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

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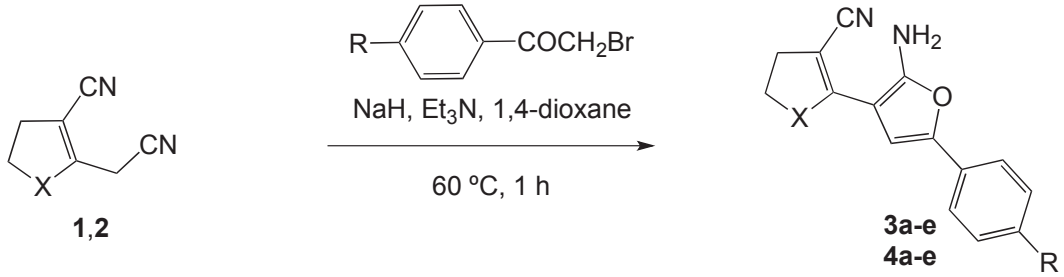
**Abstract** – The synthesis of novel tricyclic fused furo[2,3-*b*]pyridine derivatives is described. 3-Cyano-4,5-dihydro-2-furan(and 2-thiophene)acetonitriles **1**,**2** were reacted with phenacyl bromides to give 5'-arylfuran-2'-amines **3**,**4**. Compounds **3**,**4** were intramolecularly cyclized 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[1] and reported to exhibit various biological activities.[2] Recently, our laboratory has developed an efficient synthetic method of fused 5-6-5 heterocyclic compounds.[3,4] 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,[5] and bronchodilator activity.[6] 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.[7]

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.[8] 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 $cm^{-1}$ due to a primary amino group, and a band at 2186 $cm^{-1}$ due to a conjugated cyano group. The $^1H$ NMR spectrum

of **3a** in DMSO-$d_6$ exhibits $D_2O$ exchangeable a two-proton signal at δ 6.92 assignable to the primary amine, and a signal at δ 6.98 assignable to the 4'-H. The $^{13}C$ NMR spectrum of **3a** shows signals at δ 87.4, δ 104.0, δ 143.3 and δ 159.0 corresponding C-3', C-4', C-5' and C-2' carbons, respectively.




**1**, **3**: X = O, **2**, **4**: X = S, **a**: R = H, **b**: R = Me, **c**: R = OMe, **d**: R = Cl, **e**: R = Br

**Scheme 1**

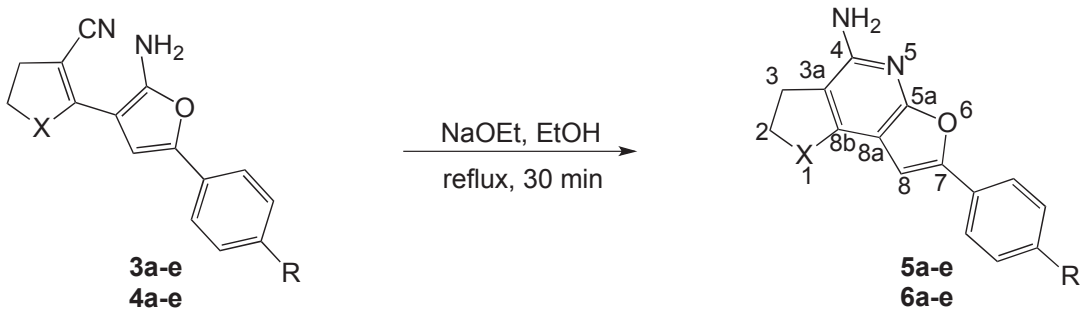
**Table 1.** Synthesis of **3a-e** and **4a-e** according to Scheme 1

| Entry | Substrate | X | R | Product | Yield (%)[a)] |
|---|---|---|---|---|---|
| 1 | **1** | O | H | **3a** | 37 |
| 2 | **1** | O | Me | **3b** | 24 |
| 3 | **1** | O | OMe | **3c** | 18 |
| 4 | **1** | O | Cl | **3d** | 34 |
| 5 | **1** | O | Br | **3e** | 39 |
| 6 | **2** | S | H | **4a** | 50 |
| 7 | **2** | S | Me | **4b** | 36 |
| 8 | **2** | S | OMe | **4c** | 37 |
| 9 | **2** | S | Cl | **4d** | 42 |
| 10 | **2** | S | Br | **4e** | 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.[9] 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, $^{1}H$ and $^{13}C$ 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 $cm^{-1}$ due to a primary amino group. The $^{1}H$ NMR spectrum of **5a** in DMSO-$d_6$ exhibits the $D_2O$ exchangeable a two-proton signal at δ 6.02 assignable to the primary amine, and a proton signal at δ 7.13 assignable to the 8-H. The $^{13}C$ NMR spectrum of **5a** in DMSO-$d_6$ shows signals at δ 97.5, δ 100.3, δ 153.8, δ 161.2, and δ 163.8 corresponding to C-8a, C-3a, C-4, C-8b, and C-5a carbons, respectively.




**5**: X = O, **6**: X = S, **a**: R = H, **b**: R = Me, **c**: R = OMe, **d**: R = Cl, **e**: R = Br

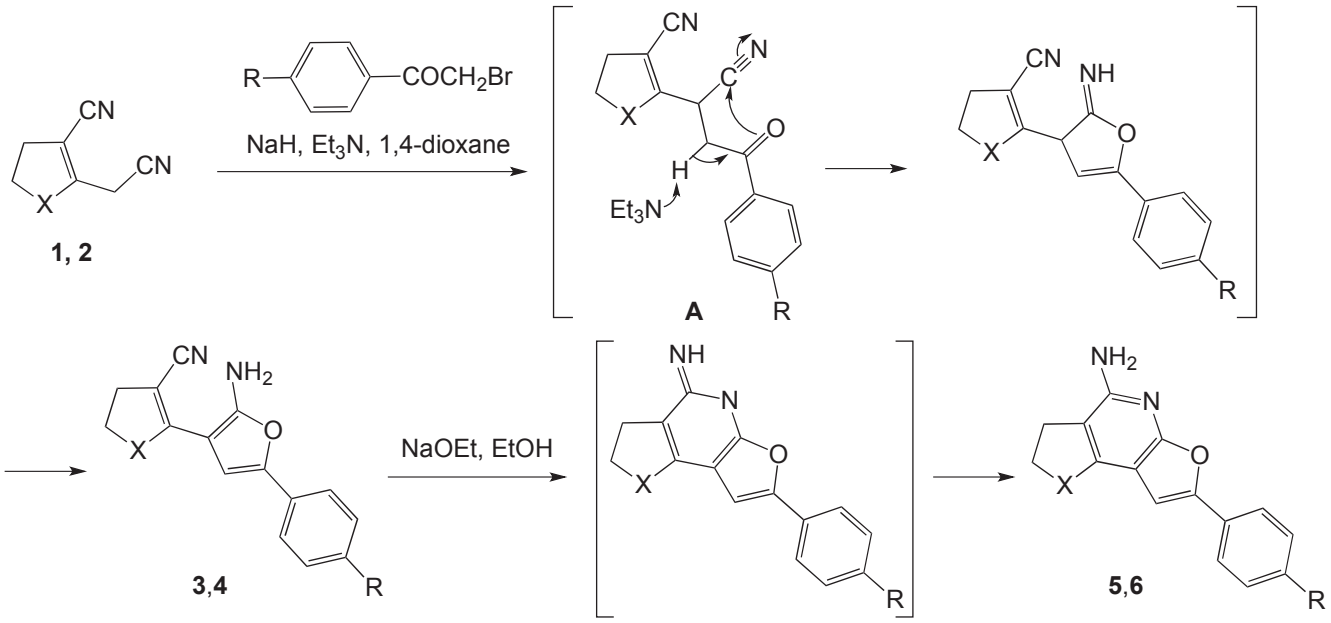
**Scheme 2**

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

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

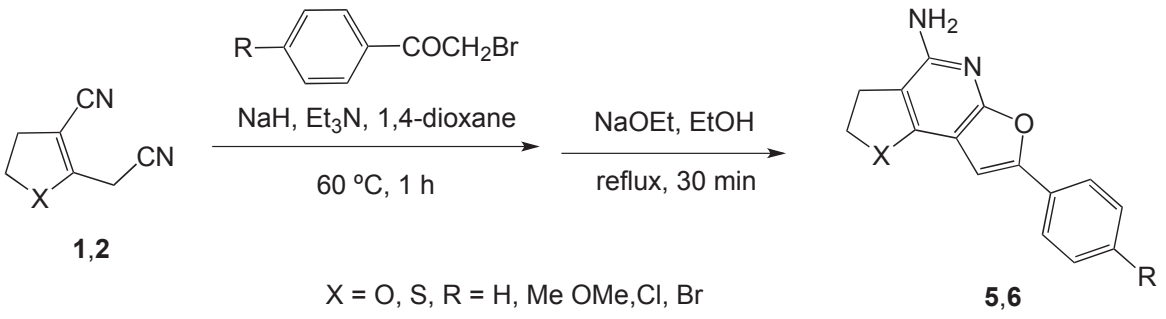
a) Yield of isolated products.

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.




**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 | **1** | O | H | **5a** | 28 |
| 2 | **1** | O | Me | **5b** | 17 |
| 3 | **1** | O | OMe | **5c** | 20 |
| 4 | **1** | O | Cl | **5d** | 23 |
| 5 | **1** | O | Br | **5e** | 29 |
| 6 | **2** | S | H | **6a** | 36 |
| 7 | **2** | S | Me | **6b** | 17 |
| 8 | **2** | S | OMe | **6c** | 27 |
| 9 | **2** | S | Cl | **6d** | 24 |
| 10 | **2** | S | Br | **6e** | 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 Therom Fishier Scientific using iD7 ATR accessory with a diamond crystal accessory. The $^{1}$H and $^{13}$C NMR spectra were measured with a JEOL JNM-ECZ R spectrometer 600.17 and 150.91 MHz respectively. The $^{1}$H and $^{13}$C NMR chemical shifts (δ) 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.[10]

**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 $Et_3N$ (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 $CH_2Cl_2$. The extract was washed with water, dried over by $Na_2SO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on alumina with $CH_2Cl_2$ 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 ($Et_2O$); IR (ATR) 3460, 3345 (NH), 2186 (CN) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): 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, $NH_2$), 6.98 (s, 1H, 4'-H), 7.15-7.18 (m, 1H, ary1 H), 7.32-7.35 (m, 2H, ary1 H), 7.43-7.44 (m, 2H, ary1 H); $^{13}C$ NMR (DMSO-$d_6$): 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 $[M+H]^+$. Anal. Calcd for $C_{15}H_{12}N_2O_2$: 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) ($Et_2O$) ; IR (ATR) 3463, 3352 (NH), 2187 (CN) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.25 (s, 3H, $CH_3$), 2.86 (t, $J$ = 9.3 Hz, 2H, 4-H), 4.51 (t, $J$ = 9.3 Hz, 2H, 5-H), 6.87 (brs, 2H, $NH_2$), 6.90 (s, 1H, 4'-H), 7.15 (d, $J$ = 8.4 Hz, 2H, ary1 H), 7.33 (d, $J$ = 8.4 Hz, 2H, ary1 H); $^{13}C$ NMR (DMSO-$d_6$): δ 21.3 ($CH_3$), 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 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_2O_2$: 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 ($Et_2O$); IR (ATR) 3458, 3347 (NH), 2185 (CN) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.86 (t, $J$ = 9.0 Hz, 2H, 4-H), 3.72 (s, 3H, $OCH_3$), 4.50 (t, $J$ = 9.0 Hz, 2H, 5-H), 6.80 (s, 1H, 4'-H), 6.82 (brs, 2H, $NH_2$), 6.91-6.93 (m, 2H, ary1 H), 7.36-7.38 (m, 2H, ary1 H); $^{13}C$ NMR (DMSO-$d_6$): δ 30.0 (C-4), 55.7 ($OCH_3$), 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 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_2O_3$: 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) ($Et_2O$); IR (ATR) 3459, 3348 (NH), 2187 (CN) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): 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, $NH_2$), 7.01 (s, 1H, 4'-H), 7.37-7.39 (m, 2H, ary1 H), 7.43-7.45 (m, 2H, ary1 H); $^{13}C$ NMR (DMSO-$d_6$): 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-$d_6$): δ 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, ary1 H), 7.50-7.53 (m, 2H, ary1 H); $^{13}C$ NMR (DMSO-$d_6$): δ 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-$d_6$): δ 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, ary1 H), 7.32-7.35 (m, 2H, ary1 H), 7.44-7.46 (m, 2H, ary1 H); $^{13}C$ NMR (DMSO-$d_6$): δ 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-$d_6$): δ 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, ary1 H), 7.34 (d, $J$ = 8.4 Hz, 2H, ary1 H); $^{13}C$ NMR (DMSO-$d_6$): δ 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-$d_6$): δ 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, ary1 H), 7.37-7.40 (m, 2H, ary1 H); $^{13}C$ NMR (DMSO-$d_6$): δ 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-$d_6$): δ 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); $^{13}$C NMR (DMSO-$d_6$): δ 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 $[M+H]^+$. Anal. Calcd for $C_{15}H_{11}ClN_2OS$: 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) ($Et_2O$); IR (ATR) 3444, 3345, 3300 (NH), 2188 (CN) cm$^{-1}$; $^1$H NMR (DMSO-$d_6$): δ 2.97-3.00 (m, 2H, 4-H), 3.32-3.35 (m, 2H, 5-H), 6.77 (brs, 2H, $NH_2$), 7.08 (s, 1H, 4'-H), 7.38-7.40 (m, 2H, aryl H), 7.50-7.53 (m, 2H, aryl H); $^{13}$C NMR (DMSO-$d_6$): δ 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 $[M+H]^+$. Anal. Calcd for $C_{15}H_{11}BrN_2OS$: 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 $Et_3N$ (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) ($CH_2Cl_2$); IR (ATR) 3452, 3301, 3190 (NH) cm$^{-1}$; $^1$H NMR (DMSO-$d_6$) δ 2.97 (t, $J$ = 9.0 Hz, 2H, 3-H), 4.71 (t, $J$ = 9.0 Hz, 2H, 2-H), 6.02 (brs, 2H, $NH_2$), 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); $^{13}$C NMR (DMSO-$d_6$): δ 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 $[M+H]^+$. Anal. Calcd for $C_{15}H_{12}N_2O_2$: 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) ($CH_2Cl_2$); IR (ATR) 3470, 3446, 3297, 3170 (NH) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.28 (s, 3H, $CH_3$), 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, $NH_2$), 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); $^{13}C$ NMR (DMSO-$d_6$): δ 21.4 ($CH_3$), 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 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_2O_2$: 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) ($CH_2Cl_2$); IR (ATR) 3471, 3293, 3259, 3163 (NH) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.96 (t, $J$ = 9.0 Hz 2H, 3-H), 3.75 (s, 3H, $OCH_3$), 4.70 (t, $J$ = 9.0 Hz, 2H, 2-H), 5.93 (br s, 2H, $NH_2$), 6.94 (s, 1H, 8-H), 6.95-6.97 (m, 2H, aryl H), 7.64-7.66 (m, 2H, aryl H); $^{13}C$ NMR (DMSO-$d_6$): δ 26.7 (C-3), 55.7 ($OCH_3$), 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 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_2O_3$: 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) ($CH_2Cl_2$); IR (KBr) 3396, 3313, 3205 (NH) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): 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, $NH_2$), 7.18 (s, 1H, 8-H), 7.43-7.45 (m, 2H, aryl H), 7.72-7.76 (m, 2H, aryl H); $^{13}C$ NMR (DMSO-$d_6$): 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 $[M+H]^+$. Anal. Calcd for $C_{15}H_{11}ClN_2O_2$: 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 coloreless needles; mp 252-253 ˚C (decomp) ($CH_2Cl_2$); IR (ATR) 3397, 3311, 3202 (NH) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): 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, $NH_2$), 7.19 (s, 1H, 8-H), 7.56-7.59 (m, 2H, aryl H), 7.65-7.67 (m, 2H, aryl H); $^{13}C$ NMR (DMSO-$d_6$): 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 $[M+H]^+$. Anal. Calcd for $C_{15}H_{11}BrN_2O_2$: 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 ($CH_2Cl_2$); IR (ATR) 3458, 3291, 3179 (NH) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): 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, $NH_2$), 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); $^{13}C$ NMR

(DMSO-$d_6$): δ 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 $[M+H]^+$. Anal. Calcd for $C_{15}H_{12}N_2OS \cdot 0.2H_2O$: 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) ($CH_2Cl_2$); IR (ATR) 3473, 3422, 3290, 3169 (NH) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 2.28 (s, 3H, $CH_3$), 3.08 (t, *J* = 7.8 Hz, 2H, 3-H), 3.49 (t, *J* = 7.8 Hz, 2H, 2-H), 6.00 (brs, 2H, $NH_2$), 7.03 (s, 1H, 8-H), 7.21 (d, *J* = 8.4 Hz, 2H, ary1 H), 7.63 (d, *J* = 8.4 Hz, 2H, ary1 H); $^{13}C$ NMR (DMSO-$d_6$): δ 21.4 ($CH_3$), 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 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_2OS \cdot 0.2H_2O$: 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) ($CH_2Cl_2$); IR (ATR) 3473, 3294, 3175 (NH) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.06-3.09 (m, 2H, 3-H), 3.48-3.51 (m, 2H, 2-H), 3.75 (s, 3H, $OCH_3$), 5.94 (brs, 2H, $NH_2$), 6.94 (s, 1H, 8-H), 6.94-6.98 (m, 2H, ary1 H), 7.66-7.69 (m, 2H, ary1 H); $^{13}C$ NMR (DMSO-$d_6$): δ 32.2 (C-3), 33.6 (C-2), 55.8 ($OCH_3$), 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 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}N_2OS \cdot 0.1H_2O$: 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) ($CH_2Cl_2$); IR (ATR) 3453, 3357, 3276, 3173 (NH) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.07-3.10 (m, 2H, 3-H), 3.49-3.52 (m, 2H, 2-H), 6.08 (brs, 2H, $NH_2$), 7.18 (s, 1H, 8-H), 7.44-7.46 (m, 2H, ary1 H), 7.73-7.75 (m, 2H, ary1 H); $^{13}C$ NMR (DMSO-$d_6$): δ 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 $[M+H]^+$. Anal. Calcd for $C_{15}H_{11}ClN_2OS \cdot 0.2H_2O$: 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) ($CH_2Cl_2$); IR (ATR) 3452, 3355 (NH) $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$): δ 3.07-3.10 (m, 2H, 3-H), 3.49-3.51 (m, 2H, 2-H), 6.09 (brs, 2H, $NH_2$), 7.19 (s, 1H, 8-H), 7.57-7.59 (m, 2H, ary1 H), 7.66-7.68 (m, 2H, ary1 H); $^{13}C$ NMR (DMSO-$d_6$): δ 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 $[M+H]^+$. Anal. Calcd for $C_{15}H_{11}BrN_2OS \cdot 0.3H_2O$: C, 51.09; H, 3.32; N, 7.94. Found: C, 51.08; H, 3.15; N, 7.85.

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