Synthesis of functionalised bipyridines by sequential nucleophilic substitution of hydrogen and cycloaddition in 1,2,4-triazine rings

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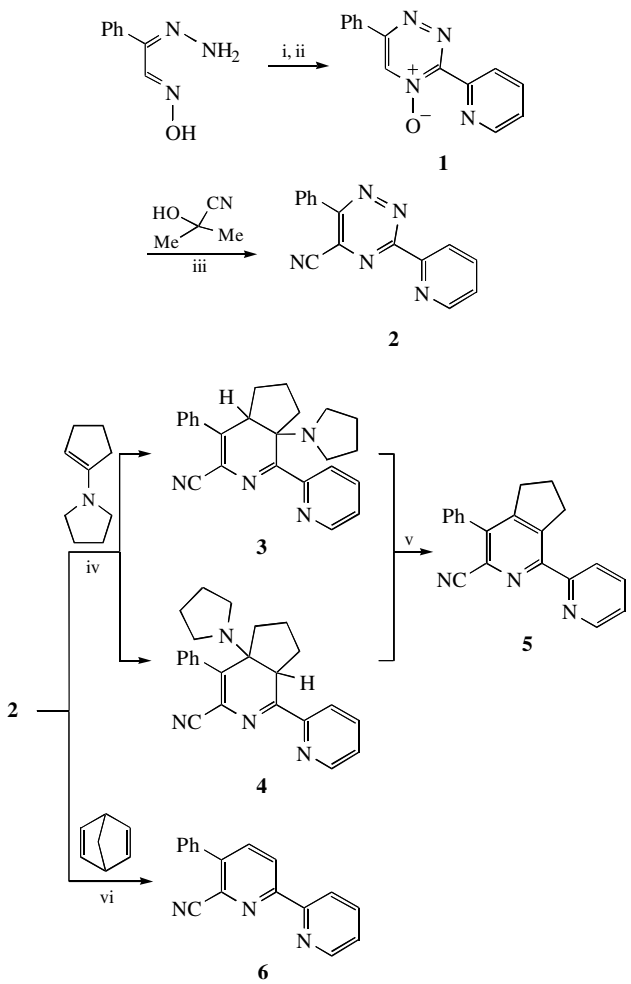
A new methodology for the synthesis of functionalised bipyridines by the direct cyanation of 3-(2-pyridyl)-1,2,4-triazine 4-oxide through nucleophilic substitution for hydrogen followed by the transformation of the 1,2,4-triazine ring into the pyridine ring by the Diels–Alder reaction and, finally, the chemical conversion of the cyano group is described.

The 2,2′-bipyridine system is a well-known ligand for the design of supramolecular metal complex systems.[1] In spite of the large number of publications, methods for the synthesis of asymmetric bipyridines and terpyridines bearing different functional groups are scantily known.[2]

Here, we describe a new methodology for the design of asymmetrically substituted bipyridines involving the synthesis of 3-(2′-pyridyl)-1,2,4-triazine 4-oxides, their functionalization by nucleophilic substitution for hydrogen and finally, formation of the bipyridine system by an inverse electron demand Diels–Alder reaction. The high reactivity of 1,2,4-triazines towards nucleophiles and dienophiles allows oligopyridines bearing different types of substituents (the residues of the nucleophiles and products of their chemical transformation) to be prepared. A modified method[3] was used to form the 1,2,4-triazine ring. Thus, the condensation of pyridine-2-carbaldehyde with isonitrosoacetophenone hydrazone followed by aromatization of the intermediate by oxidation with $KMnO_4$ in acetone results in the formation of 6-phenyl-3-(2′-pyridyl)-1,2,4-triazine 4-oxide **1**.† The *N*-oxide group makes the 1,2,4-triazine ring more susceptible towards nucleophilic substitution for hydrogen. We chose the cyanide anion as a nucleophile for two main reasons. One of them is the high electron-withdrawing property of the cyano group, which increases the reactivity of a heterocycle in the inverse electron demand Diels–Alder reaction with electron-rich dienophiles. The other is the easy conversion of the cyano group into other functional groups, which opens a way to substituted ligands. Thus, the treatment of compound **1** with acetone cyanohydrin in the presence of triethylamine leads to 5-cyano-6-phenyl-3-(2′-pyridyl)-1,2,4-triazine **2** (Scheme 1). In this case, the cyanide anion formed *in situ* adds at the 5-position of the 1,2,4-triazine ring resulting in the intermediate σ-adduct, the dehydration of which forms aromatised product **2**. The reaction proceeds very smoothly in 91% yield.

Cyano-1,2,4-triazine **2** was found to accelerate the Diels–Alder reaction. In our case, a enamine and bicyclo[2.2.1]hepta-2,5-diene were used as electron-rich dienophiles. Thus, 5-cyano-1,2,4-triazine **2** reacts with 1-pyrrolidino-1-cyclopentene at room temperature forming two isomeric cycloadducts **3** and **4** as a result of cycloaddition of the dienophile to the C-3 and C-6 atoms of the 1,2,4-triazine ring followed by the elimination of nitrogen. The formation of an isomer mixture does not play a crucial role because the refluxing of cycloadducts **3** and **4** in acetic acid leads to their aromatization *via* the elimination of pyrrolidine to give 6-cyano-5-phenyl-2-(2′-pyridyl)-3,4-cyclopentenopyridine **5** in almost 100% yield (Scheme 1).

Similarly, 5-cyano-1,2,4-triazine **2** reacts with bicyclo[2.2.1]-hepta-2,5-diene. However, in this case, more severe conditions are required, at least refluxing in toluene. The reaction proceeds with the elimination of nitrogen and cyclopentadiene yielding 6-cyano-5-phenyl-2,2′-bipyridine **6**. In the reaction with bicyclo-[2.2.1]hepta-2,5-diene, the cyano group facilitates the reaction significantly in comparison with unsubstituted pyridyl-1,2,4-triazine.[4]



Scheme 1 *Reagents and conditions*: i, Py-2-CHO, EtOH, room temperature, 12 h; ii, $KMnO_4$–acetone, 0 °C; iii, NEt_3, CH_2Cl_2, reflux; iv, benzene, reflux, 1 h; v, AcOH, reflux, 0.5 h; vi, toluene, reflux, 4 h.

The presence of a cyano group in bipyridine **5** allows the further functionalization, which opens way to new building blocks for the bipyridine series. Thus, the hydrolysis of the cyano group in cyanobipyridine **5** in 95% sulfuric acid leads to 6-carbamoyl-5-phenyl-2-(2′-pyridyl)-3,4-cyclopentenopyridine **7**. Further hydrolysis of amide **7** in concentrated hydrochloric acid forms 5-phenyl-2-(2′-pyridyl)-3,4-cyclopentenopyridine-6-carboxylic acid **8**. The esterification of acid **8** *via* the intermediate formation of an acid chloride yields 6-ethoxycarbonyl-5-phenyl-2-(2′-pyridyl)-3,4-cyclopentenopyridine **9**. The reduction of ester **9** with sodium borohydride results in 6-hydroxymethyl-5-phenyl-2-(2′-pyridyl)-3,4-cyclopentenopyridine **10** (Scheme 2).

Thus, the sequential use of nucleophilic substitution for

hydrogen and the Diels–Alder reaction in the 1,2,4-triazine series is a convenient route for the synthesis of a wide range of functionalised bipyridines.

† *6-Phenyl-3-(2-pyridyl)-1,2,4-triazine-4-oxide* **1**. Pyridine 2-carboxaldehyde (1.07 g, 10.0 mmol) was added to a stirred solution of isonitrosoacetophenone hydrazone (1.63 g, 10.0 mmol) in ethanol (10 ml). The reaction mixture was kept at room temperature for 12 h. The resulting precipitate was filtered off, washed with ethanol, dried and then dissolved in acetone (100 ml). Potassium permanganate (1 g, 6.3 mmol) in acetone (50 ml) was added dropwise to this solution at 0 °C in 30 min. The reaction mixture was additionally stirred at 0 °C for 30 min. The precipitated MnO_2 was removed by filtration and washed with acetone (3×10 ml). Filtrates were combined, the solvent was evaporated at a reduced pressure and the residue was recrystallised from ethanol to give **1** (1.28 g, 57%): mp 173–174 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.54–7.61 (m, 4H), 7.94–8.06 (m, 2H), 8.20–8.26 (m, 2H), 8.77–8.79 (m, 1H), 9.32 (s, 1H). EI-MS, *m*/*z* (*I*, %): 250 (M^+, 23). Found (%): C, 67.14; H, 4.13; N, 22.42. Calc. for $C_{14}H_{10}N_4O$ (250.26) (%): C, 67.19; H, 4.03; N, 22.39.

5-Cyano-6-phenyl-3-(2-pyridyl)-1,2,4-triazine **2**. To a solution of 1,2,4-triazine-4-oxide **1** (1 g, 4 mmol) in dichloromethane (30 ml) acetonecyanohydrin (0.73 ml, 8 mmol) and triethylamine (0.56 ml, 4 mmol) were added with stirring, and the solution was refluxed for 30 min. The solvent was evaporated *in vacuo*, and the residue was treated with diethyl ether (10 ml). The precipitate obtained was filtered off and washed with isopropanol (2 ml) and diethyl ether (5 ml) to give **2** (0.94 g, 91%). No further purification was required; mp 128–129 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.60–7.71 (m, 4H), 8.03–8.15 (m, 3H), 8.55–8.60 (m, 1H), 8.85–8.88 (m, 1H). EI-MS, *m*/*z* (*I*, %): 259 (M^+, 4), 231 (M – N_2, 21). Found (%): C, 69.35; H, 3.47; N, 27.14. Calc. for $C_{15}H_9N_5$ (259.27) (%): C, 69.49; H, 3.50; N, 27.01.

6-Cyano-5-phenyl-2-(2'-pyridyl)-3,4-cyclopentenopyridine **5**. 1-Pyrrolidino-1-cyclopentene (0.32 ml, 2.2 mmol) was added to a solution of 5-cyano-6-phenyl-3-(2-pyridyl)-1,2,4-triazine **2** (0.52 g, 2 mmol) in benzene (10 ml). As a result, immediate nitrogen evolution took place. The reaction mixture was stirred at room temperature for 1 h and then refluxed for 1 h. The solvent was evaporated *in vacuo*, and the residue was refluxed in acetic acid (3 ml) for 30 min. Crystals of **5** were filtered off and washed with acetic acid (2 ml). Yield of **5** as a colourless needles: 0.58 g, 97%; mp 192–193 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.02–2.20 (m, 2H), 2.86–2.93 (m, 2H), 3.53–3.60 (m, 2H), 7.42–7.58 (m, 6H), 7.90–7.97 (m, 1H), 8.30–8.33 (m, 1H), 8.66–8.69 (m, 1H). EI-MS, *m*/*z* (*I*, %): 297 (M^+, 100). Found (%): C, 80.74; H, 4.98; N, 14.27. Calc. for $C_{20}H_{15}N_3$ (297.36) (%): C, 80.78; H, 5.08; N, 14.13.

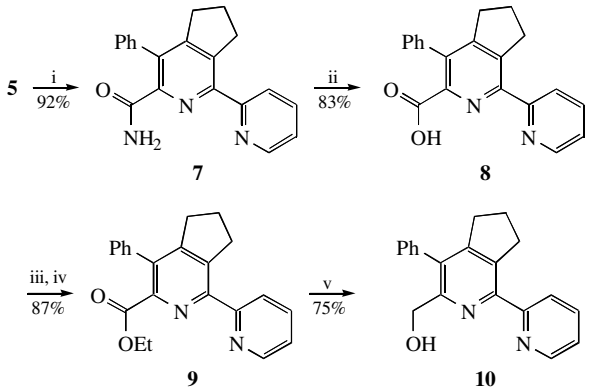
6-Cyano-5-phenyl-2,2'-bipyridine **6**. A mixture of 5-cyano-6-phenyl-3-(2-pyridyl)-1,2,4-triazine **2** (0.52 g, 2 mmol) and bicyclo[2.2.1]hepta-2,5-diene (0.86 ml, 8 mmol) was refluxed in toluene (10 ml) for 4 h. The solvent was removed on a rotary evaporator, and the residue was recrystallised from ethanol to give **6** (0.47 g, 92%); mp 194–195 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.44–7.70 (m, 6H), 7.74–8.00 (m, 1H), 8.17 (d, 1H, *J* 8.1 Hz), 8.43–8.47 (m, 1H), 8.68–8.75 (m, 1H), 8.73 (d, 1H, *J* 8.1 Hz). EI-MS, *m*/*z* (*I*, %): 257 (M^+, 100). Found (%): C, 79.52; H, 4.41; N, 16.31. Calc. for $C_{17}H_{11}N_3$ (257.30) (%): C, 79.36; H, 4.31; N, 16.33.

6-Carbamoyl-5-phenyl-2-(2'-pyridyl)-3,4-cyclopentenopyridine **7**: mp 197–198 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.96–2.10 (m, 2H), 2.72 (t, 2H, *J* 7.7 Hz), 3.50 (t, 2H, *J* 7.7 Hz), 7.12 (br. s, 1H, amide), 7.22–7.41 (m, 6H), 7.72 (br. s, 1H, amide), 8.845–8.93 (m, 1H), 8.42–8.47 (m, 1H), 8.63–6.67 (m, 1H). EI-MS, *m*/*z* (*I*, %): 315 (M^+, 36). Found (%): C, 76.19; H, 5.54; N, 13.30. Calc. for $C_{20}H_{17}N_3O$ (315.38) (%): C, 76.17; H, 5.43; N, 13.32.

6-Carboxy-5-phenyl-2-(2'-pyridyl)-3,4-cyclopentenopyridine hydrochloride **8**: mp 209–210 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 2.04–2.19 (m, 2H), 2.84 (t, 2H, *J* 7.3 Hz), 3.48 (t, 2H, *J* 7.3 Hz), 7.29–7.49 (m, 5H), 7.78–7.86 (m, 1H), 8.33–8.50 (m, 2H), 8.86–8.92 (m, 1H). EI-MS, *m*/*z* (*I*, %): 316 (M^+, 11), 272 (M^+ – CO_2). Found (%): C, 68.07; H, 4.56; N, 7.73. Calc. for $C_{20}H_{16}N_2O_2$·HCl (%): C, 68.08; H, 4.86; N, 7.94.

6-Ethoxycarbonyl-5-phenyl-2-(2'-pyridyl)-3,4-cyclopentenopyridine **9**: mp 126–127 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 0.97 (t, 3H, *J* 7.5 Hz), 1.98–2.16 (m, 2H), 2.82 (t, 2H, *J* 7.5 Hz), 3.53 (t, 2H, *J* 7.5 Hz), 4.03 (q, 2H, *J* 7.5 Hz), 7.25–7.46 (m, 6H), 7.82–7.92 (m, 1H), 8.30–8.36 (m, 1H), 8.64–8.67 (m, 1H). Found (%): C, 76.67; H, 5.90; N, 8.17. Calc. for $C_{22}H_{20}N_2O_2$ (344.42) (%): C, 76.72; H, 5.85; N, 8.13.

6-Hydroxymethyl-5-phenyl-2-(2'-pyridyl)-3,4-cyclopentenopyridine **10**: mp 140–141 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 1.98–2.09 (m, 2H), 2.70 (t, 2H, *J* 7.4 Hz), 3.46 (t, 2H, *J* 7.4 Hz), 4.38 (br. s, 2H), 4.69 (br. s, 1H), 7.30–7.50 (m, 6H), 7.84–7.93 (m, 1H), 8.38–8.43 (m, 1H), 8.63–8.66 (m, 1H). EI-MS, *m*/*z* (*I*, %): 302 (M^+, 100). Found (%): C, 79.44; H, 5.94; N, 9.40. Calc. for $C_{20}H_{18}N_2O$ (302.38) (%): C, 79.44; H, 6.00; N, 9.26.



Scheme 2 *Reagents and conditions*: i, H_2SO_4 (95%), 100 °C, 6 h; ii, HCl (conc.), reflux, 7 h; iii, $SOCl_2$, reflux, 7 h; iv, EtOH, reflux, 1 h; v, $NaBH_4$, EtOH, reflux, 5 h.

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