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Diimidazo[4,5-*b*:4′,5′-*e*]pyridine: synthesis and nucleophilic aromatic substitution reaction

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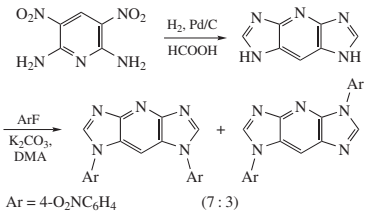
1,7-Dihydrodiimidazo[4,5-*b*:4′,5′-*e*]pyridine obtained by reductive heterocyclization was N-arylated with 4-fluoronitrobenzene to form two regioisomers in 7 : 3 ratio. This N-arylation is considered as a model reaction for the polymer synthesis.

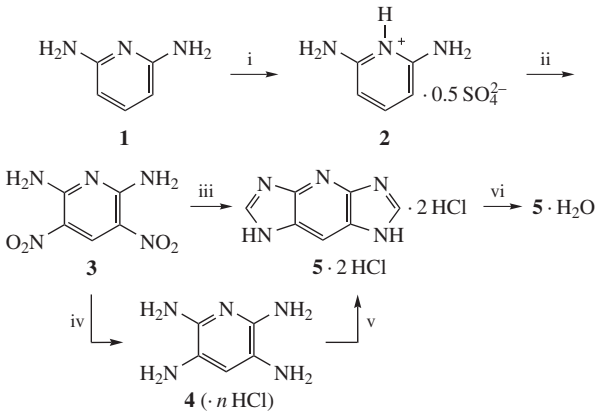


Heterocyclic polymers are useful as high-performance materials including proton-conductive membranes for fuel cells. In these membranes, heterocyclic polymers, usually containing benzimidazole or pyridine moieties, are doped with H_3PO_4 that provides proton conductivity at higher temperatures (120–200 °C)[1] compared to those for Nafion-type or other membranes with different acidic groups.[2,3] The majority of known syntheses of such heterocyclic polymers involve hazardous substances such as tetraamines, require corrosive solvents like polyphosphoric acid and Eaton's reagent, and produce significant amounts of acidic waste. Therefore, the search for cleaner procedures towards such polymers is still actual.[4] Previously, we prepared poly(*N*-phenylenebenzimidazoles) by nucleophilic aromatic substitution[5] and bis(benzimidazole) monomers from bis(*o*-nitroanilines)[6] depriving tetraamine intermediates. In the following work we considered the similar pathway for 1,7-dihydrodiimidazo[4,5-*b*:4′,5′-*e*]pyridine (DIP) – a potential monomer for M5-like fibers.[7] This compound contains five nitrogen atoms, so we supposed that in a polymer chain they would effectively bind with H_3PO_4 to form a polymer-electrolyte complex required for proton-conductive membranes.

Despite of the simple-looking formula of DIP, its synthesis has been documented scarcely.[8–10] Bredereck[8] reported on 7% yield as a result of cyclization between aminoacetonitrile and formamidine, with the product having been characterized with elemental analysis and paper chromatography only. Wang[9] performed cyclocondensation of 2,3,5,6-teraaminopyridine with formaldehyde with further air oxidation providing 74% yield of DIP. This substance was characterized by NMR spectrum, which was later proved to closely agree with that for the product obtained by us. Guozheng and Ming[10] reported the synthesis of DIP from 2,3,5,6-tetraaminopyridine and triethyl orthoformate, however, their NMR data were completely different and controversial.

Our reductive heterocyclization procedure was inspired by the work of Hanan,[11] in which various aromatic and heteroaromatic *o*-nitro amines were converted to benzimidazoles in formic acid/Pr^{i}OH media with iron powder and NH_4Cl within 1–2 h. To synthesize bis(benzimidazole) from bis(*o*-nitroanilines), we had to modify this method, using Pd/C catalyst and hydrogen bubbling through the mixture at atmospheric pressure instead of iron metal as a reducing agent, the solvent was changed to HCOOH/H_2O mixtures, and the reaction time had to be prolonged up to 20 h to obtain products in high yields (95–99%).[6]

We supposed that a similar approach should work for DIP synthesis. Commercial 2,6-diaminopyridine **1** was transformed into hydrosulfate **2** and then nitrated with sodium nitrate in oleum to obtain 2,6-diamino-3,5-dinitropyridine **3** (Scheme 1).[†] Unfortunately, under the conditions suitable for the reductive heterocyclization synthesis of bis(benzimidazole) in the case of



Scheme 1 *Reagents and conditions*: i, H_2SO_4, Pr^{i}OH; ii, $NaNO_3$, oleum; iii, H_2 (90 atm), Pd/C, HCOOH, MeOH, 100 °C, 12 h, then HCl; iv, H_2, autoclave, Pd/C, then HCl; v, HCOOH, HCl, Δ; vi, NH_3/H_2O.

[†] 2,6-Diaminopyridine **1** (20 g, 0.18 mol) was dissolved in propan-2-ol (180 ml), the solution was filtered, and concentrated sulfuric acid (8 g) was slowly added. The mixture was cooled to room temperature, the precipitated 2,6-diaminopyridine hydrosulfate was filtered and washed with a small amount of ethanol and propan-2-ol, then dried *in vacuo* to give 22.8 g (79%) of a yellowish powder. Oleum (40 ml) was poured into a three-necked flask equipped with a magnetic stirrer and placed in an ice bath. After cooling, 2,6-diaminopyridine hydrosulfate **2** (10.0 g, 6.3 mmol) was added portionwise with vigorous stirring. Sodium nitrate (11.0 g, 7.7 mmol) was slowly added, then the mixture was poured onto ice (1 kg), the orange-brown precipitate was filtered off, washed and dried to give 9.2 g (80%) of compound **3**. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.01 (s, 1H), 8.44 (s, 2H), 8.28 (s, 2H). Lit.,[5] δ: 9.00 (s, 1H), 8.43 (s, 2H), 8.27 (s, 2H).

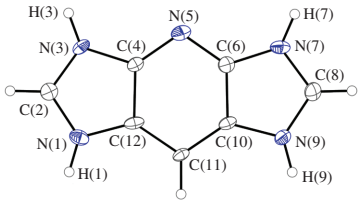
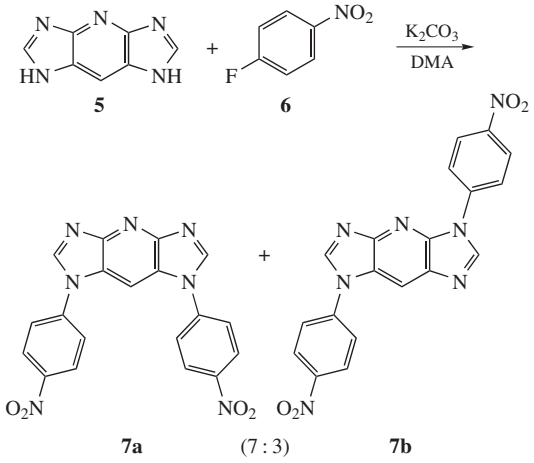


Figure 1 General view of the dication of DIP·2H$^+$ (**5**·2HCl) in thermal ellipsoid representation (p = 50%). Chloride anions are omitted for clarity.

compound **3** a complex mixture of hardly identified substances was formed. The reaction was incomplete even after 3 days, so we decided to carry out the process at higher pressure in an autoclave. Under these conditions, the desired DIP **5** was obtained in 31% yield‡ (see Scheme 1). For better purification, HCl was used to recrystallize DIP in hydrochloride form, and the obtained crystals were characterized by the X-ray data (Figure 1).§

The molecular structure of compound **5** is the first example of the crystal containing the 1,7-dihydrodiimidazo[4,5-*b*:4′,5′-*e*]-pyridine heterocyclic system. Due to dicationic character, the bond lengths C–N with atoms C(2) and C(8) in five-membered rings of the hererocycles are almost equalized, as well as C–N bonds with exocyclic to pyridine ring. The four H atoms attached to nitrogen atoms participate in N–H···Cl hydrogen bonds of the moderate strength [N···Cl 3.056(4)–3.102(4) Å], connecting the ions into zigzag-like layers.

Alternatively, DIP **5** was synthesized *via* tetraamine pathway (see Scheme 1). 2,3,5,6-Teraaminopyridine **4** hydrochloride was prepared by a known method in autoclave,[5] that required large amounts of HCl and THF for its sedimentation. The obtained tetraamine **4** was refluxed in a mixture of formic acid and 18% HCl for 4 h, which is a common procedure for benzimidazole synthesis,[12] to get identical DIP·2HCl in 30% yield. Salt DIP·2HCl was converted into hydrate form (DIP·H_2O) by heating in aqueous ammonia. Both hydrate and hydrochloride forms were tested in a model reaction of nucleophilic aromatic substitution with 4-fluoronitrobenzene (Scheme 2).¶



Scheme 2

The conditions of the model reaction were chosen to be close to the polymer synthesis with bis(benzimidazole) monomers.[4,5] According to our previous experience, sonification of the monomer with K_2CO_3 at the beginning of the synthesis increases the reaction rate and helps to obtain polymers with higher molecular weights. The role of K_2CO_3 here is to deprotonate NH from the imidazole cycle, and so, additional quantity of K_2CO_3 is required to scavenge HCl from salt DIP·2HCl. Theoretically, DIP has five tautomeric forms, so one may suppose that this could affect the reaction outcome. Yet, the deprotonation of these forms leads to a single anion structure. The nitrogen atom in the central

‡ 2,6-Diamino-3,5-dinitropyridine **3** (10 g, 5 mmol), Pd/C (0.7 g, 5%), formic acid (225 ml, 90%) and methanol (75 ml) were placed in a 500 ml autoclave, the vessel was filled with hydrogen (90 atm). The autoclave was heated at 100 °C for 12 h, then cooled to room temperature to reveal that 15 atm of H_2 were consumed. The mixture was concentrated with rotary evaporator at 80 °C (140 mbar), dissolved in hot concentrated HCl (200 ml) and filtered from the catalyst. The precipitate obtained after cooling was filtered and once again recrystallized from HCl with addition of activated charcoal to obtain 3.67 (31%) of pure DIP·2HCl as yellowish crystals. ^{1}H NMR (400 MHz, D_2O) δ: 9.07 (s, 2H), 8.32 (s, 1H). ^{1}H NMR (400 MHz, DMSO-d_6, NEt_3) δ: 8.39 (s, 2H), 8.18 (s, 1H). Found (%): Cl, 30.43. Calc. for $C_7H_5N_5$·2HCl (%): Cl, 30.55.

Salt DIP·2HCl (1 g, 4.7 mmol) was heated in 20 ml of 10% aq. NH_3, filtered and dried at 50 °C *in vacuo* to obtain white powder of neutralized form DIP·H_2O in quantitative yield (0.76 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.87 (s, 2H), 8.40 (s, 2H), 8.19 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 148.51, 143.94, 128.60, 111.21. Found (%): C, 47.73; H, 3.83; N, 39.51. Calc. for $C_7H_5N_5$·H_2O (%): C, 47.46; H, 3.98; N, 39.53. Lit.,[9] ^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.77–12.72 (s, 2H), 8.38 (s, 2H), 8.18–8.14 (s, 1H).

§ *Crystal data for* **5**: monoclinic, space group $P2_1$, a = 4.7530(6), b = = 10.9303(14) and c = 8.6048(11) Å, β = 95.439(3)°, V = 445.02(10) Å^3, Z = 2 (Z' = 1), d_{calc} = 1.732 g cm^{-3}, R_1 = 0.0342 [for 2301 reflections with $I > 2\sigma(I)$], wR_2 = 0.0819, GOF = 1.030.

Crystal data for **7a**: monoclinic, space group $C2/c$, a = 22.399(3), b = = 14.2557(16) and c = 7.1186(8) Å, β = 99.297(2)°, V = 2243.2(4) Å^3, Z = 4 (Z' = 0.5), d_{calc} = 1.461 g cm^{-3} (without SQUEEZed solvent), R_1 = = 0.0424 [for 2547 reflections with $I > 2\sigma(I)$], wR_2 = 0.1190, GOF = 1.054.

Crystal data for **7b**: monoclinic, space group $P2_1/n$, a = 10.0092(3), b = 13.7495(4) and c = 15.3130(5) Å, β = 94.4884(16)°, V = 2100.93(11) Å^3, Z = 2 (Z' = 0.5), d_{calc} = 1.716 g cm^{-3}, R_1 = 0.0532 [for 5034 reflections with $I > 2\sigma(I)$], wR_2 = 0.1371, GOF = 1.007.

The diffraction experiment for **5** was performed on a Bruker Smart Apex II, and for **7a**,**b** on a Bruker Apex DUO diffractometer; for all samples at 120 K using MoKα radiation (λ = 0.71072 Å).

CCDC 1868389–1868391 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

¶ Salt DIP·2HCl (0.464 g, 2 mmol), K_2CO_3 (0.691 g, 5 mmol), *N*,*N*-dimethylacetamide (DMA, 5 ml) and toluene (2 ml) were placed in a two-necked flask with a mechanical stirrer and argon inlet and sonicated at 80 °C for 20 min in ultrasonic bath. Then 4-fluoronitrobenzene (0.564 g, 4 mmol) was added, and the flask was placed into a silicon bath and heated up to 110 °C. Soon the mixture acquired a rich violet color, which then faded into light yellow. After 20 h of heating the mixture was poured into water, the precipitate was filtered off, washed and dried *in vacuo* to give 0.73 g (87%) of the product.

Similar procedure was performed for DIP·H_2O (0.354 g, 2 mmol) with a reduced quantity of K_2CO_3 (0.414 g, 3 mmol) and an additional 1 h heating of the reaction mixture at 110 °C to remove the hydrate water before the addition of 4-fluoronitrobenzene, 0.836 g (99%) of the product were obtained.

The reaction product (100 mg) was dissolved in DMA (6 ml), centrifuged for 1 h at 3000 rpm, the supernatant was separated from the residue of 'trans' (**7b**) product (19 mg) and precipitated with water to give 60 mg of 'cis-1' (**7a**) product. NMR spectra of the products are presented and discussed in Online Supplementary Materials.

*Major product, 1,7-bis(4-nitrophenyl)-1,7-dihydrodiimidazo[4,5-*b*:4′,5′-*e*]-pyridine* **7a**: mp 370–380 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.09 (s, 2H), 8.52 (s, 1H), 8.47 (d, 4H, J 8.9 Hz), 8.15 (d, 4H, J 8.9 Hz). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 154.34, 146.95, 146.46, 141.48, 126.09, 124.53, 123.31, 103.31. Found (%): C, 55.99; H, 3.01; N, 23.88. Calc. for $C_{19}H_{11}N_7O_4$·H_2O (%): C, 54.42; H, 3.12; N, 23.38.

*Minor product, 1,5-bis(4-nitrophenyl)-1,5-dihydrodiimidazo[4,5-*b*:5′,4′-*e*]-pyridine* **7b**: mp > 400 °C. ^{1}H NMR (400 MHz, CF_3COOD) δ: 10.44 (s, 1H), 10.37 (s, 1H), 9.51 (s, 1H), 9.07 (d, 2H, J 8.7 Hz), 9.03 (d, 2H, J 8.4 Hz), 8.59 (d, 2H, J 8.7 Hz), 8.46 (d, 2H, J 8.4 Hz). ^{13}C NMR (101 MHz, CF_3COOD) δ: 153.13, 152.52, 148.95, 148.66, 146.52, 146.39, 140.48, 139.98, 130.02, 129.85, 129.45, 129.29, 128.37, 127.88. Found (%): C, 54.44; H, 3.24; N, 23.03. Calc. for $C_{19}H_{11}N_7O_4$·H_2O (%): C, 54.42; H, 3.12; N, 23.38.

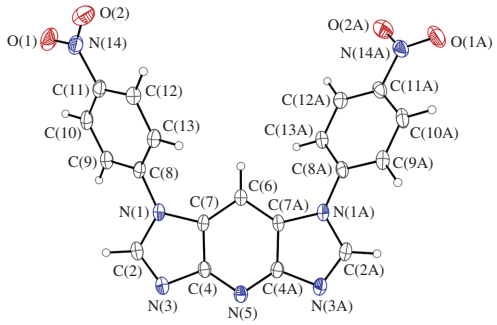


Figure 2 General view of the molecule of **7a** in thermal ellipsoid representation (p = 50%). Solvate formic acid molecules are omitted for clarity.

six-membered ring seems less likely to be involved into C–N coupling, so three potential products can be expected for this reaction: two 'cis' and one 'trans'. The analysis of the reaction products by NMR showed mainly the presence of two isomers: 'cis-1' (**7a**) and 'trans' (**7b**) in 7 : 3 ratio, which was almost unaffected by the form of DIP used. The solubility of these substances in organic solvents appeared to be different, so they were separated by centrifugation and analyzed individually.

The crystals of the isolated isomers, required for the X-ray study, were prepared in formic and trifluoroacetic acid for 'cis' and 'trans' products, respectively. In contrast to structure **5**, the crystal **7a** (Figure 2)[§] contains the substituted heterocyclic molecule in neutral form, as well as neutral formic acid molecule and heavily disordered unidentified solvate in channel-like voids. The strength of the formic acid is therefore insufficient to protonate the heterocycle. The heterocyclic molecule lies on crystallographic axis 2, only the half of it being symmetry independent. In contrast to dication **5**, the lengths of the N(1)–C(2) and C(2)–N(3) bonds indicate their single and double character in full accordance with a canonical structure. The solvate formic acid molecules disordered by two positions participate in H-bonds with nitrogen atom N(3).

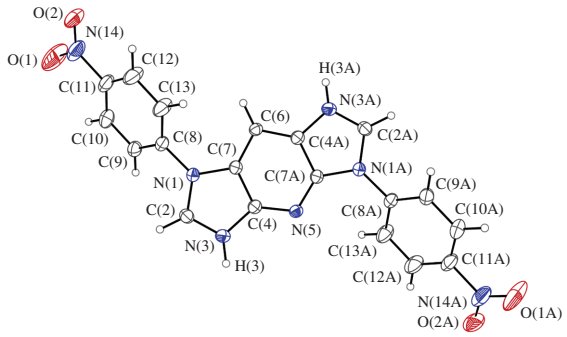


Figure 3 General view of the cation of **7b** in thermal ellipsoid representation (p = 50%). Only one part of the overlapping pseudo-centrosymmetric heterocycles is shown. The trifluoroacetate anions and trifluoroacetic acid solvate molecules are omitted for clarity.

The crystal structure of 'trans' isomer **7b** (Figure 3)[§] corresponds to hydrotrifluoroacetate which also contains four neutral solvate trifluoroacetic acid molecules. It is pseudo-centrosymmetric, with the exception of N(5) and C(6) atoms of the pyridine ring. In the centrosymmetric crystal structure **7b** (space group $P2_1/c$), the substituted dication lies on the inversion center in two different orientations, with almost overlapping positions of N(5) and C(6) atoms. Like in dication **5**, the lengths of N(1)–C(2) and C(2)–N(3) bonds of the five-membered rings are closer to values between double and single bonds.[§]

In summary, DIP can be readily subjected to aromatic nucleophilic substitution reaction resulting in C–N coupling with both imidazole rings, so it can be considered a promising monomer for the polymer synthesis. Its synthesis from 1,5-diamino-2,4-dinitropyridine has yet to be optimized to achieve higher yields.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.03.022.

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