A novel approach to the synthesis of partially hydrogenated dipyridothiophenes

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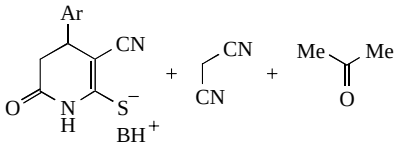
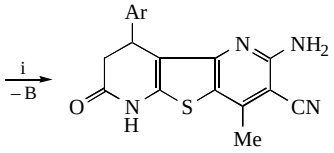
A new methodology for the synthesis of substituted tetrahydropyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines and the mechanism of their formation are described.

Dipyridothiophenes belong to a new class of compounds.[1] Previously, we reported on a novel approach to pyrido[3′,2′:4,5]-thieno[3,2-*b*]pyridines *via* polycomponent condensation of thiolates **1**, malononitrile **2** and acetone **3** in ethanol under reflux[2,3] (Method A, Scheme 1).



1 **2** **3**



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Scheme 1 *Reagents and conditions*: i, EtOH, reflux 15–25 h; B = *N*-methylmorpholine.

However, the mechanism of this reaction remained obscured. We presumed that oxygen is an oxidant required in this case. Proving this intention, we carried out the above synthesis under conditions that excepted the presence of oxygen in the reaction mixture. Thus, the heating of thiolate **1a** (Ar = 2-ClC_6H_4), nitrile **2** and acetone **3** in refluxing EtOH in an argon atmosphere for 15 h followed by cooling to room temperature led to the precipitating of initial salt **1a** in 52% yield. According to TLC data, the target pyridothienopyridine was absent from the reaction mixture. However, the exposure of the filtrate that was obtained when thiolate **1** was separated to air for 8 days gave compound **4a** in 41% yield (calculated for the remained quantity of salt **1**). Thus, oxygen is the oxidant that promotes this reaction.

It is well known that certain pyridinethiones and thiolates could be easily transformed into the corresponding disulfides by standing in air in solution.[4,5] Although a similar reaction was never observed previously in the series of compounds **1**, we suggested that under reaction conditions the transformation of pyridinethiolates **1** into disulfides **5** proceeds (Scheme 2). In fact, the long-term refluxing of thiolate **1a** in EtOH in air gives corresponding disulfide **5a**, although in a low (15%) yield. Generally, disulfides are known as sulfenylating agents related to C-nucleophiles.[6] It is highly probable that bis(pyridyl)-disulfides **5** formed undergo further transformations with S–S bond cleavage to give, finally, desirable pyrido[3′,2′:4,5]thieno-[3,2-*b*]pyridines **4**. Substituted 2,2′-bis(pyridyl)disulfides can be easily obtained by the oxidation of corresponding pyridine-2-thiolates or -thiones under mild conditions (I_2, EtOH, room temperature).[5,7] Justifying our hypothesis, we synthesised disulfides **5** by an independent way† and put them into reaction with malononitrile **2** and acetone **3** in the presence of a base in EtOH under reflux.

We found that such a reaction can serve as a novel convenient approach to pyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines (method B).‡ The use of tertiary amines (Et_3N and *N*-methylmorpholine) led to the best results. Thus, the mechanism of the reaction reported earlier[2,3] could be described as follows (Scheme 2).

At the first stage, nitrile **2** reacts with acetone **3** in a basic medium to give isopropylidenemalononitrile **6**. Earlier, this intention was confirmed by an independent synthesis.[3] Further, anion **7**, which exists in equilibrium with unsaturated nitrile **6**, attacks the molecule of disulfide **5**, resulted *in situ* by oxidation, to give sulfide **8** and thiolate **1**. The latter undergoes oxidation to disulfide **5** under reaction conditions, and the process may repeat. Intramolecular cyclization of intermediate **8** by the Thorpe–Ziegler reaction leads to thienopyridine **9**, which, in turn, undergoes the transformation into target ring-fused structure **4**. Although compounds **8** and **9** were not isolated, the latest two stages are highly probable and confirmed by analogy in the literature.[1] We also found only one instance for cascade reaction including the same consecution of stages: disulfide formation, S–S bond cleavage and heterocyclization; thus, thiazolo-[3,2-*a*]benzimidazoles were obtained.[8]

The advantages of the synthesis of dipyridothiophenes result in higher yields and higher purity of target compounds. Taking into account that disulfides **5** could be obtained in good to

† *Typical procedure for the synthesis of 6,6′-bis(4-aryl-5-cyano-2-oxo-1,2,3,4-tetrahydropyridyl)disulfides* **5**. To the stirred suspension of pyridinethiolate **1** (5 mmol) in 85% EtOH (30 ml) iodine (0.64 g, 2.5 mmol) was added. The mixture was heated to the boiling point and then left to stand at room temperature for 24 h. The reaction mixture was diluted with H_2O (10 ml); the precipitate was filtered off, washed with aqueous EtOH and dried. Resulting crude disulfides **5a**,**b** were put into the reaction without purification. Initial thiolates **1a**,**b** were obtained by the known procedures.[9,10]

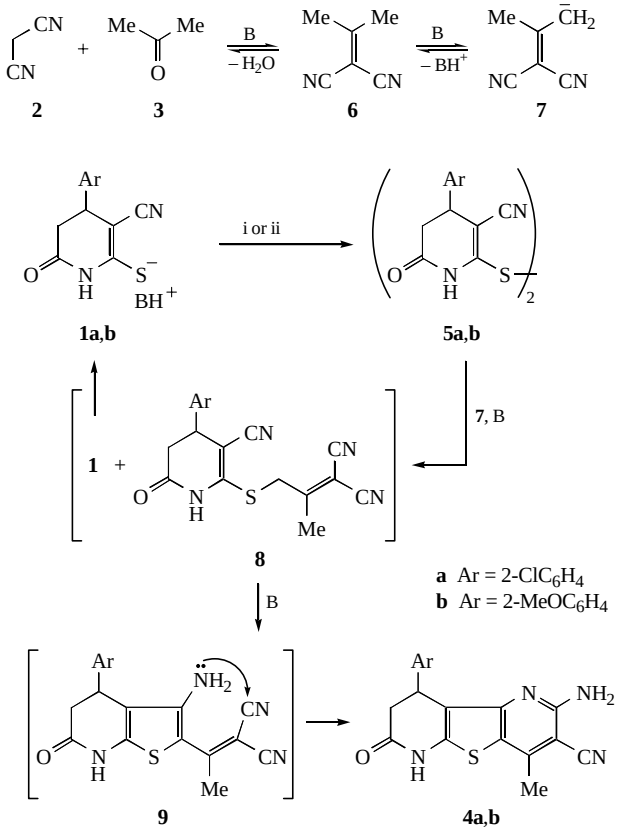
6,6′-Bis[4-(2-chlorophenyl)-5-cyano-2-oxo-1,2,3,4-tetrahydropyridyl]-disulfide **5a**: yield 98%, mp 240–245 °C (decomp.). ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 2.58 (dd, 2H, ^3J 6.5 Hz, ^2J 16.3 Hz), 2.88 (dd, 2H, ^3J 7.9 Hz, ^2J 16.3 Hz), 4.48 (pseudo-t, 2H), 7.39 (m, 8H, 2Ar), 11.10 (s, 2H, 2NH). IR (Nujol, ν/cm^{-1}): 3420 [2C(O)NH], 2212 (2CN), 1700, 1590 (2CO). Found (%): C, 55.03; H, 3.08; N, 10.51. Calc. for $C_{24}H_{16}Cl_2N_4O_2S_2$ (527.45) (%): C, 54.65; H, 3.06; N, 10.62.

6,6′-Bis[5-cyano-4-(2-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyridyl]-disulfide **5b**: yield 95%, mp 230–235 °C (decomp.). ^{1}H NMR (200 MHz, [$^2H_6$]DMSO) δ: 2.60 (br. pseudo-d, 2H), 2.90 (br. pseudo-d, 2H), 3.07 (s, 6H, 2MeO), 4.35 (pseudo-t, 2H), 7.10 (m, 8H, 2Ar), 10.95 (s, 2H, 2NH). IR (Nujol, ν/cm^{-1}): 3420 [2C(O)NH], 2215 (2CN), 1690, 1590 (2C=O). Found (%): C, 60.89; H, 4.30; N, 10.85. Calc. for $C_{26}H_{22}N_4O_4S_2$ (518.62) (%): C, 60.22; H, 4.28; N, 10.80.

‡ *General procedure for the synthesis of 2-amino-9-aryl-3-cyano-4-methyl-7-oxo-6,7,8,9-tetrahydropyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines* **4**. *Method B.* A mixture of disulfide **5** (4 mmol), malononitrile **2** (0.79 g, 12 mmol), acetone **3** (5.9 ml, 80 mmol) and an organic base (*N*-methylmorpholine or Et_3N) (12 mmol) in 96% EtOH (25 ml) was heated under reflux for 8 h and then kept at room temperature for 24 h. The resulting precipitate of dipyridothiophene **4a**,**b** was filtered off, washed with EtOH and recrystallised from AcOH.

*2-Amino-9-(2-chlorophenyl)-3-cyano-4-methyl-7-oxo-6,7,8,9-tetrahydropyrido[3′,2′:4,5]thieno[3,2-*b*]pyridine* **4a** was obtained by method B in 62% yield (37% by method A),[2] mp 297–298 °C (297–298 °C for a previously obtained sample).[3]

*2-Amino-3-cyano-9-(2-methoxyphenyl)-4-methyl-7-oxo-6,7,8,9-tetrahydropyrido[3′,2′:4,5]thieno[3,2-*b*]pyridine* **4b** was obtained by method B in 77% yield (29% by method A),[3] mp 325–327 °C (325–327 °C for a previously obtained sample).[3] The spectral characteristics of compounds **4a**,**b** correspond to published data.[2,3]



Scheme 2 *Reagents and conditions*: i, O_2, EtOH, reflux; ii, I_2, 85% EtOH; B = *N*-methylmorpholine.

excellent yields, we concluded that the path to 6,7,8,9-tetrahydropyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines reported hereby is optimum for the present moment.

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References

1 V. A. Artyomov, V. L. Ivanov, L. A. Rodinovskaya, A. M. Shestopalov and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1996, 553 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1996, **32**, 483].

2 V. V. Dotsenko, S. G. Krivokolysko, V. P. Litvinov and A. N. Chernega, *Izv. Akad. Nauk, Ser. Khim.*, 2002, 339 (*Russ. Chem. Bull., Int. Ed.*, 2002, **51**, 362).

3 V. V. Dotsenko, S. G. Krivokolysko, A. N. Chernega and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2003, 918 (*Russ. Chem. Bull., Int. Ed.*, 2003, **52**, 969).

4 A. A. Krauze, E. E. Liepinsh, Yu. E. Pelcher, Z. A. Kalme and G. Ya. Dubur, *Khim. Geterotsikl. Soedin.*, 1987, 75 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1987, **23**, 61].

5 V. P. Litvinov, V. K. Promonenkov, Yu. A. Sharanin and A. M. Shestopalov, in *Itogi nauki i tekhniki. Organicheskaya khimiya* (*Results in Science and Techniques. Organic Chemistry*), ed. M. I. Kabachnik, VINITI, Moscow, 1989, vol. 17, p. 124 (in Russian).

6 F. M. Stoyanovich, in *Poluchenie i svoistva organicheskikh soedinenii sery* (*Synthesis and Reactions of Organosulfur Compounds*), ed. L. I. Belen'kii, Khimiya, Moscow, 1998, pp. 57, 60 (in Russian).

7 V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 2123 (*Russ. Chem. Bull.*, 1998, **47**, 2053).

8 A. E. A. O. Sarhan, H. A. H. El-Sherief and A. M. Mahmoud, *Tetrahedron*, 1996, **52**, 10485.

9 V. N. Nesterov, S. G. Krivokolysko, V. D. Dyachenko, V. V. Dotsenko and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 1997, 1029 (*Russ. Chem. Bull.*, 1997, **46**, 990).

10 S. G. Krivokolysko, V. D. Dyachenko and V. P. Litvinov, *Izv. Akad. Nauk, Ser. Khim.*, 2000, 485 (*Russ. Chem. Bull., Int. Ed.*, 2000, **49**, 487).

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