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Synthesis of pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridines by reductive cyclisation of pyridinium salts

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The reduction of *N*-(3-nitro-2-pyridyl)pyridinium chlorides by $SnCl_2$ resulted in the formation of pyrido[3′,2′:4,5]imidazo[1,2-*a*]-pyridines or *N*-(3-amino-2-pyridyl)-3,5-dimethylpyridinium chloride depending on the structure of the substrate.

The annealing of heterocycles with participation of the amino group formed by the reduction of nitroarenes[1] is a convenient procedure for the synthesis of heterocyclic compounds.

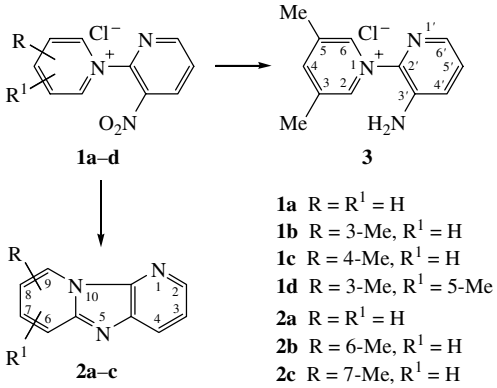
Previously,[2,3] we described the preparation of substituted benzo[4,5]imidazo[1,2-*a*]pyridines by the reductive cyclisation of *N*-(2-nitro-4-R-phenyl)pyridinium salts. This methodology can also be used for the synthesis of other heterocyclic systems.

In the present work we extended the intramolecular amination reaction to the synthesis of pyrido[3′,2′:4,5]imidazo[1,2-*a*]-pyridines, biologically active compounds isolated from naturally occurring raw materials.[4,5] These condensed heterocyclic arenes are synthesised from inaccessible 2-aminoimidazo[1,2-*a*]-pyridine.[6,7]

We experimentally found that, depending on the structure of the substrate, the interaction of *N*-(3-nitro-2-pyridyl)pyridinium salts **1a–d** with tin(II) chloride resulted in the formation of various substances: pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridines **2a–c**, which are the products of reductive amination of **1a–c**, respectively, and *N*-(3-amino-2-pyridyl)-3,5-dimethylpyridinium chloride **3**, which is the product of the reduction of **1d**.† The structures of the prepared compounds were determined by ^{1}H NMR spectroscopy, mass spectrometry and elemental analysis.‡

It was found that steric hindrances have no effect on the reductive amination process. Thus, in the reduction of *N*-(3-nitro-2-pyridyl)-3-methylpyridinium chloride, intramolecular amination occurred at the α-carbon atom in the *ortho* position to the methyl group. As a result, 6-methylpyrido[3′,2′:4,5]imidazo-[1,2-*a*]pyridine **2b** was isolated from the reaction mass.

The absence of cyclisation in the case of **1d** and, consequently, the formation of product **3** were explained by the presence of two strong electron-releasing substituents at the *ortho* and *para* positions to the electrophilic reaction centre in reduced substrate **1d**. As a result of this, its reactivity towards a nucleophile (the amino group formed in the course of reduction) dramatically decreased.



1a R = R^1 = H
1b R = 3-Me, R^1 = H
1c R = 4-Me, R^1 = H
1d R = 3-Me, R^1 = 5-Me
2a R = R^1 = H
2b R = 6-Me, R^1 = H
2c R = 7-Me, R^1 = H

† Solutions of compounds **1a–d** (0.01 mol) in 20 ml of ethanol were added to a solution of 0.03 mol of $SnCl_2 \cdot 2H_2O$ in 15 ml of 3% hydrochloric acid under stirring. After 10 min, the reaction mixture was alkalised with a 25% aqueous ammonia solution to pH 7–8 and extracted with several portions of chloroform (150 ml). After the distillation of chloroform, the yields of compounds were 91% for **2a**, 82% for **2b**, 84% for **2c** and 87% for **3**.

‡ The ^{1}H NMR spectra were recorded on a Bruker DRX500 spectrometer (500 MHz) in [$^2H_6$]DMSO using TMS as an internal standard. The mass spectra were measured on an MX-1310 instrument. Elemental analysis was performed on a CHN-1 analyser.

2a: mp 120–122 °C (lit.,[6] 130 °C). ^{1}H NMR, δ: 8.95 (d, 1H, H-9, *J* 8.5 Hz), 8.51 (d, 1H, H-2, *J* 7.0 Hz), 8.24 (d, 1H, H-4, *J* 10.0 Hz), 7.65–7.75 (m, 2H, H-6 and H-7), 7.59 (m, 1H, H-3), 7.08 (t, 1H, H-8, *J* 9.5 Hz). MS, *m/z* (%): 169 (100) [M]$^+$, 142 (7), 78 (28), 51 (12). Found (%): C, 70.8; H, 4.1; N, 25.0. Calc. for $C_{10}H_7N_3$ (%): C, 71.0; H, 4.2; N, 24.8.

2b: mp 111–113 °C (lit.,[6] 117 °C). ^{1}H NMR, δ: 8.59 (dd, 1H, H-9, *J* 8.0 and 1.5 Hz), 8.42 (d, 1H, H-2, *J* 7.0 Hz), 8.20 (d, 1H, H-4, *J* 10.0 Hz), 7.30–7.45 (m, 2H, H-3 and H-7), 6.83 (t, 1H, H-8, *J* 9.5 Hz), 2.61 (s, 3H, Me). MS, *m/z* (%): 183 (100) [M]$^+$, 169 (8), 157 (26), 78 (31), 51 (10). Found (%): C, 71.7; H, 5.1; N, 23.3. Calc. for $C_{11}H_9N_3$ (%): C, 72.1; H, 4.9; N, 23.0.

2c: mp 135–137 °C (lit.,[6] 148 °C). ^{1}H NMR, δ: 8.61 (d, 1H, H-9, *J* 7.5 Hz), 8.41 (d, 1H, H-2, *J* 7.0 Hz), 8.20 (d, 1H, H-4, *J* 9.5 Hz), 7.45 (m, 1H, H-3), 7.23 (s, 1H, H-6), 6.81 (d, 1H, H-8, *J* 8.0 Hz), 2.46 (s, 3H, Me). MS, *m/z* (%): 184 (19) [M]$^+$ + 1, 183 (100) [M]$^+$, 157 (31), 78 (37), 65 (8), 51 (13). Found (%): C, 71.7; H, 5.1; N, 23.1. Calc. for $C_{11}H_9N_3$ (%): C, 72.1; H, 4.9; N, 23.0.

3: mp 204–206 °C. ^{1}H NMR, δ: 9.05 (s, 2H, H-2 and H-6), 8.50 (s, 1H, H-4), 7.85 (d, 1H, H-6′, *J* 6.5 Hz), 7.44–7.50 (m, 2H, H-4′ and H-5′), 6.05 (s, 2H, NH_2), 2.51 (s, 6H, Me). MS, *m/z* (%): 200 (50) [M]$^+$, 198 (100), 184 (34), 120 (39), 108 (17), 77 (10), 36 (26). Found (%): C, 60.21; H, 6.24; Cl, 15.39; N, 18.01. Calc. for $C_{12}H_{14}ClN_3$ (%): C, 61.15; H, 5.95; Cl, 15.07; N, 17.83.

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