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Chemistry of Heterocyclic Compounds **2018**, *54*(4), 447–450

New approach to the synthesis of 2,3-dihydrofuro[2,3-*b*]pyridine derivatives: double reduction and double heterocyclization of 2-(3-cyano-5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ylidene)malononitriles in the presence of sodium borohydride

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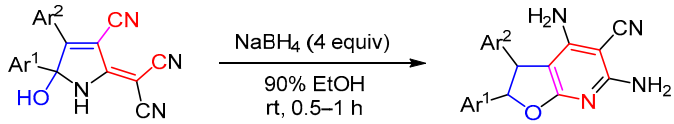


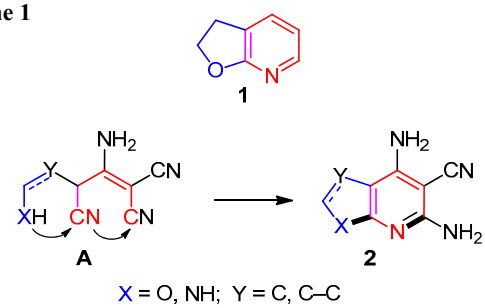
The reaction of 2-(3-cyano-5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ylidene)malononitriles with an excess of sodium borohydride resulted in diastereoselective formation of 2,3-diaryl-substituted 4,6-diamino-2,3-dihydrofuro[2,3-*b*]pyridine-5-carbonitriles. This process was accompanied by opening of the pyrrole ring in the starting compounds, followed by a double reduction and tandem closure of furan and pyridine rings.

Keywords: 2,3-dihydrofuro[2,3-*b*]pyridines, sodium borohydride, diastereoselectivity, reduction.

2,3-Dihydrofuro[2,3-*b*]pyridine derivatives **1** (Scheme 1) have attracted an increasing attention of researchers over recent years due to various types of biological activity that have been observed for these fused heterocyclic systems. For example, the structural moiety of 2,3-dihydrofuro[2,3-*b*]-pyridine is a part of the naturally occurring nicotinic receptor agonist phantasmidine,[1,2] as well as synthetic agonists of nicotinic receptors.[3] Dihydrofuropyridine motif is present in the structure of an aza analog of the pharmaceutical compound ramelteon – a ligand of melatonin receptors.[4] Compounds of this group have also shown promise for the treatment of Alzheimer's disease.[5] For this reason, it is quite important to continue the development of new methods for the synthesis of 2,3-dihydrofuro[2,3-*b*]pyridine derivatives.

One of previously published procedures for the synthesis of fused [2,3-*b*]pyridine systems involves the assembly of structures **A** on the basis of malononitrile dimer derivatives (Scheme 1), in which the molecule contains both a propene-1,3-dicarbonitrile fragment and a nucleophilic group at the γ- or δ-position relative to the cyano group. Structures of type **A**, as a rule, are formed *in situ* by the reactions of substrates containing amino or hydroxy groups with derivatives of malononitrile dimer. The use of this approach allows to synthesize a broad range of [2,3-*b*]pyridi-

Scheme 1



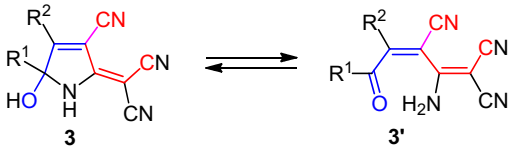
nes that are fused with pyridine,[6,7] pyran,[8] or dihydrofuran[9] rings.

Our goal was to modify this approach in order to enable its use for the synthesis of new 2,3-dihydrofuro[2,3-*b*]-pyridine derivatives, which would be difficult to obtain otherwise. The salient features of the modified approach include creating the conditions for the formation of structures of type **A**, in which the hydroxy group is formed from a preexisting functional group, instead of an intermolecular process, as described before.[6–9]

2-(3-Cyano-5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ylidene)-malononitriles **3** were selected as suitable substrates for the synthesis of derivatives **1** (Schemes 2, 3). Compounds **3** were synthesized by our recently discovered rearrangement

of 4-oxoalkane-1,1,2,2-tetracarbonitriles **4** in acetic acid in the presence of ammonium acetate (Scheme 3).[10,11] The specific selection of these compounds was associated with their structural features: pyrroles **3** contain a hemiaminal moiety which points to the existence of these structures in an equilibrium with the open-chain form **3'**.

Scheme 2



Stable compounds analogous to the structures **3'**, which lack a carbonyl group, have been described in the literature quite frequently.[6–8] The open-chain structure **3'** contains both a carbonyl group that potentially can be reduced to a nucleophilic hydroxyl group and cyano groups at β- and δ-positions, therefore pyrroles **3** can be expected to undergo a cascade of reactions analogous to that described for the synthesis of condensed pyridines **2** (Scheme 1). The presence of a masked hydroxy group in combination with cyano groups in structure **3'** represents the main difference of our approach in this work compared to the process for the formation of structures **2** that is illustrated in Scheme 1. We should also note that, in contrast to the previously known routes of synthesis,[6–9] malononitrile dimer was not used as starting material in this work.

During the development of our synthetic approach, we studied the possibility of reducing the carbonyl group in structures **3'** with sodium borohydride. We found that the treatment of pyrroles **3a**–**e** with a fourfold excess of $NaBH_4$ in aqueous ethanol resulted in a complex transformation leading to 2,3-diaryl-substituted 4,6-diamino-2,3-dihydrofuro[2,3-*b*]pyridine-5-carbonitriles **5a**–**e** in 53–72% yields (Scheme 3, Table 1).

The structure of compounds **5a**–**e** was confirmed using the data of IR, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. An important feature of the process leading to the formation of heterocyclic products **5** was its diastereoselectivity: structure **5** contains two asymmetric centers, but diastereomeric mixture was not obtained according to the data of NMR spectroscopy. The signals of protons bonded to the C-2 and C-3 atoms of the heterocyclic system were observed in the chemical shift range of 4.50–6.02 ppm as two doublets with spin-spin coupling constants of 8.0–8.3 Hz. In addition to that, ^{1}H NMR spectra of compounds **5a**–**e** contained characteristic singlet signals of protons belonging to two amino groups at 6.10–6.48 ppm. ^{13}C NMR spectra contained three characteristic signals of α- and γ-carbon atoms of pyridine ring at 153.9–169.8 ppm, as well as a signal of the cyano group carbon atom at 117 ppm.

In order to resolve the issue of *cis* or *trans* configuration of protons at the C-2 and C-3 carbon atoms of compounds **5a**–**e**, we performed a literature survey on the stereochemistry of analogous structures. It was found that

Scheme 3

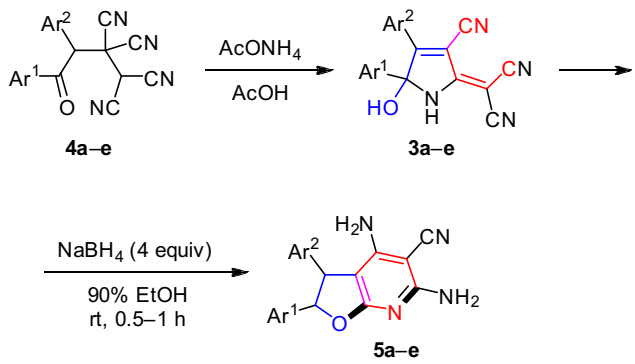
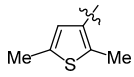
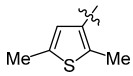
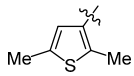
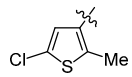
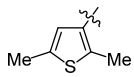
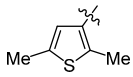


Table 1. Yields of compounds **5a**–**e**

Compound	Ar(Het)^1	Ar(Het)^2	Yield, %
5a	Ph	Ph	72
5b	Ph		54
5c			59
5d			68
5e			53

no published data were available on 2,3-diaryl-substituted 2,3-dihydrofuro[2,3-*b*]pyridines. The closest structural analogs of compounds **5a**–**e**, which were thoroughly described in the literature, were derivatives of 2,3-diaryl-2,3-dihydrobenzofuran. In the case of such structures it was shown that the spin-spin coupling constants for geminal protons at aryl (hetaryl) substituents at the *cis* position were 8.7–10.2 Hz[12] (8.0 Hz according to other data[13]). The spin-spin coupling constants for compounds having a *trans* configuration were 4.3–5.9,[13] 5.7–5.9,[14] 7.5,[15] or 5–8 Hz.[16] According to our data, the spin-spin coupling constants of 8.0–8.3 Hz between the protons of dihydrofuran ring in compounds **5** can correspond to either *cis*- or *trans*-isomers. In order to solve this issue, we performed an additional structural study of compound **5a** by using NOESY experiments. It has been previously shown[16] that NOESY spectra acquired for the *trans*-isomers of 2,3-diaryl-2,3-dihydrobenzofurans lacked correlation between the protons bonded to the C-2 and C-3 carbon atoms of the furan ring, while these protons showed cross peaks with the *ortho* protons of both the geminal and vicinal aryl substituents. NOESY spectrum of compound **5a** featured a cross peak between the proton bonded to the C-2 carbon atom (6.02 ppm) and the proton at the C-3 carbon atom (4.70 ppm) of the furan ring (Fig. 1). Besides that, the proton at the C-3 carbon atom showed a correlation with the *ortho* proton (6.67 ppm) of the adjacent phenyl ring **A**, as well as there was a correlation of the hydrogen atom at

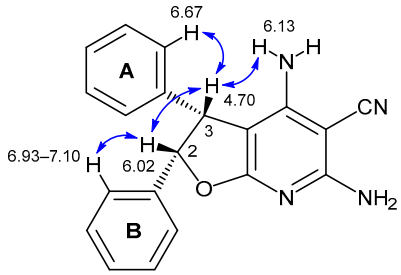


Figure 1. Correlations in NOESY spectrum of compound **5a**.

the C-2 carbon atom with the *ortho* proton of the phenyl substituent **B** (6.93–7.10 ppm). The proton at the C-3 carbon atom also gave a cross peak with the amino group proton (6.13 ppm) at position 4 of the pyridine ring.

Thus, our obtained data on the spatial proximity between certain protons in the molecule of compound **5a** provide evidence that heterocyclic products **5** are more likely to form as *cis*-isomers. Such conclusion was also supported by the absence of correlations between the 2-CH proton and the *ortho* proton of the phenyl ring **A**, as well as between the 3-CH proton and the *ortho* proton of the phenyl ring **B**.

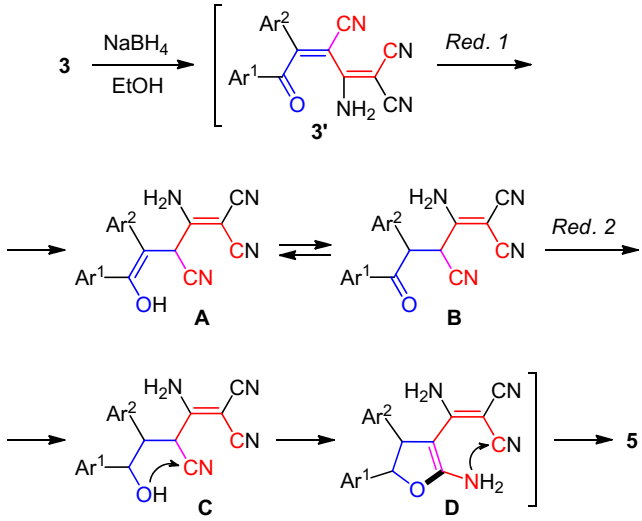
According to the structure of compounds **5a**–**e**, their molecular mass is higher by four atomic mass units compared to the molecular mass of the starting pyrroles **3a**–**e**. The same was confirmed by mass spectral data, which showed molecular ion peaks with the intensity of 18–100%. This fact indicated that a double reduction of pyrroles **3a**–**e** had occurred by the action of sodium borohydride.

The relatively complex rearrangement of the starting structures **3**, accompanied by pyrrole ring opening and tandem closure of furan and pyridine rings, was explained by the cleavage of one N–C bond during the reaction and the formation of two new O–C and N–C bonds. In the case of the synthesis of compounds **5**, the following sequence of mechanistic steps can be proposed: base-catalyzed opening of the hydroxypyrrole ring with the formation of ketone **3'** occurred during the first stage (Scheme 4). This was followed by 1,4-reduction of α,β-unsaturated ketone moiety to enol **A**, which was further converted through the ketone form **B** and reduced to the γ-hydroxynitrile **C**. The process concluded with a double heterocyclization: intramolecular interaction of hydroxy and cyano groups produced dihydrofuran **D**, in which the interaction of amino group with cyano group led to the formation of the final furopyridines **5a**–**e**.

It should be noted that using an equimolar amount of the reducing agent also resulted in the formation of compounds **5**, but in that case part of the starting pyrrole **3** remained in the reaction mixture. This provided an indirect evidence about the greater rate of reduction of the intermediate structures **A** (**B**) compared to the reduction of the initial ring opening product – ketone **3'**.

Thus, using the reduction of 2-(5-R^1-4-R^2-3-cyano-5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ylidene)malononitriles with an excess of sodium borohydride we demonstrated a new method for diastereoselective synthesis of 2,3-dihydrofuro[2,3-*b*]pyridine derivatives. The formation of these

Scheme 4



products reflected the tendency for pyrrole ring opening in the starting compounds in basic media and pointed to their possible use in directed cascade transformations.

Experimental

IR spectra were recorded on an FSM-1202 FTIR spectrometer for thin layers of Nujol mulls. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DRX-500 spectrometer (500 and 125 MHz, respectively) in DMSO-d_6, using TMS as internal standard. Thiophene ring protons are denoted as "H Th". Mass spectra were recorded on a Finnigan MAT INCOS-50 instrument (EI ionization, 70 eV). Elemental analysis was performed on a PerkinElmer 2400 CHN-analyzer. Melting points were determined on an OptiMelt MPA100 apparatus. The reaction progress and purity of the synthesized compounds were controlled by TLC on Sorbfil PTSKh-AF-A-UF plates (eluent EtOAc–hexane, 9:1, visualization under UV light, in iodine vapor, or by thermal decomposition).

The starting compounds **3a**–**e** were synthesized according to a published procedure.[10]

Preparation of 2,3-diaryl-substituted 4,6-diamino-2,3-dihydrofuro[2,3-*b*]pyridine-5-carbonitriles 5a–e (General method). $NaBH_4$ (76 mg, 2 mmol) was added portionwise with vigorous stirring to a suspension of pyrrole **3a**–**e** (0.5 mmol) in aqueous 90% EtOH solution (2–3 ml), while keeping the temperature of the reaction mixture at or below 30°C. The obtained solution was stirred at room temperature for 0.5–1 h, then the mixture was cooled to 5–10°C, maintained at this temperature for 1 h, and the precipitated solid product was filtered off, washed with H_2O (2 ml) and cold (5–10°C) EtOH (2 ml). The product was dried at reduced pressure over $CaCl_2$.

4,6-Diamino-2,3-diphenyl-2,3-dihydrofuro[2,3-*b*]pyridine-5-carbonitrile (5a). Yield 118 mg (72%), white powder, mp 301–302°C (decomp.) (mp 305°C[9]). IR spectrum, ν, cm^{-1}: 3453, 3348 (NH_2), 2191 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.70 (1H, d, *J* = 8.3, 3-CH); 6.02 (1H, d, *J* = 8.3, 2-CH); 6.13 (2H, s, NH_2); 6.47 (2H, s, NH_2); 6.67 (2H, d, *J* = 7.0, H Ph); 6.93–7.10 (8H, m,

H Ph). ^{13}C NMR spectrum, δ, ppm: 48.4; 68.2; 86.2; 92.6; 117.1; 124.9; 126.2; 127.0; 127.3; 128.5; 128.7; 136.6; 137.9; 154.1; 162.7; 169.8. Mass spectrum, *m*/*z* (I_{rel}, %): 328 $[M]^+$ (100). Found, %: C 73.01; H 4.97; N 16.93. $C_{20}H_{16}N_4O$. Calculated, %: C 73.15; H 4.91; N 17.06.

4,6-Diamino-3-(2,5-dimethylthiophen-3-yl)-2-phenyl-2,3-dihydrofuro[2,3-*b*]pyridine-5-carbonitrile (5b). Yield 98 mg (54%), white powder, mp 285–286°C (decomp.). IR spectrum, ν, cm^{-1}: 3462, 3341 (NH_2), 2192 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.83 (3H, s, CH_3); 2.17 (3H, s, CH_3); 4.62 (1H, d, *J* = 8.2, 3-CH); 5.84 (1H, s, H Th); 5.86 (1H, d, *J* = 8.2, 2-CH); 6.12 (2H, s, NH_2); 6.44 (2H, s, NH_2); 7.03–7.07 (2H, m, H Ph); 7.12–7.17 (3H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 12.5; 14.6; 41.8; 68.0; 86.2; 92.5; 117.2; 125.9; 126.5; 127.2; 127.4; 132.0; 133.1; 134.3; 136.5; 153.9; 162.5; 169.6. Mass spectrum, *m*/*z* (I_{rel}, %): 362 $[M]^+$ (30). Found, %: C 66.09; H 5.08; N 15.29. $C_{20}H_{18}N_4OS$. Calculated, %: C 66.28; H 5.01; N 15.46.

4,6-Diamino-2,3-bis(2,5-dimethylthiophen-3-yl)-2,3-dihydrofuro[2,3-*b*]pyridine-5-carbonitrile (5c). Yield 117 mg (59%), white powder, mp 251–252°C (decomp.). IR spectrum, ν, cm^{-1}: 3451, 3361 (NH_2), 2198 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.87 (3H, s, CH_3); 2.15 (3H, s, CH_3); 2.23 (3H, s, CH_3); 2.27 (3H, s, CH_3); 4.50 (1H, d, *J* = 8.0, 3-CH); 5.80 (1H, d, *J* = 8.0, 2-CH); 5.87 (2H, br. s, H Th); 6.10 (2H, s, NH_2); 6.41 (2H, s, NH_2). ^{13}C NMR spectrum, δ, ppm: 12.1; 12.4; 14.5; 14.6; 41.1; 68.0; 81.5; 92.5; 117.3; 125.1; 125.8; 132.5 (2C); 133.0; 133.1; 133.3; 133.9; 153.9; 162.5; 169.6. Mass spectrum, *m*/*z* (I_{rel}, %): 396 $[M]^+$ (21). Found, %: C 60.37; H 5.14; N 13.97. $C_{20}H_{20}N_4OS_2$. Calculated, %: C 60.58; H 5.08; N 14.13.

4,6-Diamino-2-(5-chloro-2-methylthiophen-3-yl)-3-(2,5-dimethylthiophen-3-yl)-2,3-dihydrofuro[2,3-*b*]pyridine-5-carbonitrile (5d). Yield 142 mg (68%), white powder, mp 245–246°C (decomp.). IR spectrum, ν, cm^{-1}: 3446, 3352 (NH_2), 2203 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.92 (3H, s, CH_3); 2.24 (3H, s, CH_3); 2.33 (3H, s, CH_3); 4.53 (1H, d, *J* = 8.0, 3-CH); 5.86 (1H, d, *J* = 8.0, 2-CH); 5.89 (1H, s, H Th); 6.08 (1H, s, H Th); 6.19 (2H, s, NH_2); 6.45 (2H, s, NH_2). ^{13}C NMR spectrum, δ, ppm: 12.4; 12.6; 14.7; 41.2; 68.3; 81.0; 92.4; 117.3; 122.7; 125.1; 125.2; 126.3; 132.7; 133.2; 133.8; 135.1; 154.1; 162.7; 169.5. Mass spectrum, *m*/*z* (I_{rel}, %): 416 $[M(^{35}Cl)]^+$ (26). Found, %: C 54.53; H 4.19; N 13.31. $C_{19}H_{17}ClN_4OS_2$. Calculated, %: C 54.73; H 4.11; N 13.44.

4,6-Diamino-2-(2,5-dimethylthiophen-3-yl)-3-(thiophen-2-yl)-2,3-dihydrofuro[2,3-*b*]pyridine-5-carbonitrile (5e). Yield 98 mg (53%), white powder, mp 185–186°C (decomp.). IR spectrum, ν, cm^{-1}: 3449, 3339 (NH_2), 2199 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.14 (3H, s, CH_3); 2.26 (3H, s, CH_3); 4.85 (1H, d, *J* = 8.0, 3-CH); 5.88 (1H, d, *J* = 8.0, 2-CH); 6.06 (1H, s, H Th); 6.25 (2H, s, NH_2); 6.39–6.41 (1H, m, H Th); 6.48 (2H, s, NH_2); 6.76–6.79 (1H, m, H Th); 7.20–7.22 (1H, m, H Th). ^{13}C NMR spectrum, δ, ppm: 12.8; 14.7; 43.1; 68.2; 82.5; 92.7; 117.3; 124.9 (2C); 125.4; 126.4; 132.2; 132.5; 134.0; 142.5; 154.4; 162.8; 169.5. Mass spectrum, *m*/*z* (I_{rel}, %): 368 $[M]^+$ (18). Found, %: C 58.51; H 4.46; N 15.04. $C_{18}H_{16}N_4OS_2$. Calculated, %: C 58.67; H 4.38; N 15.20.

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