–Crafts reaction of readily accessible 2-phenoxypyridin-3-amines and aromatic acids.

Keywords: 2-phenoxypyridin-3-amine, pyrido[2,3-*b*][1,4]benzoxazepine, tricyclic compounds, Friedel–Crafts cyclization.

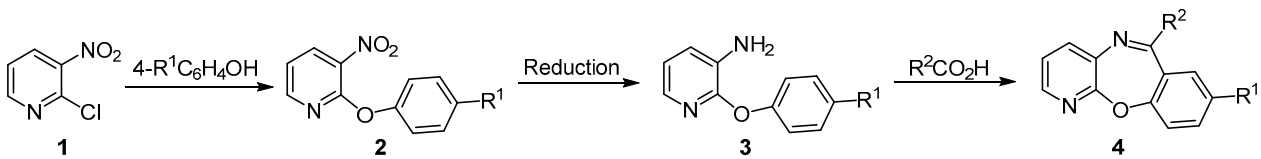
The development of practical methods to provide access to drug-like heterocycles often plays an important role in drug discovery projects.[1] Pyrido[2,3-*b*][1,4]benzoxazepine derivatives represent an exciting field of research in medicinal chemistry due to their biological activity, including the effects as non-nucleoside inhibitors of HIV-1 reverse transcriptase[2] and the influence on central nervous system.[3] However, the synthesis of 6-aryl-substituted pyrido[2,3-*b*][1,4]benzoxazepine derivatives has rarely appeared in literature. Thus far only one five-stage route for the synthesis of 6-aryl-substituted pyrido[2,3-*b*][1,4]-benzoxazepine derivatives has been reported, which entailed the Suzuki coupling of 6-chlorobenzo[*f*]pyrido[2,3-*b*]-[1,4]oxazepine with phenylboronic acid.[4] An efficient synthetic method to access 6-aryl-substituted pyrido[2,3-*b*]-[1,4]benzoxazepines would be useful for the exploration of biological activity of this class of compounds.

The research performed at our Center of Combinatorial Chemistry to prepare heterocyclic scaffolds and libraries led to the development of several methodologies employing Friedel–Crafts cyclization reactions as the key transformations.[5–7] We envisioned that 6-aryl-substituted pyrido-[2,3-*b*][1,4]benzoxazepines **4** could be readily prepared by the reaction of key precursors **3**, prepared from simple 2-chloro-3-nitropyridine (**1**) and phenol, with different commercially available carboxylic acids (Scheme 1).

The key precursors **3** were synthesized in a two-step sequence as depicted in Scheme 2. The commercially available 2-chloro-3-nitropyridine (**1**) was treated with phenols in DMF in the presence of K_2CO_3, giving the respective substituted 3-nitropyridines **2a–c** in excellent yields. The reduction of nitro groups in compounds **2a–c** with H_2 in the presence of Pd/C in EtOAc/MeOH[8] or with Fe/NH_4Cl in refluxing EtOH/H_2O[9] furnished the desired precursors **3** in high yields.

Initially, the precursor **3a** was selected to test the reaction conditions required to generate pyrido[2,3-*b*][1,4]benzoxaze-pines **4**. Previously, polyphosphoric acid (PPA)/$POCl_3$,[5] $SnCl_4$/$POCl_3$,[6] and $POCl_3$/MeCN[7] were reported to be effective reagents for promoting Friedel–Crafts cyclization reactions. When compound **3a** and $PhCO_2H$ were treated with PPA in refluxing $POCl_3$ for 14 h, the cyclization product **4a** was obtained in only 28% yield, and the intermediate amide **5a** was obtained in 48% yield (Table 1,

Scheme 1



Scheme 2

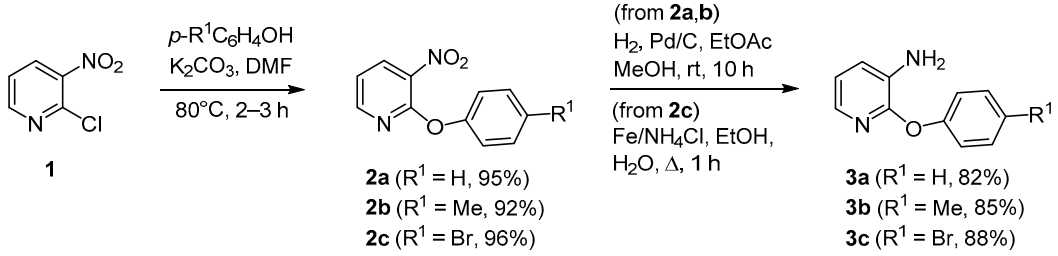
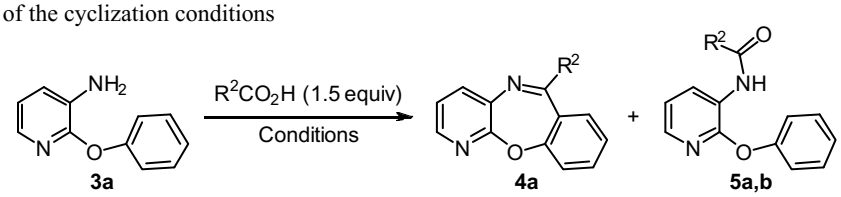


Table 1. Optimization of the cyclization conditions

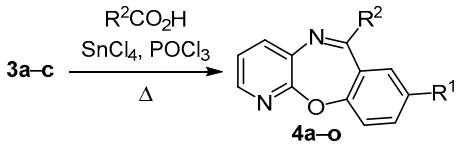


Entry	R^2	Conditions	Time	Product **4** (yield, %)	Product **5** (yield, %)
1	Ph	PPA (1.5 equiv), $POCl_3$, Δ	14 h	**4a** (28)	**5a** (48)
2	Ph	$SnCl_4$ (2.0 equiv), $POCl_3$, Δ	12 h	**4a** (90)	–
3	Ph	$POCl_3$ (4.0 equiv), MeCN, Δ	21 h	–	**5a** (88)
4	Et	$SnCl_4$ (2.0 equiv), $POCl_3$, Δ	10 min	–	**5b** (76)
5	Et	$SnCl_4$ (2.0 equiv), $POCl_3$, Δ	1 h	–	–
6	Et	$SnCl_4$ (2.0 equiv), $POCl_3$, 80°C	2 h	–	**5b** (85)
7	Et	$SnCl_4$ (2.0 equiv), $POCl_3$, 80°C	14 h	–	–

entry 1). The treatment of precursor **3a** and $PhCO_2H$ with $SnCl_4$ in refluxing $POCl_3$ for 12 h gave the desired product **4a** in 90% yield (entry 2). When the above reaction was carried out with $POCl_3$ in refluxing MeCN, only the intermediate amide **5a** was produced (entry 3). We also attempted to expand the cyclization reaction to aliphatic acids. However, the treatment of precursor **3a** and propionic acid with $SnCl_4$ in $POCl_3$ did not give the desired pyridobenzoxazepine; the amide **5b** was isolated instead in 76% yield (entry 4). The amide **5b** appeared to be labile under the reaction conditions, as the longer reaction time resulted in its decomposition (entry 5). Decreasing of the reaction temperature generated the amide **5b** in 85% yield without the desired cyclization product (entry 6), while prolonged reaction time again led to decomposition (entry 7). Having identified the optimal reaction conditions (entry 2), we investigated the reactions of precursors **3a–c** with several aromatic acids. The results are summarized in Table 2.

As presented in Table 2, various aromatic acids participated in the cyclization reaction effectively to produce the expected pyrido[2,3-*b*][1,4]benzoxazepines **4** in good to excellent yields (entries 1–7). Both electron-donating (entries 2, 3) and electron-withdrawing (entries 4, 5) substituted benzoic acids were tolerated. The reaction proceeded faster when benzoic acids with an electron-donating group were employed (entries 2 and 3 *vs* entries 4 and 5). Two examples of heteroaromatic acids were also tested: 2-furoic acid and nicotinic acid (entries 6 and 7), and the reactions gave lower yields of oxazepines than the reactions with benzoic acid derivatives. The application of (*E*)-cinnamic

Table 2. Preparation of pyrido[2,3-*b*][1,4]benzoxazepines **4a–o**



Entry	R^1	R^2	Time, h	Product	Yield, %
1	H	Ph	12	**4a**	90
2	H	*p*-MeC_6H_4	9	**4b**	92
3	H	*p*-$MeOC_6H_4$	11	**4c**	89
4	H	*p*-FC_6H_4	20	**4d**	88
5	H	*m*-$O_2NC_6H_4$	25	**4e**	93
6	H	Furan-2-yl	12	**4f**	64
7	H	Pyridin-3-yl	20	**4g**	72
8	H	(*E*)-2-Phenylethenyl	12	**4h**	0*
9	Me	Ph	11	**4i**	91
10	Me	*p*-MeC_6H_4	9	**4j**	93
11	Me	*p*-FC_6H_4	21	**4k**	92
12	Me	*p*-$O_2NC_6H_4$	22	**4l**	95
13	Br	Ph	50	**4m**	68
14	Br	*p*-MeC_6H_4	48	**4n**	64
15	Br	*p*-$O_2NC_6H_4$	120	**4o**	72

* *N*-(2-Phenoxypyridin-3-yl)cinnamamide (**5h**) was isolated in 80% yield after 10 min, while longer reaction time led to its decomposition.

acid in this reaction failed to give the desired product **4h** (entry 8). In order to determine the electronic effects of the substituents, precursors **3** with either electron-donating or electron-withdrawing functional groups were tested (entries 9–15). Tuning the electron density of the benzene ring had significant effects on both the reaction rates and yields (entry 9 *vs* entry 1 *vs* entry 13). The presence of a bromo substituent in precursors **3** appears to reduce both the reaction rate and yield of the final products.

In conclusion, we have developed an efficient and practical strategy for the synthesis of 6-aryl-substituted pyrido[2,3-*b*][1,4]benzoxazepines *via* a Friedel−Crafts reaction of readily accessible 2-phenoxypyridin-3-amines and aromatic acids in good to excellent yields. Drug-like structures based on these heterocycles could be of interest in chemical biology and drug discovery.

Experimental

^{1}H and ^{13}C NMR data were obtained on a Varian Mercury 300 NMR spectrometer (300 and 75 MHz, respectively) with TMS as internal standard and $CDCl_3$ as solvent unless otherwise stated. Mass spectra and HPLC data was recorded on an Agilent 1100 LC/MS system with Alltech ELSD 2000 (ESI). High-resolution mass spectra (HRMS) were obtained on a time-of-flight (TOF) mass spectrometer (ESI). Melting points were determined on a XT5 melting point apparatus and were not corrected. Phosphorus oxychloride ($POCl_3$) was freshly distilled. DMF was dried on CaH_2 and distilled. All other commercial reagents were used as received without additional purification.

Synthesis of 3-nitro-2-phenoxypyridines 2a–c (General method). Anhydrous K_2CO_3 (10.4 g, 75.2 mmol) was added to a stirred solution of 2-chloro-3-nitropyridine (**1**) (10.0 g, 63.0 mmol) and the appropriate phenol (75.2 mmol) in DMF (150 ml). The resulting solution was stirred for 2–3 h at 80°C. The reaction mixture was then poured into water and the precipitate was filtered off, washed with water, and then dried to give the desired product **2**.

3-Nitro-2-phenoxypyridine (2a). Yield 13.0 g (95%). Yellow solid. Mp 90–91°C (DMF–H_2O) (mp 94°C (EtOH)[10]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.13–7.20 (3H, m, H Ph, H Py); 7.29 (1H, t, *J* = 7.5, H Ph); 7.43–7.48 (2H, m, H Ph); 8.33–8.38 (2H, m, H Py). ^{13}C NMR spectrum, δ, ppm: 118.4; 121.8; 125.9; 129.8; 134.7; 135.5; 151.9; 152.7; 155.9. Mass spectrum, *m*/*z*: 217 $[M+H]^+$.

3-Nitro-2-(*p*-tolyloxy)pyridine (2b). Yield 13.4 g (92%). Yellow solid. Mp 95–96°C (DMF–H_2O) (mp 112°C (benzene–petroleum ether)[11]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.38 (3H, s, CH_3); 7.06 (2H, d, *J* = 8.4, H Ph); 7.11–7.15 (1H, m, H Py); 7.24 (2H, d, *J* = 9.0, H Ph); 8.33–8.37 (2H, m, H Py). ^{13}C NMR spectrum, δ, ppm: 21.0; 118.2; 121.5; 130.4; 134.6; 135.5; 135.6; 150.4; 151.9; 156.2. Mass spectrum, *m*/*z*: 231 $[M+H]^+$.

2-(4-Bromophenoxy)-3-nitropyridine (2c). Yield 17.8 g (96%). Yellow solid. Mp 91–93°C (DMF–H_2O) (mp 95°C (benzene–petroleum ether)[11]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.07–7.10 (2H, m, H Ph); 7.17–7.21 (1H, m, H Py); 7.54–7.57 (2H, m, H Ph); 8.33–8.40 (2H, m, H Py). ^{13}C NMR spectrum, δ, ppm: 118.8; 119.0; 123.7; 132.9; 134.6; 135.7; 151.7; 151.8; 155.5. Mass spectrum, *m*/*z*: 295 $[M+H]^+$.

Synthesis of 2-aryloxy-substituted pyridin-3-amines 3a,b (General method). A 10% Pd/C catalyst (1.22 g) was added to a stirred solution of 2-aryloxy-3-nitropyridine **2a** (12.2 g, 56.5 mmol) or **2b** (12.2 g, 53.0 mmol) in EtOAc (100 ml) and MeOH (100 ml). The resulting suspension was stirred at room temperature under H_2 atmosphere (1 bar) for 10 h. The reaction mixture was filtered through Celite and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (petroleum ether–EtOAc, 3:1 (v/v)) afforded the desired product **3a** or **3b**.

2-Phenoxypyridin-3-amine (3a). Yield 8.6 g (82%). White solid. Mp 105–107°C (petroleum ether–EtOAc) (mp 106°C (petroleum ether)[10a]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.93 (2H, br. s, NH_2); 6.81–6.85 (1H, m, H Py); 7.01 (1H, d, *J* = 7.5, H Py); 7.12–7.19 (3H, m, H Ph); 7.38 (2H, t, *J* = 7.8, H Ph); 7.56 (1H, d, *J* = 4.8, H Py). ^{13}C NMR spectrum, δ, ppm: 119.6; 120.8; 122.2; 124.3; 129.6; 132.1; 135.8; 151.7; 154.4. Mass spectrum, *m*/*z*: 187 $[M+H]^+$.

2-(*p*-Tolyloxy)pyridin-3-amine (3b). Yield 9.0 g (85%). White solid. Mp 129–131°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.34 (3H, s, CH_3); 3.94 (2H, br. s, NH_2); 6.79–6.83 (1H, m, H Py); 6.99–7.04 (3H, m, H Ph, H Py); 7.18 (2H, d, *J* = 8.7, H Ph); 7.55 (1H, dd, *J* = 5.7, *J* = 1.5, H Py). ^{13}C NMR spectrum, δ, ppm: 20.9; 119.2; 120.9; 121.9; 130.1; 131.8; 134.0; 135.8; 151.9; 152.2. Found, *m*/*z*: 201.1034 $[M+H]^+$. $C_{12}H_{13}N_2O$. Calculated, *m*/*z*: 201.1022.

Synthesis of 2-(4-bromophenoxy)pyridin-3-amine (3c). 2-(4-Bromophenoxy)-3-nitropyridine (**2c**) (10.3 g, 35 mmol), iron powder (5.90 g, 105 mmol), and NH_4Cl (1.87 g, 35 mmol) were added in sequence to a mixture of water (30 ml) and EtOH (120 ml). The reaction mixture was stirred and heated to reflux for 1 h and filtered through Celite, and the filtrate was concentrated *in vacuo*. The residue was diluted with water (120 ml) and extracted with EtOAc (3×40 ml). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give 2-(4-bromophenoxy)pyridin-3-amine (**3c**). Yield 8.2 g (88%). Light-red solid. Mp 117–119°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.91 (2H, br. s, NH_2); 6.84–6.88 (1H, m, H Py); 7.04 (3H, d, *J* = 9.0, H Ph, H Py); 7.49 (2H, d, *J* = 8.7, H Ph); 7.55 (1H, dd, *J* = 4.8, *J* = 1.5, H Py). ^{13}C NMR spectrum, δ, ppm: 117.2; 119.9; 122.4; 122.8; 131.9; 132.6; 135.7; 151.4; 153.3. Found, *m*/*z*: 264.9982 $[M+H]^+$. $C_{11}H_{10}BrN_2O$. Calculated, *m*/*z*: 264.9971.

Synthesis of pyrido[2,3-*b*][1,4]benzoxazepines 4a–o and amides 5a,b,h (General method). The appropriate 2-aryloxypyridin-3-amine **3** (1.0 mmol), aromatic acid (1.5 mmol), and $SnCl_4$ (2.0 mmol) were dissolved in $POCl_3$ (5 ml). After the mixture was refluxed for the appropriate time, the mixture was poured into ice water (20 ml) and treated with 5 N aqueous NaOH to pH 9–10. The resulting solution was extracted with EtOAc (3×20 ml). The combined organic phase was washed with saturated Na_2CO_3 and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by flash chromatography (petroleum ether–EtOAc, 10:1 (v/v)) afforded the desired product **4a–o** or amide **5a**,**b**,**h**.

6-Phenylpyrido[2,3-*b*][1,4]benzoxazepine (4a). Yield 245 mg (90%). Yellow solid. Mp 102–104°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.19–7.26 (3H, m, H Ph, H Py); 7.44–7.56 (5H, m, H Ph); 7.80–7.83 (3H, m, H Ph, H Py); 8.15 (1H, dd, *J* = 4.8, *J* = 1.8, H Py). ^{13}C NMR spectrum, δ, ppm: 122.0; 122.4; 124.8; 126.7; 128.2; 129.8; 130.8; 131.2; 133.6; 135.5; 137.2; 139.4; 145.6; 156.0; 160.0; 168.4. Found, *m*/*z*: 273.1057 $[M+H]^+$. $C_{18}H_{13}N_2O$. Calculated, *m*/*z*: 273.1022.

6-(*p*-Tolyl)pyrido[2,3-*b*][1,4]benzoxazepine (4b). Yield 263 mg (92%). Yellow solid. Mp 180–182°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.43 (3H, s, CH_3); 7.16–7.28 (5H, m, H Ph, H Py); 7.46 (1H, d, *J* =7.5, H Ph); 7.52–7.58 (1H, m, H Ph); 7.72 (2H, d, *J* = 7.8, H Ph); 7.80 (1H, dd, *J* = 7.8, *J* = 1.5, H Py); 8.13 (1H, dd, *J* = 4.5, *J* = 1.5, H Py). ^{13}C NMR spectrum, δ, ppm: 21.4; 122.0; 122.3; 124.8; 126.8; 128.9; 129.8; 131.2; 133.4; 135.6; 136.7; 137.1; 141.2; 145.3; 156.1; 160.0; 168.3. Found, *m*/*z*: 287.1204 $[M+H]^+$. $C_{19}H_{15}N_2O$. Calculated, *m*/*z*: 287.1179.

6-(4-Methoxyphenyl)pyrido[2,3-*b*][1,4]benzoxazepine (4c). Yield 268 mg (89%). Yellow solid. Mp 126–128°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.88 (3H, s, CH_3); 6.97 (2H, d, *J* = 9.0, H Ph); 7.19–7.28 (3H, m, H Ph, H Py); 7.46 (1H, d, *J* = 8.1, H Ph); 7.52–7.55 (1H, m, H Ph); 7.76–7.81 (3H, m, H Ph, H Py); 8.12 (1H, dd, *J* = 4.8, *J* = 1.8, H Py). ^{13}C NMR spectrum, δ, ppm: 55.5; 113.7; 122.1; 122.5; 124.9; 126.8; 131.3; 131.7; 132.0; 133.5; 135.8; 137.1; 145.2; 156.2; 160.1; 162.0; 167.7. Found, *m*/*z*: 303.1136 $[M+H]^+$. $C_{19}H_{15}N_2O_2$. Calculated, *m*/*z*: 303.1128.

6-(4-Fluorophenyl)pyrido[2,3-*b*][1,4]benzoxazepine (4d). Yield 255 mg (88%). Yellow solid. Mp 107–109°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.14 (2H, d, *J* = 8.4, H Ph); 7.18–7.27 (3H, m, H Ph, H Py); 7.48 (1H, d, *J* = 8.1, H Ph); 7.55–7.59 (1H, m, H Ph); 7.78–7.86 (3H, m, H Ph, H Py); 8.16 (1H, dd, *J* = 4.5, *J* = 1.8, H Py). ^{13}C NMR spectrum, δ, ppm: 115.3; 115.6; 122.3; 122.6; 125.1; 126.6; 131.1; 132.0; 132.1; 133.9; 135.5; 135.62; 135.66; 137.3; 145.8; 156.0; 160.1; 162.9; 166.3; 167.2. Found, *m*/*z*: 291.0966 $[M+H]^+$. $C_{18}H_{12}FN_2O$. Calculated, *m*/*z*: 291.0928.

6-(3-Nitrophenyl)pyrido[2,3-*b*][1,4]benzoxazepine (4e). Yield 295 mg (93%). Yellow solid. Mp 233–235°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.16–7.19 (1H, m, H Ph); 7.23–7.31 (2H, m, H Py); 7.51 (1H, d, *J* = 8.4, H Ph); 7.60–7.68 (2H, m, H Ph); 7.87 (1H, dd, *J* = 7.8, *J* = 2.1, H Py); 8.12–8.15 (1H, m, H Ph); 8.20–8.22 (1H, m, H Py); 8.35–8.39 (1H, m, H Ph); 8.75 (1H, t, *J* = 1.8, H Ph). ^{13}C NMR spectrum, δ, ppm: 122.5; 122.6; 124.6; 125.2; 125.3; 125.8; 129.3; 130.3; 134.3; 135.0; 135.5; 137.5; 141.0; 146.5; 148.3; 155.7; 160.2; 165.8. Found, *m*/*z*: 318.0890 $[M+H]^+$. $C_{18}H_{12}N_3O_3$. Calculated, *m*/*z*: 318.0873.

6-(Furan-2-yl)pyrido[2,3-*b*][1,4]benzoxazepine (4f). Yield 168 mg (64%). Yellow solid. Mp 131–132°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.58–6.60 (1H, m, H furan); 6.91 (1H, d, *J* = 3.6, H furan); 7.21–7.30 (2H, m, H Ph, H Py); 7.45–7.48 (1H, m, H Ph); 7.58 (2H, t, *J* = 7.2, H Ph); 7.72 (1H, t, *J* = 0.6, H furan); 7.84 (1H, dd, *J* = 7.8, *J* = 1.8, H Py); 8.13 (1H, dd, *J* = 4.8, *J* = 1.8, H Py). ^{13}C NMR spectrum, δ, ppm: 112.3; 118.1; 122.1; 122.7; 125.2; 125.4; 130.3; 133.9; 135.5; 137.3; 145.6; 146.3; 152.2; 155.9; 157.2; 160.2. Found, *m*/*z*: 263.0831 $[M+H]^+$. $C_{16}H_{11}N_2O_2$. Calculated, *m*/*z*: 263.0815.

6-(Pyridin-3-yl)pyrido[2,3-*b*][1,4]benzoxazepine (4g). Yield 197 mg (72%). Yellow solid. Mp 124–126°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.19–7.30 (3H, m, H Ph, H Py); 7.40–7.45 (1H, m, H Ph); 7.50 (1H, d, *J* = 8.1, H Ph); 7.60–7.64 (1H, m, H Ph); 7.84 (1H, dd, *J* = 7.8, *J* = 1.8, H Py); 8.15–8.20 (2H, m, H Py); 8.75–8.76 (1H, m, H Py); 9.04 (1H, d, *J* = 1.8, H Py). ^{13}C NMR spectrum, δ, ppm: 122.5; 122.7; 123.2; 125.3; 126.1; 130.7; 134.2; 135.1; 135.3; 137.1; 137.5; 146.3; 150.9; 151.6; 155.9; 160.2; 166.0. Found, *m*/*z*: 274.0989 $[M+H]^+$. $C_{17}H_{12}N_3O$. Calculated, *m*/*z*: 274.0975.

8-Methyl-6-phenylpyrido[2,3-*b*][1,4]benzoxazepine (4i). Yield 260 mg (91%). Yellow solid. Mp 149–151°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.29 (3H, s, CH_3); 7.02 (1H, s, H Ph); 7.22–7.28 (2H, m, H Ph, H Py); 7.37 (1H, s, H Ph); 7.47–7.55 (3H, m, H Ph); 7.83 (3H, t, *J* = 7.5, H Ph, H Py); 8.15 (1H, d, *J* = 3.3, H Py). ^{13}C NMR spectrum, δ, ppm: 20.9; 121.8; 122.4; 126.4; 128.4; 129.9; 130.9; 131.3; 134.4; 134.7; 135.6; 137.3; 139.6; 145.6; 156.3; 158.1; 168.6. Found, *m*/*z*: 287.1187 $[M+H]^+$. $C_{19}H_{15}N_2O$. Calculated, *m*/*z*: 287.1179.

8-Methyl-6-(*p*-tolyl)pyrido[2,3-*b*][1,4]benzoxazepine (4j). Yield 280 mg (93%). Yellow solid. Mp 204–206°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.26 (3H, s, CH_3); 2.43 (3H, s, CH_3); 7.01 (1H, s, H Ph); 7.18–7.22 (1H, m, H Py); 7.27 (2H, d, *J* = 7.8, H Ph); 7.34 (2H, s, H Ph); 7.72 (2H, d, *J* = 8.1, H Ph); 7.77 (1H, dd, *J* = 7.2, *J* = 1.8, H Py); 8.11 (1H, dd, *J* = 4.5, *J* = 1.8, H Py). ^{13}C NMR spectrum, δ, ppm: 20.7; 21.5; 121.6; 122.3; 126.4; 129.0; 129.8; 131.3; 134.1; 134.5; 135.6; 136.7; 137.0; 141.2; 145.2; 156.2; 157.9; 168.4. Found, *m*/*z*: 301.1345 $[M+H]^+$. $C_{20}H_{17}N_2O$. Calculated, *m*/*z*: 301.1335.

6-(4-Fluorophenyl)-8-methylpyrido[2,3-*b*][1,4]benzoxazepine (4k). Yield 280 mg (92%). Yellow solid. Mp 166–168°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (3H, s, CH_3); 6.98 (1H, s, H Ph); 7.13–7.27 (3H, m, H Ph, H Py); 7.36 (2H, d, *J* = 1.2, H Ph); 7.76–7.87 (3H, m, H Ph, H Py); 8.14 (1H, dd, *J* = 4.5, *J* = 1.8, H Py). ^{13}C NMR spectrum, δ, ppm: 20.9; 115.3; 115.6; 121.9; 122.5; 126.2; 131.1; 132.0; 132.1; 134.5; 134.8; 135.5; 137.2; 145.7; 156.2; 158.0; 162.9; 166.2; 167.3. Found, *m*/*z*: 305.1101 $[M+H]^+$. $C_{19}H_{14}FN_2O$. Calculated, *m*/*z*: 305.1085.

8-Methyl-6-(4-nitrophenyl)pyrido[2,3-*b*][1,4]benzoxazepine (4l). Yield 315 mg (95%). Yellow solid. Mp 220–222°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.29 (3H, s, CH_3); 6.91 (1H, s, H Ph); 7.26–7.30 (1H, m, H Py); 7.36–7.43 (2H, m, H Ph); 7.84 (1H, dd, *J* = 7.8, *J* = 1.8, H Py); 8.02 (2H, d, *J* = 8.4, H Ph); 8.19–8.21 (1H, m, H Py); 8.33 (2H, d, *J* = 8.7, H Ph). ^{13}C NMR spectrum, δ, ppm: 20.7; 122.0; 122.5; 123.4; 125.5; 130.4; 130.6; 134.8; 134.9; 135.0; 137.5; 145.1; 146.4; 148.9; 155.7; 157.9; 166.2. Found, *m*/*z*: 332.1045 $[M+H]^+$. $C_{19}H_{14}N_3O_3$. Calculated, *m*/*z*: 332.1030.

8-Bromo-6-phenylpyrido[2,3-*b*][1,4]benzoxazepine (4m). Yield 239 mg (68%). Yellow solid. Mp 136–138°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.25–7.29 (1H, m, H Py); 7.34–7.37 (2H, m, H Ph); 7.47–7.58 (3H, m, H Ph);

7.66 (1H, dd, *J* = 8.4, *J* = 2.4, H Ph); 7.82 (3H, d, *J* = 7.8, H Ph, H Py); 8.16 (1H, dd, *J* = 4.8, *J* = 1.5, H Py). ^{13}C NMR spectrum, δ, ppm: 118.1; 122.8; 124.0; 128.5; 128.6; 129.9; 131.3; 133.6; 135.3; 136.5; 138.9; 146.0; 148.4; 155.7; 159.1; 167.0. Found, *m*/*z*: 351.0138 $[M+H]^+$. $C_{18}H_{12}BrN_2O$. Calculated, *m*/*z*: 351.0128.

8-Bromo-6-(*p*-tolyl)pyrido[2,3-*b*][1,4]benzoxazepine (4n). Yield 233 mg (64%). Yellow solid. Mp 177–179°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.45 (3H, s, CH_3); 7.23–7.36 (5H, m, H Ph, H Py); 7.65 (1H, dd, *J* = 8.7, *J* = 2.7, H Ph); 7.71 (2H, d, *J* = 8.1, H Ph); 7.80 (1H, dd, *J* = 7.5, *J* = 1.8, H Py); 8.14 (1H, dd, *J* = 4.8, *J* = 1.8, H Py). ^{13}C NMR spectrum, δ, ppm: 21.5; 117.8; 122.6; 123.7; 128.3; 129.1; 129.6; 133.5; 135.2; 135.9; 136.2; 137.2; 141.6; 145.5; 155.5; 158.8; 166.6. Found, *m*/*z*: 365.0299 $[M+H]^+$. $C_{19}H_{14}BrN_2O$. Calculated, *m*/*z*: 365.0284.

8-Bromo-6-(4-nitrophenyl)pyrido[2,3-*b*][1,4]benzoxazepine (4o). Yield 285 mg (72%). Yellow solid. Mp 235–237°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.26 (1H, s, H Ph); 7.30–7.34 (1H, m, H Ph, H Py); 7.39 (1H, d, *J* = 8.7, H Ph); 7.72 (1H, dd, *J* = 8.4, *J* = 2.1, H Ph); 7.86 (1H, dd, *J* = 7.8, *J* = 1.8, H Py); 8.02 (2H, d, *J* = 8.7, H Ph); 8.22 (1H, dd, *J* = 4.8, *J* = 1.8, H Py); 8.35 (2H, d, *J* = 8.4, H Ph). ^{13}C NMR spectrum, δ, ppm: 118.4; 123.0; 123.8; 124.4; 127.7; 130.7; 132.9; 134.8; 137.1; 137.9; 144.4; 147.0; 148.3; 155.2; 159.1; 164.7. Found, *m*/*z*: 395.9981 $[M+H]^+$. $C_{18}H_{11}BrN_3O_3$. Calculated, *m*/*z*: 395.9978.

***N*-(2-Phenoxypyridin-3-yl)benzamide (5a)**. Yield 255 mg (88%). White solid. Mp 120–122°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.05–7.09 (1H, m, H Py); 7.18–7.26 (3H, m, H Ph); 7.28–7.60 (5H, m, H Ph, H Py); 7.86–7.93 (3H, m, H Ph); 8.58 (1H, s, H Py); 8.91 (1H, d, *J* = 8.1, NH). ^{13}C NMR spectrum, δ, ppm: 119.3; 121.6; 123.7; 125.4; 127.2; 128.1; 129.0; 129.8; 132.3; 134.4; 141.0; 152.7; 153.4; 165.9. Found, *m*/*z*: 291.1147 $[M+H]^+$. $C_{18}H_{15}N_2O_2$. Calculated, *m*/*z*: 291.1128.

***N*-(2-Phenoxypyridin-3-yl)propionamide (5b)**. Yield 206 mg (85%). White solid. Mp 86–87°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.5, CH_3); 2.49 (2H, q, *J* = 7.5, CH_2); 6.99–7.03 (1H, m, H Py); 7.13–7.16 (2H, m, H Ph); 7.22–7.27 (1H, m, H Ph); 7.40–7.46 (2H, m, H Ph, H Py); 7.81 (2H, dd, *J* = 5.1, *J* = 1.8, H Ph, H Py); 8.76 (1H, dd, *J* = 8.1, *J* = 1.8, NH). ^{13}C NMR spectrum, δ, ppm: 9.6; 31.0; 119.3; 121.5; 123.7; 125.3; 128.0; 129.8; 140.7; 152.3; 153.4; 172.7. Found, *m*/*z*: 243.1142 $[M+H]^+$. $C_{14}H_{15}N_2O_2$. Calculated, *m*/*z*: 243.1128.

***N*-(2-Phenoxypyridin-3-yl)cinnamamide (5h)**. Yield 253 mg (80%). White solid. Mp 117–118°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.64 (1H, d, *J* = 15.3, PhCH=C<u>H</u>CO); 7.03–7.07 (1H, m, H Py); 7.16–7.19 (2H, m, H Ph); 7.23–7.28 (1H, m, H Ph); 7.39–7.47 (5H, m, H Ph, H Py); 7.56–7.59 (2H, m, H Ph); 7.80 (1H, d, *J* = 15.6, PhC<u>H</u>=CHCO); 7.82–7.86 (1H, m, H Ph); 8.01 (1H, s, H Py); 8.89 (1H, dd, *J* = 7.8, *J* = 1.8, NH). ^{13}C NMR spectrum, δ, ppm: 119.3; 120.7; 121.5; 123.9; 125.2; 128.2; 128.4; 129.0; 129.8; 130.2; 134.6; 140.9; 143.0; 152.5; 153.5; 164.5. Found, *m*/*z*: 317.1294 $[M+H]^+$. $C_{20}H_{17}N_2O_2$. Calculated, *m*/*z*: 317.1285.

The Supplementary information file containing LC-MS data and NMR spectra of the synthesized compounds is available online at http://link.springer.com/journal/10593.

This work was supported by a grant from the Sci-Tech Development Project of Jilin Province in China (No. 20160520039JH) and a grant from the Norman Bethune Program of Jilin University (No. 2015330). Additional support was provided by Changchun Discovery Sciences, Ltd.

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