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A new versatile synthesis of 4-substituted diaminopyridine derivatives

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ABSTRACT

A new convenient method for the synthesis of substituted 2,6-diacetamido pyridines has been developed. It starts from 4-hydroxypyridine and comprises the introduction of the amino groups by the Chichibabin reaction. After several protection and deprotection steps 2,6-diacetamido-4-hydroxy pyridine is obtained, which is regarded as a key compound for the synthesis of various substituted 2,6-diacetamido pyridines. It is shown that the free hydroxy group is susceptible for nucleophilic substitution. This provides an easy access to the introduction of different functional groups at 4-position of 2,6-diacetamido pyridine. The advantages over other procedures described in the literature are discussed.

Pyridine derivatives are an essential class of azaheterocycles found in many natural products, active pharmaceuticals, and functional materials. Beside its well known applications in the pharmaceutical industry, nowadays substituted pyridines especially 2,6-diaminopyridine are widely used as key compounds for the preparation of different supramolecular assemblies. A very important one is 4-hydroxy-2,6-diaminopyridine which can be used to make versatile building blocks in supramolecular networks by incorporating long chains at 4-position having different end groups.[1–6] Consequently, it is not surprising that many successful synthesis routes toward 4-substituted-2,6-diaminopyridine have been developed.

The most popular of them involves the Curtius rearrangement which was reported by Markees and Kidder in 1956.[7] Later on, in 2001 Arienzo and Kilburn described a procedure which utilizes the Hofmann rearrangement.[8] Both procedures start from chelidamic acid or esters thereof and aim at introducing desired substituents on the oxygen in 4-position first. After this the amino groups are introduced by the Curtius or the Hoffmann rearrangement as depicted in a very simplified manner in Scheme 1.

Disadvantage of these approaches is the early introduction of the substituent R_2. This may complicate further steps, especially if the substituent contains other reactive or functional groups. Furthermore, if the preparation of differently substituted 2,6-diaminopyridine derivatives is intended, the whole procedure has to be repeated each time again from the beginning which is very time consuming. Much more advantageous is an approach which comprises the introduction of the amino groups first followed by the introduction of the substituent in the last step. In the procedure described by Arienzo and Kilburn,[8] the primary substituent (R_2 = benzyl ether) is removed by hydrogenolysis so that the deprotected OH group in 4-position is available for further conversions with various substituents. This is an essential advantage compared to the procedure of Markees and Kidder,[7] however, still demands several steps to achieve the targeted products.

We are interested in using substituted 2,6-diacetamidopyridines as building blocks for polymers with self-healing characteristics. Therefore, we looked for a more effective synthetic route for this important component. This study describes a procedure which starts form 4-hydroxy-2,6-diaminopyridine which is easily available by conversion of 4-hydroxy pyridine with sodium amide according to Chichibabin. The amination of pyridine derivatives with sodium amide was reported first by Chichibabin and Seide in 1914.[9] Since then, it has been recognized as one of the most important and influential developments in pyridine chemistry. In 1955, Bojarska-Dahlig and Nantka-Namirski reported the Chichibabin reaction on 4-hydroxy pyridine to achieve 4-hydroxy-2,6-diaminopyridine.[10] Since then no attempt was reported on this specific reaction.

We synthesized 4-hydroxy-2,6-diaminopyridine (**3**) by conversion of 4-hydroxy pyridine (**1**) with sodium amide (Scheme 2) slightly modified according to the procedure described by Bojarska-Dahlig and Nantka-Namirski.[10] Liquid paraffin was used as solvent instead of paraffin wax, which makes the solvent handling more easy. The reaction mixture was heated stepwise from 180 to 230 °C up to 250 °C under nitrogen atmosphere. The evolution of hydrogen and ammonia gas indicated the beginning of the reaction. Here, a subsequent color change from orange to brown to black was

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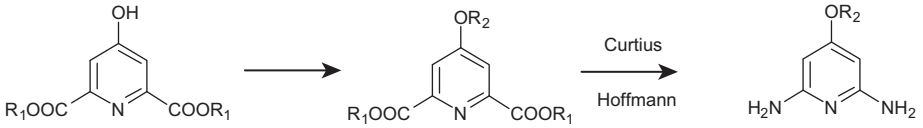
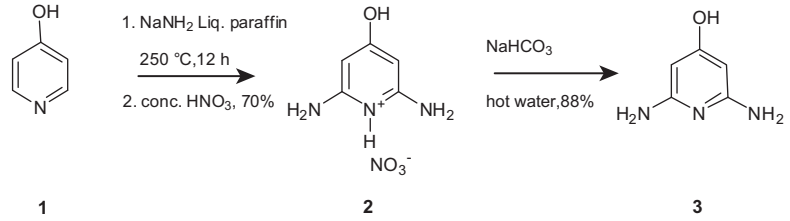


Scheme 1. Conventional preparation of substituted diamino pyridines.



Scheme 2. Chichibabin reaction of 4-hydroxy pyridine followed by neutralization.[11,12]

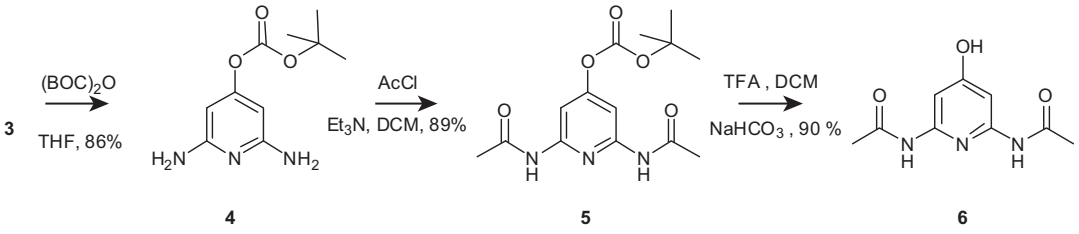
observed. After 12 h heating, diamino substitution was obtained with more than 70% yield.[11]

2,6-Diamino-4-hydroxypyridine was isolated from the post reaction mixture as its nitrate salt (**2**) which is sparingly water soluble. Isolation of the free amine (**3**) was carried out by treating the nitrate salt with sodium bicarbonate. The brown solid obtained was crystallized from water and in this step the yield was about 88%. Finally, the structure of **3** was confirmed by ^{1}H and ^{13}C NMR spectroscopy.[12]

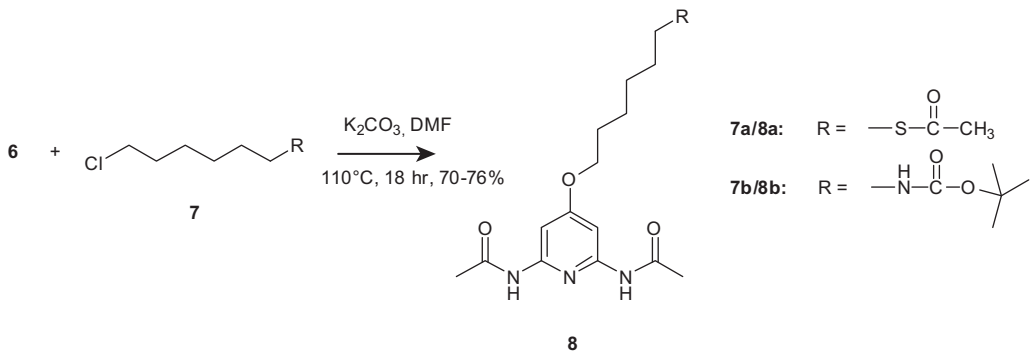
In order to introduce active substituents in 4-position, protection of the amino groups was required. For this reason, compound **3** was converted with di-*tert*-butyl dicarbonate (Boc-protection) in THF with a slight heat up to 50 °C. Surprisingly, this reaction provided the hydroxyl protected compound **4** with more than 86% yield.[13] In the case of 4-amino phenol, high selectivity was observed with respect to the carboxylation of the amino groups, while in the presence of NaOH the oxygen was converted preferably.[14] The same applies to the conversion of 4-amino phenol hydrochloride.[15] Generally, it was found that higher acidity containing functional groups are preferentially *tert*-butoxy carboxylated.[15] The high selectivity during Boc-protection of compound **3** can be explained by the strong electron withdrawing effect of the three nitrogen atoms resulting in an increased acidity of the OH group.

In the next step, compound **4** was reacted with acetyl chloride in the presence of triethylamine in dichloromethane to obtain acetamide **5** in 89% yields.[16] Finally, deprotection of **5** using TFA in DCM followed by neutralization gave compound **6** almost quantitatively (Scheme 3).[17]

Compound **6** with a free OH group and two protected amino groups is the key compound for the synthesis of various substituted diacetamidopyridines. Substitution can easily be performed by conversion of the alkali salt of **6** with alkyl halides. The following two examples demonstrate the synthesis of substituted diacetamidopyridines with additional protected amino and thiol groups, respectively (see Scheme 4).



Scheme 3. Synthesis of 2,6- diacetamido-4-hydroxy pyridine as its TFA salt.[13,16,17]



Scheme 4. Conversion of 2,6-diacetamido-4-hydroxy pyridine with functional alkyl halides.[20,21]

For the preparation of **8a** and **8b**, S-(6-chlorohexyl) ethanethioate (**7a**) and *tert*-butyl 6-chlorohexylcarbamate (**7b**) were synthesized according to the literature.[18,19] The conversions of **6** with **7a** and **7b**, respectively, were carried out for 18 h with a strong heating up to 110 °C in the presence of an excess of K_2CO_3 using DMF as solvent. After purification, solid products were obtained in both cases with more than 70% yields.[20,21] Compounds **8a** and **8b** can be regarded as potential building blocks for supramolecular assemblies which after deprotection of the thiol and amino groups, respectively, are available for surface modifications, polymer analogous reactions etc.

The advantage of the procedure described here is its versatility. With the preparation of compound **6**, a key compound is provided which serves as a starting material for various reactive or nonreactive substituted 2,6-diacetamidopyridines for various applications. This is an essential advantage compared to the procedures which start form chelidamic acid where the substituents are introduced prior to the amino groups.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.089. These data include MOL files and InChiKeys of the most important compounds described in this article.

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11. *Nitrate salt of 4-hydroxy-2,6-diaminopyridine (**2**)*: A mixture of **1** (10.0 g, 105.1 mmol), sodium amide (16.4 g, 420.6 mmol), and liquid paraffin (52 mL) was heated stepwise from 180 to 250 °C under nitrogen atmosphere for 12 h. Subsequent color change from orange to brown to black was observed. The mixture was cooled in an ice bath. Water (100 mL) was added carefully to quench the excess of sodium amide and it was stirred for 10 min. The paraffin layer was separated and washed by water. The combined aqueous solutions were acidified with concd HNO_3. The black precipitate obtained was filtered off and dried. Finally it was crystallized from hot water to give **2** as a deep brown solid (13.72 g, 70% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.34 (br, 1H), 11.22 (s, 1H), 6.84 (br, 4H), 5.40 ppm (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 170.8, 153.2, 83.6 ppm.
12. *4-Hydroxy-2,6-diaminopyridine (**3**)*: To a solution of **2** (8.0 g, 42.06 mmol) in 100 mL of hot water, sodium bicarbonate (3.5 g) was added with slow stirring. After cooling to room temperature, the precipitate was filtered off and washed with a small amount of cold water. The substance was crystallized from water to give **3** as brown crystals (5.4 g, 88% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.28 (br, 1H), 5.15 (s, 2H), 5.08 ppm (s, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.8, 159.3, 84.0 ppm.
13. *tert-Butyl (2,6-diaminopyridine-4-yl) carbonate (**4**)*: To a solution of **3** (4.0 g, 31.96 mmol) in 10 mL of THF and 10 mL of methanol, di-*tert*-butyl dicarbonate (13.95 g, 63.92 mmol) was added at room temperature. The reaction mixture was heated at 50 °C for 3 h. After the mixture was cooled to room temperature, the excess of THF and methanol was removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give compound **4** (6.1 g, 86.32%) as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 5.54 (s, 4H), 5.43 (s, 2H), 1.47 ppm (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 160.1, 159.8, 150.5, 87.6, 83.0, 27.2 ppm.
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16. *tert-Butyl (2,6-diacetamidopyridine-4-yl) carbonate (**5**)*: To a solution of **4** (6.3 g, 27.91 mmol) in 80 mL of CH_2Cl_2, triethyl amine (7.79 mL) and acetyl chloride (3.97 mL, 55.92 mmol) were added sequentially at room temperature. The reaction mixture was stirred at room temperature for 1 h under nitrogen atmosphere. The crude was directly purified by column chromatography (EtOAc/hexanes = 1/1) using silica gel without any workup to give **5** (7.72 g, 89.24%) as a light yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.23 (s, 2H), 7.59 (s, 2H), 2.11 (s, 6H), 1.50 ppm (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.6, 159.6, 151.5, 149.7, 101.5, 84.2, 27.1, 24.0 ppm.
17. *2,6-Diacetamido-4-hydroxy pyridine (**6**)*: To a stirred solution of **5** (5.0 g, 16.16 mmol) in 40 mL of CH_2Cl_2, trifluoroacetic acid was added slowly at 0 °C. The reaction mixture was stirred for 3 h at room temperature under drying condition. The excess of solvent was removed under reduced pressure. The crude product was neutralized with a saturated $NaHCO_3$ solution. The whole aqueous part was evaporated and the solid obtained was stirred in 70 mL of methanol for 1 h. The solution was filtered and the filtrate was dried over Na_2SO_4 and concentrated to give compound **6** (3.05 g, 90.23%) as an off white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.48 (s, 1H), 9.78 (s, 2H), 7.24 (s, 2H), 2.07 ppm (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.1, 166.5, 151.2, 96.7, 24.0 ppm.
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(b) *S-(6-Chlorohexyl) ethanethioate (**7a**)*: A mixture of 1-chloro-6-iodohexane (5.0 g, 20.24 mmol), 10 mL of acetone, and potassium thioacetate (2.31 g, 20.24 mmol) was stirred at room temperature for 20 h under nitrogen atmosphere. The excess of acetone was removed and the crude product was diluted with water and extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give **7a** (3.74 g, 95% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.46 (t, J = 6.6 Hz, 2H), 2.80 (t, J = 7.4 Hz, 2H), 2.25 (s, 3H), 1.70 (m, 2H), 1,52 (m, 2H), 1.40–1.30 ppm (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.8, 44.9, 32.4, 30.6, 29.3, 28.9, 28.0, 26.3 ppm.
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(b) *tert-Butyl 6-chlorohexylcarbamate (**7b**)*: To a stirred solution of 6-aminohexan-1-ol (3.0 g, 25.59 mmol) in 4 mL of chloroform thionyl chloride was added (1.98 mL, 25.59 mmol) at 0 °C. The reaction mixture was stirred for 3 h under dry conditions. The excess of solvent was removed by distillation. The crude product was triturated with ether. After this a brown solid was obtained which was identified as hydrochloride of 6-chlorohexan-1-amine (**9**) (4.08 g, 93% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.21 (s, 3H), 3.47 (t, J = 6.5 Hz, 2H), 2.95 (t, J = 8.0 Hz, 2H), 1.77–1.70 (m, 4H), 1.46-1.36 ppm (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 45.2, 38.5, 31.8, 26.7, 25.8, 25.0 ppm. To a solution of **9** (0.5 g, 2.96 mmol) in 5 mL of THF and 3 mL of methanol, triethylamine (0.41 mL, 2.96 mmol) and di-*tert*-butyl dicarbonate (0.63 g, 2.96 mmol) were added at room temperature. The reaction mixture was carried out at 40 °C for 3 h under dry conditions. After the mixture was cooled to room temperature, the excess of THF and methanol was removed under reduced pressure. The residue was dissolved in 100 mL of ethyl acetate and washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give compound **7b** (0.663 g, 83.33%) as light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.44 (br, 1H), 3.46 (t, J=6.7 Hz, 2H), 3,05 (m, 2H), 1.70 (m, 2H), 1.45-1.35 (m, 4H), 1.37 (s, 9H), 1.30–1.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 77.2, 59.6, 45.2, 31.9, 28.2, 25.9, 25.4 ppm
20. *S-6-(2,6-Diacetamidopyridine-4-yloxy)hexyl ethanethioate (**8a**)*: To a stirred solution of **6** (2.0 g, 9.56 mmol) in 15 mL of DMF, K_2CO_3 (5.29 g, 38.27 mmol) and **7a** (2.23 g, 11.47 mmol) were added at room temperature. The reaction mixture was heated at 110 °C for 24 h under nitrogen atmosphere. After being cooled to room temperature, the reaction mixture was diluted with 150 mL of water and extracted thrice with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography (MeOH/EtOAc = 1/20) using silica gel to give **8a** (2.66 g, 76% yield) as an off white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.92 (s, 2H), 7.36 (s, 2H), 3.97 (t, J = 6.1 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H), 2.31 (s, 3H), 2.08 (s, 6H), 1.70 (m, 2H), 1.52 (m, 2H), 1.41–1.35 ppm (m, 4H), ^{13}C NMR (125 MHz, DMSO-d_6): δ = 195.2, 169.3, 167.3, 151.4, 95.3, 67.5, 30.5, 28.9, 28.2, 28.1, 27.7, 24.8, 24.0 ppm.
21. *tert-Butyl (6-((2,6-diacetamidopyridine-4-yl)oxy)hexyl)carbamate (**8b**)*: To a stirred solution of **6** (1.0 g, 3.10 mmol) in 15 mL of DMF, K_2CO_3 (1.71 g, 12.42 mmol) and **7b** (0.8 g, 3.41 mmol) were added at room temperature. The reaction mixture was heated at 110 °C for 24 h under nitrogen atmosphere. After being cooled to room temperature, the reaction mixture was diluted with 150 mL of water and extracted thrice with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography (MeOH/EtOAc = 1/20) using silica gel to give **8b** (0.89 g, 71% yield) as an off white solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.91 (s, 2H), 7.36 (s, 2H), 6.71 (s, 1H), 3.97 (t, J = 6.3 Hz, 2H), 2.90 (m, 2H), 2.09 (s, 6H), 1.70 (m, 2H), 1.45-1.37 (m, 4H), 1.37 (s, 9H), 1.30 ppm (m, 2H), ^{13}C NMR (125 MHz, DMSO-d_6): δ = 169.3, 167.3, 151.4, 95.3, 67.5, 29.2, 28.3, 28.2, 25.9, 25.0, 24.0 ppm.