

HETEROCYCLES, Vol. 98, No. 7, 2019, pp. 966 - 976. © 2019 The Japan Institute of Heterocyclic Chemistry  
Received, 27th April, 2019, Accepted, 1st July, 2019, Published online, 12th July, 2019  
DOI: 10.3987/COM-19-14093

## A CONVENIENT APPROACH TO THE SYNTHESIS OF NOVEL TRICYCLIC FUSED FURO[2,3-*b*]PYRIDINE DERIVATIVES

Fumi Okabe-Nakahara,\* Kazuhiro Tomoike, Hayate Nagabuchi, Eiichi Masumoto, Hiroshi Maruoka, and Kenji Yamagata

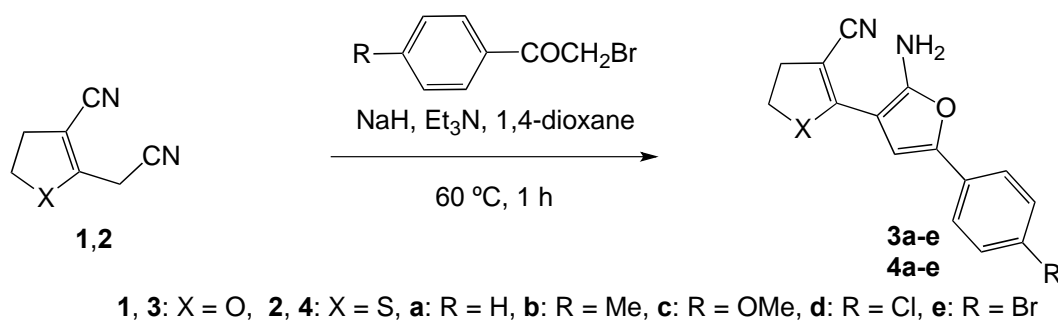
Faculty of Pharmaceutical Science, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku, Fukuoka, Japan. E-mail: fnakahara@fukuoka-u.ac.jp

**Abstract** – The synthesis of novel tricyclic fused furo[2,3-*b*]pyridine derivatives is described. 3-Cyano-4,5-dihydro-2-furan(and 2-thiophene)acetonitriles **1,2** were reacted with phenacyl bromides to give 5'-arylfuran-2'-amines **3,4**. Compounds **3,4** were intramolecularly cyclized in the presence of sodium ethoxide to yield tricyclic fused furo[2,3-*b*]pyridine derivatives **5,6**. Furthermore, one-pot synthesis of compounds **5,6** from starting materials **1,2** is also developed.

Many kinds of tricyclic 5-6-5 fused heterocyclic compounds have been synthesized<sup>1</sup> and reported to exhibit various biological activities.<sup>2</sup> Recently, our laboratory has developed an efficient synthetic method of fused 5-6-5 heterocyclic compounds.<sup>3,4</sup> Among fused 5-6-5 heterocyclic compounds, tricyclic fused furo[2,3-*b*]pyridines have been recognized for inducer of lipoprotein lipase mRNA expression for diabetes drugs,<sup>5</sup> and bronchodilator activity.<sup>6</sup> For this reason, these types of compounds are still of interest from the viewpoint of biological activity. Therefore, studies were made on the synthesis of novel tricyclic fused furo[2,3-*b*]pyridine derivatives using 3-cyano-4,5-dihydro-2-furan(and 2-thiophene)acetonitriles **1,2** as the starting materials as already reported in our previous literature.<sup>7</sup>

Initially, we examined the phenacylation and cyclization reaction of compounds **1,2** with phenacyl bromides to give 5'-arylfuran-2'-amine derivatives **3,4** (Scheme 1). Several methods for constructing a furan ring by reaction of a compound having a cyanomethyl group with phenacyl bromide have been reported.<sup>8</sup> Compounds **1,2** were reacted with phenacyl bromides in the presence of sodium hydride and triethylamine in 1,4-dioxane at 60 °C for 1 h to provide the corresponding compounds **3a-e** and **4a-e** in moderate yields (Table 1). By comparison of the IR spectra, NMR spectra, MS spectra and elemental analyses of **3a-e** and **4a-e**, the structure assignments given to these compounds seems to be correct (see experimental section). For example, the IR spectrum of **3a** displays bands at 3460, 3345 cm<sup>-1</sup> due to a primary amino group, and a band at 2186 cm<sup>-1</sup> due to a conjugated cyano group. The <sup>1</sup>H NMR spectrum

of **3a** in DMSO-*d*<sub>6</sub> exhibits D<sub>2</sub>O exchangeable a two-proton signal at  $\delta$  6.92 assignable to the primary amine, and a signal at  $\delta$  6.98 assignable to the 4'-H. The <sup>13</sup>C NMR spectrum of **3a** shows signals at  $\delta$  87.4,  $\delta$  104.0,  $\delta$  143.3 and  $\delta$  159.0 corresponding C-3', C-4', C-5' and C-2' carbons, respectively.



**Scheme 1**

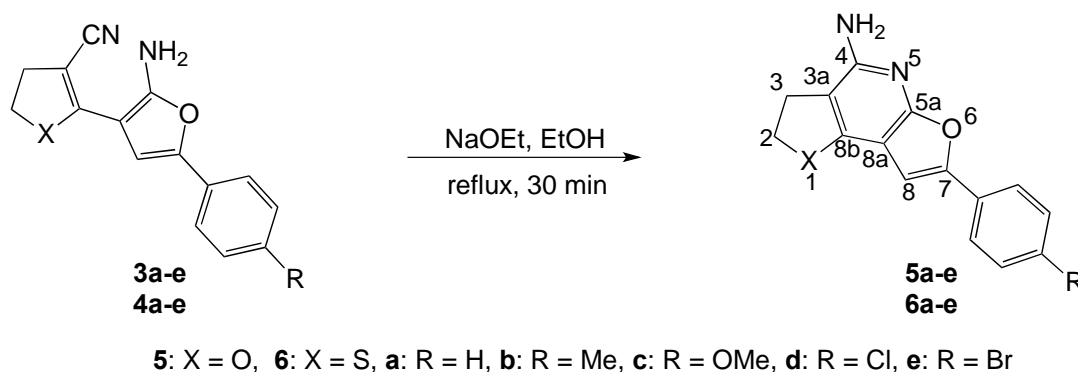
**Table 1.** Synthesis of **3a-e** and **4a-e** according to Scheme 1

Entry	Substrate	X	R	Product	Yield (%) <sup>a)</sup>
1	<b>1</b>	O	H	<b>3a</b>	37
2	<b>1</b>	O	Me	<b>3b</b>	24
3	<b>1</b>	O	OMe	<b>3c</b>	18
4	<b>1</b>	O	Cl	<b>3d</b>	34
5	<b>1</b>	O	Br	<b>3e</b>	39
6	<b>2</b>	S	H	<b>4a</b>	50
7	<b>2</b>	S	Me	<b>4b</b>	36
8	<b>2</b>	S	OMe	<b>4c</b>	37
9	<b>2</b>	S	Cl	<b>4d</b>	42
10	<b>2</b>	S	Br	<b>4e</b>	47

a) Yield of isolated products.

In the next step, we attempted intramolecular cyclization of compounds **3,4**. (Scheme 2). It has been reported that the intramolecular ring closure reaction occurs when the nitrogen atom of the amino group attacks the cyano group carbon.<sup>9</sup> The cyclization reaction of **4a** was chosen as a model. In the reaction for obtaining the intramolecular cyclized product **5a**, it was clarified that the conditions for refluxing in ethanol for 30 min using sodium ethoxide as a base gave good results. The results of reacting **3a-e** and **4a-e** with sodium ethoxide using optimized reaction conditions are summarized in Table 2. Elemental

analyses, MS spectra,  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of compounds **5a-e** and **6a-e** are consistent with the assigned structures (see experimental section). For example, the IR spectrum of **5a** shows the bands at 3452, 3301, 3190  $\text{cm}^{-1}$  due to a primary amino group. The  $^1\text{H}$  NMR spectrum of **5a** in  $\text{DMSO-}d_6$  exhibits the  $\text{D}_2\text{O}$  exchangeable a two-proton signal at  $\delta$  6.02 assignable to the primary amine, and a proton signal at  $\delta$  7.13 assignable to the 8-H. The  $^{13}\text{C}$  NMR spectrum of **5a** in  $\text{DMSO-}d_6$  shows signals at  $\delta$  97.5,  $\delta$  100.3,  $\delta$  153.8,  $\delta$  161.2, and  $\delta$  163.8 corresponding to C-8a, C-3a, C-4, C-8b, and C-5a carbons, respectively.



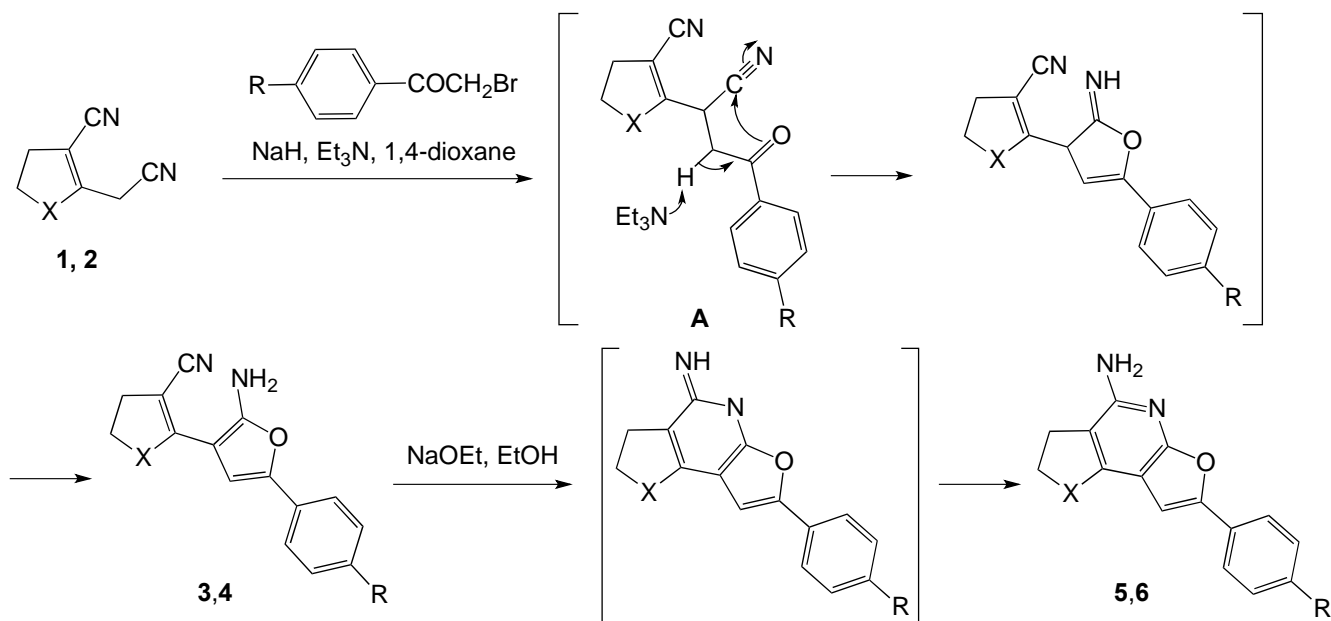
**Scheme 2**

**Table 2.** Synthesis of **5a-e** and **6a-e** according to Scheme 2

Entry	Substrate	X	R	Product	Yield (%) <sup>a)</sup>
1	<b>3a</b>	O	H	<b>5a</b>	72
2	<b>3b</b>	O	Me	<b>5b</b>	69
3	<b>3c</b>	O	OMe	<b>5c</b>	40
4	<b>3d</b>	O	Cl	<b>5d</b>	69
5	<b>3e</b>	O	Br	<b>5e</b>	75
6	<b>4a</b>	S	H	<b>6a</b>	55
7	<b>4b</b>	S	Me	<b>6b</b>	46
8	<b>4c</b>	S	OMe	<b>6c</b>	33
9	<b>4d</b>	S	Cl	<b>6d</b>	56
10	<b>4e</b>	S	Br	<b>6e</b>	57

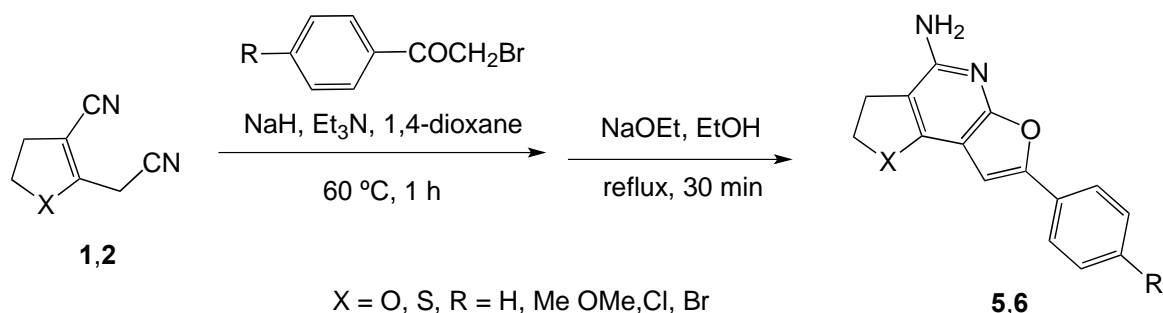
a) Yield of isolated products.

The formation of **5,6** can be explained by the mechanism shown in Scheme 3. After phenacylation reaction occurs at the active methylene site of compounds **1,2**, it is believed that a ring closure reaction occurs to form compounds **3,4**. Subsequently, an intramolecular ring closure reaction occurs in compounds **3,4** to form compounds **5,6**.



Scheme 3

On the basis of these result, we have tried to directly construct tricyclic fused furo[2,3-*b*]pyridines **5,6** from the starting materials **1,2** and phenacyl bromides in a one-pot process (Scheme 4). The results were shown in Table 3. Indeed, a mixture of **1,2** and phenacyl bromides in the presence of sodium hydride and triethylamine in 1,4-dioxane was stirred at 60 °C for 1 h. When the reaction mixture was refluxed with sodium ethoxide in ethanol for 30 min, the desired tricyclic fused furo[2,3-*b*]pyridines **5,6** were obtained. By comparison of the IR spectra, NMR spectra, MS spectra and elemental analyses of **5a-e** and **6a-e**, the structure assignments given to these compounds seems to be correct.



X = O, S, R = H, Me OMe, Cl, Br

Scheme 4

**Table 3.** One-pot synthesis of tricyclic fused furo[2,3-*b*]pyridine derivatives **5a-e** and **6a-e** starting from **1,2**.

Entry	Substrate	X	R	Product	Yield (%)
1	<b>1</b>	O	H	<b>5a</b>	28
2	<b>1</b>	O	Me	<b>5b</b>	17
3	<b>1</b>	O	OMe	<b>5c</b>	20
4	<b>1</b>	O	Cl	<b>5d</b>	23
5	<b>1</b>	O	Br	<b>5e</b>	29
6	<b>2</b>	S	H	<b>6a</b>	36
7	<b>2</b>	S	Me	<b>6b</b>	17
8	<b>2</b>	S	OMe	<b>6c</b>	27
9	<b>2</b>	S	Cl	<b>6d</b>	24
10	<b>2</b>	S	Br	<b>6e</b>	26

In conclusion, we have developed a convenient method for the synthesis of tricyclic fused furo[2,3-*b*]pyridine derivatives **5,6** proceeding by the phenacylation and cyclization reaction of **1,2** with phenacyl bromides, followed by intramolecular cyclization. This methodology offers significant advantage with regard to the simplicity of operation. Functionalized tricyclic fused furo[2,3-*b*]pyridine derivatives are important synthons in organic synthesis and for the preparation of biologically active compounds with interest in medicinal chemistry.

## EXPERIMENTAL

All melting points were obtained on a BUCHI M-560 melting and uncorrected. The IR spectra were recorded on a Nicolet iS5 FT-IR manufactured by Thermo Fisher Scientific using iD7 ATR accessory with a diamond crystal accessory. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were measured with a JEOL JNM-ECZ R spectrometer 600.17 and 150.91 MHz respectively. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts ( $\delta$ ) are reported in a part per million (ppm) relative to TMS at internal standard. Positive (+) MS FAB spectra were obtained on a JEOL JMS-700T spectrometer. Elemental analyses were performed on YANACO MT-6 CHN analyzer. The starting compounds **1,2** were prepared in this laboratory according to the procedure reported in literature.<sup>10</sup>

**General procedure for the preparation of 5-arylfuran-2-amines **3,4** from **1,2** and phenacyl bromides.** To an ice-cooled and stirred solution of **1,2** (5 mmol) in 1,4-dioxane (10 mL) was added 60% NaH (0.20 g, 5 mmol). The stirring was continued at rt until evolution of gas ceased. To the obtained

mixture were added phenacyl bromide, 4-methylphenacyl bromide, 4-methoxyphenacyl bromide, 4-chlorophenacyl bromide, or 4-bromophenacyl bromide, (5 mmol) and Et<sub>3</sub>N (0.51 g, 5 mmol) with stirring and then the mixture was stirred at 60 °C for 1 h. After removal of the solvent *in vacuo*, cold water was added to the residue. The resulting mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with water, dried over by Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography on alumina with CH<sub>2</sub>Cl<sub>2</sub> as eluent to afford 5-arylfuran-2-amines **3a-e** and **4a-e**.

**2'-Amino-4,5-dihydro-5'-phenyl-[2,3'-bifuran]-3-carbonitrile (3a):** (0.47 g, 37%); a colorless needles; mp 180-183 °C (Et<sub>2</sub>O); IR (ATR) 3460, 3345 (NH), 2186 (CN) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.87 (t, *J* = 9.2 Hz, 2H, 4-H), 4.51 (t, *J* = 9.2 Hz, 2H, 5-H), 6.92 (brs, 2H, NH<sub>2</sub>), 6.98 (s, 1H, 4'-H), 7.15-7.18 (m, 1H, aryl H), 7.32-7.35 (m, 2H, aryl H), 7.43-7.44 (m, 2H, aryl H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 30.0 (C-4), 71.2 (C-3), 72.1 (C-5), 87.4 (C-3'), 104.0 (C-4'), 119.7 (CN), 122.5, 127.0, 129.5, 130.0 (C aryl), 143.3 (C-5'), 159.0 (C-2'), 164.5 (C-2); MS: *m/z* 253 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.40; H, 4.83; N, 11.12.

**2'-Amino-4,5-dihydro-5'-(4-methylphenyl)-[2,3'-bifuran]-3-carbonitrile (3b):** (0.32 g, 24%); a pale yellow prisms; mp 204-205 °C (decomp) (Et<sub>2</sub>O); IR (ATR) 3463, 3352 (NH), 2187 (CN) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.25 (s, 3H, CH<sub>3</sub>), 2.86 (t, *J* = 9.3 Hz, 2H, 4-H), 4.51 (t, *J* = 9.3 Hz, 2H, 5-H), 6.87 (brs, 2H, NH<sub>2</sub>), 6.90 (s, 1H, 4'-H), 7.15 (d, *J* = 8.4 Hz, 2H, aryl H), 7.33 (d, *J* = 8.4 Hz, 2H, aryl H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 21.3 (CH<sub>3</sub>), 30.0 (C-4), 71.0 (C-3), 72.1 (C-5), 87.3 (C-3'), 103.0 (C-4'), 119.8 (CN), 122.6, 127.4, 130.0, 136.4 (C aryl), 143.6 (C-5'), 158.8 (C-2'), 164.5 (C-2); MS: *m/z* 267 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.17; H, 5.35; N, 10.47.

**2'-Amino-4,5-dihydro-5'-(4-methoxyphenyl)-[2,3'-bifuran]-3-carbonitrile (3c):** (0.25 g, 18%); a pale orange prisms; mp 202-203 °C (Et<sub>2</sub>O); IR (ATR) 3458, 3347 (NH), 2185 (CN) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.86 (t, *J* = 9.0 Hz, 2H, 4-H), 3.72 (s, 3H, OCH<sub>3</sub>), 4.50 (t, *J* = 9.0 Hz, 2H, 5-H), 6.80 (s, 1H, 4'-H), 6.82 (brs, 2H, NH<sub>2</sub>), 6.91-6.93 (m, 2H, aryl H), 7.36-7.38 (m, 2H, aryl H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 30.0 (C-4), 55.7 (OCH<sub>3</sub>), 70.9 (C-3), 72.0 (C-5), 87.2 (C-3'), 101.8 (C-4'), 115.0 (C aryl), 119.8 (CN), 123.0, 124.2 (C aryl), 143.6 (C-5'), 158.61 (C aryl), 158.65 (C-2'), 164.6 (C-2); MS: *m/z* 283 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.10; H, 5.02; N, 9.93.

**2'-Amino-5'-(4-chlorophenyl)-4,5-dihydro-[2,3'-bifuran]-3-carbonitrile (3d):** (0.49 g, 34%); a colorless prisms; mp 180-183 °C (decomp) (Et<sub>2</sub>O); IR (ATR) 3459, 3348 (NH), 2187 (CN) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.87 (t, *J* = 9.3 Hz, 2H, 4-H), 4.51 (t, *J* = 9.3 Hz, 2H, 5-H), 6.97 (brs, 2H, NH<sub>2</sub>), 7.01 (s, 1H, 4'-H), 7.37-7.39 (m, 2H, aryl H), 7.43-7.45 (m, 2H, aryl H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 30.0 (C-4), 71.4 (C-3), 72.1 (C-5), 87.6 (C-3'), 104.9 (C-4'), 119.6 (CN), 124.2, 128.9, 129.5, 131.1 (C aryl), 142.2

(C-5'), 159.1 (C-2'), 164.3 (C-2); MS:  $m/z$  288  $[M+H]^+$ . Anal. Calcd for  $C_{15}H_{11}ClN_2O_3$ : C, 62.84; H, 3.87; N, 9.77. Found: C, 62.74; H, 3.76; N, 9.76.

**2'-Amino-5'-(4-bromophenyl)-4,5-dihydro-[2,3'-bifuran]-3-carbonitrile (3e):** (0.64 g, 39%); a colorless prisms; mp 182-185 °C (decomp) ( $Et_2O$ ); IR (ATR) 3454, 3342 (NH), 2187 (CN)  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  2.87 (t,  $J = 9.3$  Hz, 2H, 4-H), 4.51 (t,  $J = 9.3$  Hz, 2H, 5-H), 6.99 (brs, 2H,  $NH_2$ ), 7.02 (s, 1H, 4'-H), 7.37-7.38 (m, 2H, aryl H), 7.50-7.53 (m, 2H, aryl H);  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  30.0 (C-4), 71.5 (C-3), 72.1 (C-5), 87.6 (C-3'), 105.0 (C-4'), 119.5 (C aryl), 119.6 (CN), 124.4, 129.2, 132.4 (C aryl), 142.2 (C-5'), 159.2 (C-2'), 164.3 (C-2); MS:  $m/z$  332  $[M+H]^+$ . Anal. Calcd for  $C_{15}H_{11}BrN_2O_2$ : C, 54.40; H, 3.35; N, 8.46. Found: C, 54.25; H, 3.34; N, 8.45.

**2-(2'-Amino-5'-phenylfuran-3'-yl)-4,5-dihydrothiophene-3-carbonitrile (4a):** (0.66 g, 50%); a yellow prisms; mp 125-126 °C (decomp) ( $Et_2O$ ); IR (ATR) 3413, 3323, 3297 (NH), 2185 (CN)  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  2.98 (t,  $J = 8.4$  Hz, 2H, 4-H), 3.34 (t,  $J = 8.4$  Hz, 2H, 5-H), 6.71 (brs, 2H,  $NH_2$ ), 7.03 (s, 1H, 4'-H), 7.15-7.17 (m, 1H, aryl H), 7.32-7.35 (m, 2H, aryl H), 7.44-7.46 (m, 2H, aryl H);  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  32.7 (C-5), 36.6 (C-4), 91.0 (C-3), 91.8 (C-3'), 106.2 (C-4'), 118.7 (CN), 122.5, 126.9, 129.4, 130.1 (C aryl), 143.0 (C-5'), 152.7 (C-2), 157.7 (C-2'); MS:  $m/z$  269  $[M+H]^+$ . Anal. Calcd for  $C_{15}H_{12}N_2OS$ : C, 67.14; H, 4.51; N, 10.44. Found: C, 67.12; H, 4.49; N, 10.40.

**2-(2'-Amino-5'-(4-methylphenyl)furan-3'-yl)-4,5-dihydrothiophene-3-carbonitrile (4b):** (0.51 g, 36%); a yellow prisms; mp 133-134 °C (decomp) ( $Et_2O$ ); IR (ATR) 3432, 3337 (NH), 2186 (CN)  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  2.25 (s, 3H,  $CH_3$ ), 2.96-2.99 (m, 2H, 4-H), 3.32-3.34 (m, 2H, 5-H), 6.65 (brs, 2H,  $NH_2$ ), 6.96 (s, 1H, 4'-H), 7.15 (d,  $J = 8.4$  Hz, 2H, aryl H), 7.34 (d,  $J = 8.4$  Hz, 2H, aryl H);  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  21.3 ( $CH_3$ ), 32.7 (C-5), 36.6 (C-4), 90.7 (C-3), 91.7 (C-3'), 105.2 (C-4'), 118.8 (CN), 122.6, 127.5, 130.0, 136.3 (C aryl), 143.3 (C-5'), 152.7 (C-2), 157.5 (C-2'); MS:  $m/z$  283  $[M+H]^+$ . Anal. Calcd for  $C_{16}H_{14}N_2OS \cdot 0.35H_2O$ : C, 66.57; H, 5.13; N, 9.70. Found: C, 66.68; H, 5.00; N, 9.92.

**2-(2'-Amino-5'-(4-methoxyphenyl)furan-3'-yl)-4,5-dihydrothiophene-3-carbonitrile (4c):** (0.55 g, 37%); a orange prisms; mp 127-128 °C (decomp) ( $Et_2O$ ); IR (ATR) 3420, 3327 (NH), 2183 (CN)  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  2.96-2.99 (m, 2H, 4-H), 3.31-3.34 (m, 2H, 5-H), 3.73 (s, 3H,  $OCH_3$ ), 6.60 (brs, 2H,  $NH_2$ ), 6.87 (s, 1H, 4'-H), 6.91-6.93 (m, 2H, aryl H), 7.37-7.40 (m, 2H, aryl H);  $^{13}C$  NMR (DMSO- $d_6$ ):  $\delta$  32.7 (C-5), 36.6 (C-4), 55.7 ( $OCH_3$ ), 90.5 (C-3), 91.7 (C-3'), 104.0 (C-4'), 115.0 (C aryl), 118.9 (CN), 123.0, 124.2 (C aryl), 143.3 (C-5'), 152.7 (C-2), 157.5 (C-2'), 158.6 (C aryl); MS:  $m/z$  300  $[M+H]^+$ . Anal. Calcd for  $C_{16}H_{14}N_2O_2S$ : C, 64.41; H, 4.73; N, 9.39. Found: C, 64.38; H, 4.77; N, 9.41.

**2-(2'-Amino-5'-(4-chlorophenyl)furan-3'-yl)-4,5-dihydrothiophene-3-carbonitrile (4d):** (0.64 g, 42%); a colorless prisms; mp 128-130 °C (decomp) ( $Et_2O$ ); IR (ATR) 3456, 3360 (NH), 2187 (CN)  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ ):  $\delta$  2.97-3.00 (m, 2H, 4-H), 3.32-3.35 (m, 2H, 5-H), 6.77 (brs, 2H,  $NH_2$ ), 7.07 (s, 1H,

4'-H), 7.37-7.39 (m, 2H, aryl H), 7.44-7.46 (m, 2H, aryl H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  32.7 (C-5), 36.6 (C-4), 91.5 (C-3), 91.8 (C-3'), 107.2 (C-4'), 118.6 (CN), 124.1, 129.0, 129.5, 131.0 (C aryl), 141.9 (C-5'), 152.6 (C-2), 157.8 (C-2'); MS:  $m/z$  304  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{OS}$ : C, 59.50; H, 3.66; N, 9.25. Found: C, 59.56; H, 3.64; N, 9.05.

**2-(2'-Amino-5'-(4-bromophenyl)furan-3'-yl)-4,5-dihydrothiophene-3-carbonitrile (4e):** (0.82 g, 47%); a yellow prisms; mp 143-145 °C (decomp) ( $\text{Et}_2\text{O}$ ); IR (ATR) 3444, 3345, 3300 (NH), 2188 (CN)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  2.97-3.00 (m, 2H, 4-H), 3.32-3.35 (m, 2H, 5-H), 6.77 (brs, 2H,  $\text{NH}_2$ ), 7.08 (s, 1H, 4'-H), 7.38-7.40 (m, 2H, aryl H), 7.50-7.53 (m, 2H, aryl H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  32.7 (C-5), 36.6 (C-4), 91.5 (C-3), 91.8 (C-3'), 107.4 (C-4'), 118.6 (CN), 119.4, 124.4, 129.3, 132.3 (C aryl), 141.9 (C-5'), 152.6 (C-2), 157.8 (C-2'); MS:  $m/z$  348  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{15}\text{H}_{11}\text{BrN}_2\text{OS}$ : C, 51.89; H, 3.19; N, 8.07. Found: C, 51.80; H, 3.16; N, 8.02.

**General procedure for the preparation of fused furo[2,3-*b*]pyridines 5,6 from 3,4 and sodium ethoxide.** A suspension of **3a-e**, **4a-e** (1 mmol) and NaOEt (0.14 g, 1 mmol) in EtOH (10 mL) was refluxed for 30 min. After removal of the solvent *in vacuo*, cold water was added to the residue. The precipitate was filtered off, washed with water dried and recrystallized from appropriate solvent to give fused furopyridine **5a-e** and **6a-e**.

**General procedure for the preparation of fused furo[2,3-*b*]pyridines 5,6 from 1,2, phenacyl bromides, sodium hydride, triethylamine and sodium ethoxide.** To an ice-cooled and stirred solution of **1**, **2** (10 mmol) in 1,4-dioxane (10 mL) was added 60% NaH (0.40 g, 10 mmol). The stirring was continued at rt until evolution of gas ceased. To the obtained mixture were added phenacyl bromide, 4-chlorophenacyl bromide, 4-bromophenacyl bromide, 4-methylphenacyl bromide and/or 4-methoxyphenacyl bromide (10 mmol) and  $\text{Et}_3\text{N}$  (1.01 g, 10 mmol) with stirring and then the mixture was stirred at 60 °C for 1 h. After removal of the solvent *in vacuo*, the residue added NaOEt (0.14 g, 10 mmol) in EtOH (100 mL) was refluxed for 30 min. After removal of the solvent *in vacuo*, cold water was added to the residue. The precipitate was filtered off, washed with water dried and recrystallized from appropriate solvent to give fused furopyridine **5a-e** and **6a-e**.

**2,3-Dihydro-7-phenyldifuro[2,3-*b*:2',3'-*d*]pyridin-4-amine (5a):** (0.18 g, 72% from **3a**) (0.71 g, 28% from **1**); a pale orange prisms; mp 217-218 °C (decomp) ( $\text{CH}_2\text{Cl}_2$ ); IR (ATR) 3452, 3301, 3190 (NH)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  2.97 (t,  $J = 9.0$  Hz, 2H, 3-H), 4.71 (t,  $J = 9.0$  Hz, 2H, 2-H), 6.02 (brs, 2H,  $\text{NH}_2$ ), 7.13 (s, 1H, 8-H), 7.24-7.27 (m, 1H, aryl H), 7.38-7.40 (m, 2H, aryl H), 7.71-7.73 (m, 2H, aryl H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ ):  $\delta$  26.7 (C-3), 73.9 (C-2), 97.5 (C-8a), 98.8 (C-8), 100.3 (C-3a), 124.0, 128.1, 129.4, 130.7 (C aryl), 149.0 (C-7), 153.8 (C-4), 161.2 (C-8b), 163.8 (C-5a); MS:  $m/z$  253  $[\text{M}+\text{H}]^+$ . Anal. Calcd for  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2$ : C, 71.42; H, 4.79; N, 11.10. Found: C, 71.40; H, 4.83; N, 11.12.

**2,3-Dihydro-7-(4-methylphenyl)difuro[2,3-*b*:2',3'-*d*]pyridin-4-amine (5b):** (0.18 g, 69% from **3b**) (0.45 g, 17% from **1**); a pale orange needles; mp 207-208 °C (decomp) (CH<sub>2</sub>Cl<sub>2</sub>); IR (ATR) 3470, 3446, 3297, 3170 (NH) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.28 (s, 3H, CH<sub>3</sub>), 2.97 (t, *J* = 9.0 Hz 2H, 3-H), 4.70 (t, *J* = 9.0 Hz, 2H, 2-H), 5.97 (br s, 2H, NH<sub>2</sub>), 7.03 (s, 1H, 8-H), 7.20 (d, *J* = 8.4 Hz, 2H, aryl H), 7.61 (d, *J* = 8.4 Hz, 2H, aryl H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 21.4 (CH<sub>3</sub>), 26.7 (C-3), 73.8 (C-2), 97.5 (C-8a), 97.9 (C-8), 100.3 (C-3a), 124.0, 128.0, 130.0, 137.6 (C aryl), 149.3 (C-7), 153.6 (C-4), 161.1 (C-8b), 163.7 (C-5a); MS: *m/z* 267 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.11; H, 5.27; N, 10.45.

**2,3-Dihydro-7-(4-methoxyphenyl)difuro[2,3-*b*:2',3'-*d*]pyridin-4-amine (5c):** (0.11 g, 40% from **3c**) (0.57 g, 20% from **1**); a pale orange prisms; mp 246-248 °C (decomp) (CH<sub>2</sub>Cl<sub>2</sub>); IR (ATR) 3471, 3293, 3259, 3163 (NH) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.96 (t, *J* = 9.0 Hz 2H, 3-H), 3.75 (s, 3H, OCH<sub>3</sub>), 4.70 (t, *J* = 9.0 Hz, 2H, 2-H), 5.93 (br s, 2H, NH<sub>2</sub>), 6.94 (s, 1H, 8-H), 6.95-6.97 (m, 2H, aryl H), 7.64-7.66 (m, 2H, aryl H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 26.7 (C-3), 55.7 (OCH<sub>3</sub>), 73.8 (C-2), 96.8 (C-8), 97.6 (C-8a), 100.2 (C-3a), 114.9, 123.5, 125.6 (C aryl), 149.3 (C-7), 153.3 (C-4), 159.5 (C aryl), 161.0 (C-8b), 163.6 (C-5a); MS: *m/z* 283 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: C, 68.07; H, 5.00; N, 9.92. Found: C, 67.95; H, 4.98; N, 9.87.

**7-(4-Chlorophenyl)-2,3-dihydrodifuro[2,3-*b*:2',3'-*d*]pyridin-4-amine (5d):** (0.20 g, 69%, from **3d**) (0.66 g, 23% from **1**); a pale yellow prisms; mp 220-221 °C (decomp) (CH<sub>2</sub>Cl<sub>2</sub>); IR (KBr) 3396, 3313, 3205 (NH) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.97 (t, *J* = 8.7 Hz, 2H, 3-H), 4.71 (t, *J* = 8.7 Hz, 2H, 2-H), 6.06 (br s, 2H, NH<sub>2</sub>), 7.18 (s, 1H, 8-H), 7.43-7.45 (m, 2H, aryl H), 7.72-7.76 (m, 2H, aryl H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 26.7 (C-3), 74.0 (C-2), 97.5 (C-8a), 99.6 (C-8), 100.4 (C-3a), 125.6, 129.5, 129.6, 132.3 (C aryl), 147.9 (C-7), 154.0 (C-4), 161.3 (C-8b), 163.8 (C-5a); MS: *m/z* 288 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>15</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>2</sub>: C, 62.84; H, 3.87; N, 9.77. Found: C, 62.83; H, 3.78; N, 9.75.

**7-(4-Bromophenyl)-2,3-dihydrodifuro[2,3-*b*:2',3'-*d*]pyridin-4-amine (5e):** (0.25 g, 75% from **3e**) (0.96 g, 29% from **1**); a colorless needles; mp 252-253 °C (decomp) (CH<sub>2</sub>Cl<sub>2</sub>); IR (ATR) 3397, 3311, 3202 (NH) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 2.97 (t, *J* = 9.0 Hz, 2H, 3-H), 4.71 (t, *J* = 9.0 Hz, 2H, 2-H), 6.06 (br s, 2H, NH<sub>2</sub>), 7.19 (s, 1H, 8-H), 7.56-7.59 (m, 2H, aryl H), 7.65-7.67 (m, 2H, aryl H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): δ 26.7 (C-3), 74.0 (C-2), 97.5 (C-8a), 99.7 (C-8), 100.5 (C-3a), 120.9, 125.9, 130.0, 132.3 (C aryl), 147.9 (C-7), 154.0 (C-4), 161.3 (C-8b), 163.8 (C-5a); MS: *m/z* 332 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>15</sub>H<sub>11</sub>BrN<sub>2</sub>O<sub>2</sub>: C, 54.40; H, 3.35; N, 8.46. Found: C, 54.20; H, 3.49; N, 8.37.

**2,3-Dihydro-7-phenylfuro[2,3-*b*]thieno[2,3-*d*]pyridin-4-amine (6a):** (0.15 g, 55% from **4a**) (0.98 g, 36% from **2**); a colorless needles; mp 211-212 °C (CH<sub>2</sub>Cl<sub>2</sub>); IR (ATR) 3458, 3291, 3179 (NH) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): δ 3.09 (t, *J* = 7.8 Hz, 2H, 3-H), 3.50 (t, *J* = 7.8 Hz, 2H, 2-H), 6.03 (brs, 2H, NH<sub>2</sub>), 7.12 (s, 1H, 8-H), 7.25-7.28 (m, 1H, aryl H), 7.38-7.41 (m, 2H, aryl H), 7.73-7.75 (m, 2H, aryl H); <sup>13</sup>C NMR

(DMSO-*d*<sub>6</sub>):  $\delta$  32.2 (C-3), 33.6 (C-2), 100.8 (C-8), 106.4 (C-8a), 114.3 (C-3a), 124.1, 128.2, 129.4, 130.6 (C aryl), 145.9 (C-8b), 149.7 (C-7), 152.7 (C-4), 161.8 (C-5a); MS:  $m/z$  269 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>OS·0.2H<sub>2</sub>O: C, 66.25; H, 4.60; N, 10.30. Found: C, 66.28; H, 4.57; N, 10.29.

**2,3-Dihydro-7-(4-methylphenyl)furo[2,3-*b*]thieno[2,3-*d*]pyridin-4-amine (6b):** (0.13 g, 46% from **4b**) (0.49 g, 17% from **2**); a colorless needles; mp 217-218 °C (decomp) (CH<sub>2</sub>Cl<sub>2</sub>); IR (ATR) 3473, 3422, 3290, 3169 (NH) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  2.28 (s, 3H, CH<sub>3</sub>), 3.08 (t,  $J$  = 7.8 Hz, 2H, 3-H), 3.49 (t,  $J$  = 7.8 Hz, 2H, 2-H), 6.00 (brs, 2H, NH<sub>2</sub>), 7.03 (s, 1H, 8-H), 7.21 (d,  $J$  = 8.4 Hz, 2H, aryl H), 7.63 (d,  $J$  = 8.4 Hz, 2H, aryl H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>):  $\delta$  21.4 (CH<sub>3</sub>), 32.2 (C-3), 33.6 (C-2), 100.0 (C-8), 106.5 (C-8a), 114.2 (C-3a), 124.1, 127.9, 130.0, 137.8 (C aryl), 145.7 (C-8b), 150.0 (C-7), 152.5 (C-4), 161.6 (C-5a); MS:  $m/z$  283 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>OS·0.2H<sub>2</sub>O: C, 67.20; H, 5.08; N, 9.80. Found: C, 67.15; H, 4.98; N, 9.72.

**2,3-Dihydro-7-(4-methoxyphenyl)furo[2,3-*b*]thieno[2,3-*d*]pyridin-4-amine (6c):** (0.10 g, 33% from **4c**) (0.80 g, 27% from **2**); a colorless needles; mp 219-221 °C (decomp) (CH<sub>2</sub>Cl<sub>2</sub>); IR (ATR) 3473, 3294, 3175 (NH) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  3.06-3.09 (m, 2H, 3-H), 3.48-3.51 (m, 2H, 2-H), 3.75 (s, 3H, OCH<sub>3</sub>), 5.94 (brs, 2H, NH<sub>2</sub>), 6.94 (s, 1H, 8-H), 6.94-6.98 (m, 2H, aryl H), 7.66-7.69 (m, 2H, aryl H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>):  $\delta$  32.2 (C-3), 33.6 (C-2), 55.8 (OCH<sub>3</sub>), 98.9 (C-8), 106.6 (C-8a), 114.1 (C-3a), 115.0, 123.4, 125.7 (C aryl), 145.5 (C-8b), 150.0 (C-7), 152.2 (C-4), 159.6 (C aryl), 161.5 (C-5a); MS:  $m/z$  299 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>OS·0.1H<sub>2</sub>O: C, 64.02; H, 4.77; N, 9.33. Found: C, 63.95; H, 4.63; N, 9.26.

**7-(4-Chlorophenyl)-2,3-dihydrofuro[2,3-*b*]thieno[2,3-*d*]pyridin-4-amine (6d):** (0.17 g, 56% from **4d**) (0.73 g, 24% from **2**); a colorless prisms; mp 224-226 °C (decomp) (CH<sub>2</sub>Cl<sub>2</sub>); IR (ATR) 3453, 3357, 3276, 3173 (NH) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  3.07-3.10 (m, 2H, 3-H), 3.49-3.52 (m, 2H, 2-H), 6.08 (brs, 2H, NH<sub>2</sub>), 7.18 (s, 1H, 8-H), 7.44-7.46 (m, 2H, aryl H), 7.73-7.75 (m, 2H, aryl H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>):  $\delta$  32.2 (C-3), 33.6 (C-2), 101.7 (C-8), 106.3 (C-8a), 114.5 (C-3a), 125.7, 129.5, 132.5 (C aryl), 146.1 (C-8b), 148.5 (C-7), 152.8 (C-4), 161.9 (C-5a); MS:  $m/z$  303 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>15</sub>H<sub>11</sub>ClN<sub>2</sub>OS·0.2H<sub>2</sub>O: C, 58.80; H, 3.75; N, 9.14. Found: C, 58.73; H, 3.78; N, 9.13.

**7-(4-Bromophenyl)-2,3-dihydrofuro[2,3-*b*]thieno[2,3-*d*]pyridin-4-amine (6e):** (0.20 g, 57% from **4e**) (0.90 g, 26% from **2**); a pale orange prisms; mp 237-239 °C (decomp) (CH<sub>2</sub>Cl<sub>2</sub>); IR (ATR) 3452, 3355 (NH) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>):  $\delta$  3.07-3.10 (m, 2H, 3-H), 3.49-3.51 (m, 2H, 2-H), 6.09 (brs, 2H, NH<sub>2</sub>), 7.19 (s, 1H, 8-H), 7.57-7.59 (m, 2H, aryl H), 7.66-7.68 (m, 2H, aryl H); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>):  $\delta$  32.2 (C-3), 33.6 (C-2), 101.8 (C-8), 106.3 (C-8a), 114.5 (C-3a), 121.1, 126.0, 129.8, 132.4 (C aryl), 146.1 (C-8b), 148.6 (C-7), 152.9 (C-4), 161.9 (C-5a); MS:  $m/z$  348 [M+H]<sup>+</sup>. Anal. Calcd for C<sub>15</sub>H<sub>11</sub>BrN<sub>2</sub>OS·0.3H<sub>2</sub>O: C, 51.09; H, 3.32; N, 7.94. Found: C, 51.08; H, 3.15; N, 7.85.

## ACKNOWLEDGEMENTS

The authors deeply appreciate Mr. Hiroshi Hanazono conducted the MS spectra measurement and Ms. Junko Honda who performed the elemental analyses measurement.

## REFERENCES

1. S. Hilton and S. Rossiter, 'Comprehensive Heterocyclic Chemistry III: Three Heterocyclic Rings Fused (5-6-5)', Vol. 12, ed. by A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven, and R. J. K. Taylor, Elsevier Ltd., United Kingdom, 2008, p 711.
2. (a) J. Kempson, J. Guo, J. Das, R. V. Moquin, S. H. Spergel, S. H. Watterson, C. M. Langevine, A. J. Dyckman, M. Pattoli, J. R. Burke, X. Yang, K. M. Gillooly, K. W. McIntyre, L. Chen, J. H. Dodd, M. McKinnon, J. C. Barrish, and W. J. Pitts, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 2646; (b) C. A. Hurley, W. S. Blair, R. J. Bull, C. Chang, P. H. Crackett, G. Deshmukh, H. J. Dyke, R. Fong, N. Ghilardi, P. Gibbons, P. R. Hewitt, A. Johnson, T. Johnson, J. R. Kenny, P. B. Kohli, J. J. Kulagowski, M. Liimatta, P. J. Lupardus, R. J. Maxey, R. Mendonca, R. Narukulla, R. Pulk, S. Ubhayakar, A. Abbema, S. I. Ward, B. Waszkowycz, and M. Zak, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 3592; (c) P. G. Baraldi, G. Saponaro, M. A. Tabrizi, S. Baraldi, R. Romagnoli, A. R. Moorman, K. Varani, P. A. Borea, and D. Preti, *Bioorg. Med. Chem.*, 2012, **20**, 1046; (d) S. L. Cheong, S. Federico, G. Venkatesan, P. Paira, Y.-M. Shao, G. Spalluto, C. W. Yap, and G. Pastorin, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 2898.
3. F. Okabe-Nakahara, E. Masumoto, H. Maruoka, and K. Yamagata, *Heterocycles*, 2018, **96**, 664.
4. K. Tomoike, H. Maruoka, F. Okabe, E. Masumoto, T. Fujioka, and K. Yamagata, *Heterocycles*, 2014, **89**, 1025.
5. K. Okuda, M. Yoshida, T. Hirota, and K. Sasaki, *J. Heterocycl. Chem.*, 2013, **50**, E9.
6. K. Okuda, T. Matsushita, T. Hirota, and K. Sasaki, *J. Heterocycl. Chem.*, 2012, **49**, 742.
7. K. Yamagata, Y. Hashimoto, and M. Yamazaki, *Liebigs Ann. Chem.*, 1994, 791.
8. (a) M. Bakavoli, M. Rahimizadeh, and Z. Gordi, *J. Chem. Res.*, 2008, **10**, 564; (b) X. Feng, J.-C. Lancelot, A.-C. Gillard, H. Landelle, and S. Rault, *J. Heterocycl. Chem.*, 1998, 35, 1313; (c) J. Han, S. J. Kaspersen, S. Nervik, K. G. Nørsett, E. Sundby, and B. H. Hoff, *Eur. J. Med. Chem.*, 2016, **119**, 278.
9. (a) A. S. Tyaglivy, A. V. Gulevskaya, A. F. Pozharskii, and O. I. Askalepova, *Tetrahedron*, 2013, **69**, 9804; (b) R. Clayton and C. A. Ramsden, *J. Heterocycl. Chem.*, 2004, **41**, 701.