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An efficient route to 5-(hetero)aryl-2,4′- and 2,2′-bipyridines through readily available 3-pyridyl-1,2,4-triazines

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Abstract—A new route to substituted bipyridines based on a new method for the synthesis of substituted 3-pyridyl-1,2,4-triazines and their aza-Diels–Alder reactions is shown to be an efficient strategy for the preparation of structurally diverse bipyridine ligands.

2,2′-Bipyridines (bpy) are undoubtedly among the most widely used ligands in coordination and supramolecular chemistry.[1,2] In particular, the photophysical properties of their metal complexes are of special interest. It was shown in numerous studies that the transition metal bpy complexes find various applications: from catalysis[3] and photocatalysis[4] to chemosensors[5] and luminescent probes for biomolecular systems.[6] Among bipyridines, 5-aryl-2,2′-bipyridines (arbpy) exhibit the best luminescent properties with emission quantum yields (Φ_f) up to 0.80, due to the effect of the aromatic substituents making the bipyridines attractive as chromophores and 'antennae'.[7] Strong fungicidal activity of 5-aryl-2,2′-bipyridines against different plant diseases is another application to be described.[8] However, the study of these interesting and useful compounds is hampered by inefficient chemical synthesis. The typical Kroehnke synthesis was modified to prepare 5-substituted-2,2′-bipyridines giving mixtures of isomers and poor yields.[8] Alternative cross-coupling[9] approaches are limited by inaccessible starting compounds.

In this letter we report an efficient strategy for the synthesis of 5-(hetero)aryl-2,2′-bipyridines **1** based on the conversion of 3-(2-pyridyl)-1,2,4-triazines to substituted bpys via an aza-Diels–Alder reaction.[10] The key-step of our strategy is the regiospecific and easy synthesis of 3-pyridyl-1,2,4-triazines bearing an aryl substituent at the 6-position of the 1,2,4-triazine ring. It should be noted that 3-pyridyl-1,2,4-triazines are interesting compounds in their own right due to their application in transition metal analysis[11] or in the separation of lanthanides and actinides in the management of nuclear waste.[12]

We devised a new method for the synthesis of 6-aryl-3-(2-pyridyl)-1,2,4-triazines **2** starting from readily available acylarenes **3** bearing various substituents on the aryl moiety, for example, fluoro-, chloro-, bromo-, methyl-, methoxy- or nitrophenyl. Nitrosation of **3** yielded the corresponding 1-aryl-2-oximino-1-ethanones **4**, then treatment with hydrazine hydrate resulted in the formation of 1-aryl-1-hydrazono-2-oximinoethanes **5** in good yields. Condensation of hydrazones **5** with pyridine-2-carboxaldehyde gave 1-aryl-2-oximino-1-(2-pyridylmethylenehydrazono)ethanes **6** in excellent yields. The open-chain compounds **6** exist in equilibrium with the cyclic 6-aryl-4-hydroxy-3-(2-pyridyl)-3,4-dihydro-1,2,4-triazines **7** (the ring-chain isomerism of 4-hydroxy-3,4-dihydro-1,2,4-triazines is described elsewhere[13]). Dehydration of the dihydrotriazines **7** after brief refluxing in acetic acid yielded the aromatic pyridyltriazines **2**. The aryl substituents of the starting ketones **3** appear exactly at the defined 6-position of the 1,2,4-triazines **2** and not the 5-position as in 1,2,4-triazine synthesis from arylglyoxals.[14] Isolation of the intermediates **6** and **7** from the reaction mixtures can be omitted to make the synthetic procedure easier.[15]

Conversion of triazines **2** to arbpys **1** was achieved by aza-Diels–Alder reactions with a strained dienophile—2,5-norbornadiene—following a typical procedure.[10]

Keywords: Bipyridines; Polypyridines; 1,2,4-Triazines; Ligands.
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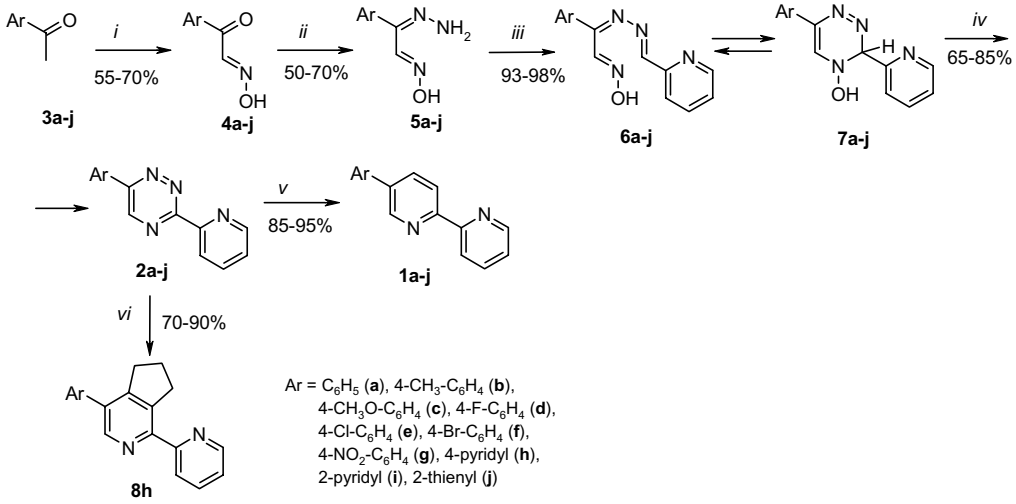


Scheme 1. Reagents and conditions: (i) *i*-PrONO, EtONa, EtOH, 10 °C, then AcOH; (ii) N_2H_4–H_2O, EtOH, rt; (iii) pyridine-2-carboxaldehyde, EtOH; (iv) AcOH, reflux; (v) 2,5-norbornadiene, xylene, reflux, 8–15 h; (vi) morpholinocyclopentene, dioxane, reflux.

The reaction proceeded slowly and at high temperature (refluxing in xylene) to give 5-aryl-2,2′-bipyridines **1** in high yields.

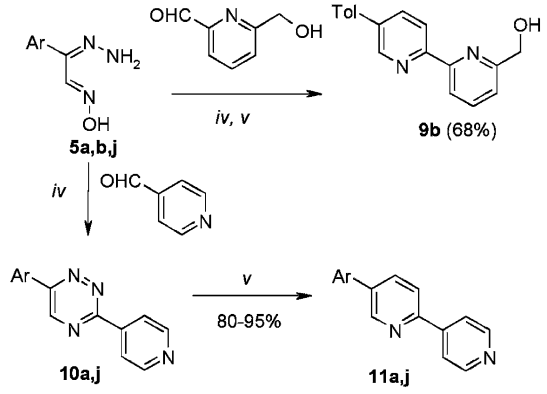
Starting from acylheteroarenes, for example, acetylthiophene, 2- or 4-acetylpyridines, 3-(2-pyridyl)-1,2,4-triazines **2h–j**[15] bearing heteroaromatic substituents at the 6-position were obtained by this method. Next, the cycloaddition step gave 5-heteroaryl-2,2′-bipyridines **1h–j**.[16]

Additional substituent diversity was achieved using eneamines as dienophiles in inverse electron demand aza-Diels–Alder reactions[17,18] Pyridyltriazine **2h** reacted with morpholinocyclopentene more readily than with norbornadiene (refluxing in dioxane instead of xylene) yielding **8h** possessing a fused five-membered ring (Scheme 1).[19]

Finally, the arbpys diversity could be extended by varying the substituents in the starting pyridinecarboxaldehydes, for example, 5-tolyl-6′-hydroxymethyl-2,2′-bipyridine **9b** was obtained from 6-hydroxymethylpyridine-2-carboxaldehyde (Scheme 2).

Not only 2,2′- but 2,4′-bipyridines could be obtained by our method. The condensation of pyridine-4-carboxaldehyde with hydrazones **5** followed by dehydration of the intermediates resulted in the formation of 6-aryl-3-(4-pyridyl)-1,2,4-triazines **10**, then refluxing with norbornadiene yielded 5-aryl-2,4′-bipyridines **11** (Scheme 2).

It is noteworthy, that the reactions could be easily scaled up to produce multi-gram quantities of arbpys **1** (we obtained 5 g of the arbpy **1b** from one operation). The relatively harsh conditions (long time (up to 15 h) and high temperatures (refluxing in xylene) of the reaction with norbornadiene did not affect the yields or purities of the arbpys **1**.



Scheme 2. Reagents and conditions: (iv) AcOH, reflux; (v) 2,5-norbornadiene, xylene, reflux.

In conclusion it should be noted, that the good yields of all intermediates and final products, multi-gram scale, cheap and accessible starting compounds and relatively easy experimental procedure make these substituted bipyridines readily available compounds. Substituent diversity is achieved by variation of three independent components: the acyl(hetero)arenes, dienophiles and pyridinecarboxaldehyde.

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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.2005.01.135.

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15. *3-(2-Pyridyl)-6-(4-pyridyl)-1,2,4-triazine* **2h**. To a solution of 1-hydrazono-2-oximino-1-(4-pyridyl)ethane **5h** (2.74 g, 16.7 mmol) in AcOH (10 mL) was added 2-pyridinecarboxaldehyde (1.79 g, 16.7 mmol). The mixture was stirred at room temperature for 1 h, heated to reflux, allowed to cool to room temperature and then diluted with water (10 mL). The resulting precipitate was filtered off, washed with water and recrystallized from ethanol to afford a yellow crystalline solid (2.66 g, 68%), mp 193–194 °C, ^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.64 (ddd, 1H, *J* 7.5, 4.7, 1.1 Hz), 8.09 (ddd, 1H, *J* 7.8, 7.8, 1.8 Hz), 8.26 (m, 2H), 8.52 (br d, 1H, *J* 7.9 Hz), 8.85 (m, 3H), 9.65 (s, 1H); $C_{13}H_9N_5$ (235.25) calcd C, 66.37; H, 3.86; N, 29.77. Found C, 66.40; H, 3.91; N, 29.69.
16. *5-(4-Pyridyl)-2,2′-bipyridine* **1h**. A mixture of 3-(2-pyridyl)-6-(4-pyridyl)-1,2,4-triazine **2h** (730 mg, 3.1 mmol), bicyclo[2.2.1]hepta-2,5-diene (1.58 mL, 15.5 mmol) and *o*-xylene (30 mL) was refluxed for 10 h and cooled to room temperature. The resulting precipitate was filtered off, washed with benzene and dried to give the title product (638 mg, 88%), mp 185–187 °C, ^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.48 (ddd, 1H, *J* 7.6, 4.9, 1.2 Hz), 7.85 (m, 2H), 7.98 (ddd, 1H, *J* 7.9, 7.9, 1.8 Hz), 8.37 (dd, 1H, *J* 8.2, 2.1 Hz), 8.45 (m, 1H), 8.52 (dd, 1H, *J* 8.2, 0.6 Hz), 8.70 (m, 3H), 9.13 (dd, 1H, *J* 2.1, 0.6 Hz); $C_{15}H_{11}N_3$ (233.28) calcd C, 77.23; H, 4.75; N, 18.01. Found C, 77.25; H, 4.72; N, 17.96.
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19. *2-(2-Pyridyl)-5-(4-pyridyl)cyclopenteno[c]pyridine* **8h**. A mixture of 3-(2-pyridyl)-6-(4-pyridyl)-1,2,4-triazine **2h** (400 mg, 1.7 mmol), 1-morpholinocyclopentene (0.3 mL, 287 mg, 1.8 mmol) and 1,4-dioxane (20 mL) was refluxed for 24 h. Then acetic acid (2 mL) was added and the reaction mixture was heated at reflux for 1 h, cooled to room temperature and made basic with an aqueous solution of NaOH (1 M, 50 mL). The resulting precipitate was filtered, washed with water and recrystallized from ethanol–water (1:1) to give the titled compound (320 mg, 79%), mp 154–155 °C, ^{1}H NMR (250 MHz, DMSO-d_6): δ = 2.02 (p, 2H, *J* 7.6 Hz), 3.04 (t, 2H, *J* 7.6 Hz), 3.43 (t, 2H, *J* 7.6 Hz), 7.42 (ddd, 1H, *J* 7.3, 4.9, 1.2 Hz), 7.61 (m, 2H), 7.94 (ddd, 1H, *J* 7.9, 7.9, 1.8 Hz), 8.31 (ddd, 1H, *J* 7.9, 0.9, 0.9 Hz), 8.59 (s, 1H), 8.70 (m, 3H); $C_{18}H_{15}N_3$ (273.34) calcd C, 79.10; H, 5.53; N. 15.37. Found C, 79.15; H, 5.42; N, 15.36.