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A New and Simple 'LEGO' System for the Synthesis of 2,6-Oligopyridines

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Abstract

The condensation of α-arylglyoxals with carboxamidrazones **1** - **2** is the best method for the synthesis of aryl or hetaryl substituted 1,2,4-triazines **3** - **4** . These 1,2,4-triazines can be easily transformed to pyridines by [4+2] cycloaddition with bicyclo[2.2.1]hepta-2,5-diene followed by [4+2] cycloreversions of nitrogen and cyclopentadiene This reaction sequence offers a new, simple and general access to 2,6-oligopyridines **8** - **11**

Keywords: *Cycloadditions; Oligomers, Pyridines, Triazines*

Terpyridines and higher oligopyridines have been demonstrated to be useful building blocks in metallosupramolecular chemistry [1,2,3,4]. In order to investigate the coordinating behaviour of these polydendate ligands it is necessary to develop direct high-yield synthethic methods for easy access. Up to now there are two different approaches for the synthesis of oligopyridine ligands: the coupling of pyridine units [5,6,7,8] or halopyridine nuclei [9] and the construction of central pyridine rings [10,11]. Here we report on a new and simple 'LEGO' system for the synthesis of linear 2,6-oligopyridines **8** - **11** and hetaryl substituted 1,2,4-triazines **3** - **4** as their precursors.

3,5-Disubstituted 1,2,4-triazines are easily prepared by heating of carboxamidrazones with α-aryl-glyoxals in ethanol under reflux for 4-6 hours [12,13]. But these reaction conditions fail for 3,5-di-(2-pyridyl)-1,2,4-triazines because of the thermolabile 2-pyridylglyoxal, which is only available in aqueous solution [14]. Therefore, we have treated 2-pyridylglyoxal with the corresponding carboxamidrazone in ethanol-water (4:1 v/v) for 3-9 days at ambient temperature with eventually heating of the isolated precipitate in *N,N*-dimethylformamide at 100°C for 0.5 hours to complete condensation (Table 1, Scheme 1).

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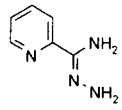
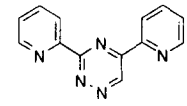
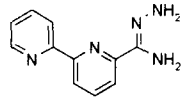
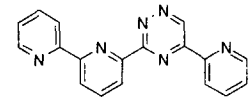
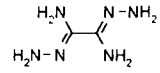
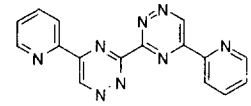
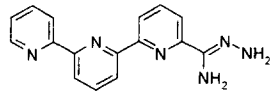
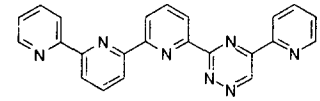
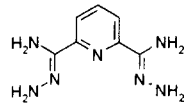
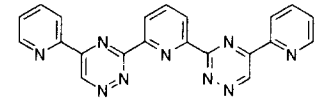
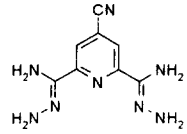
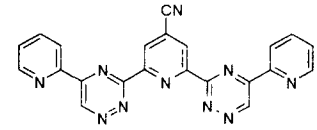
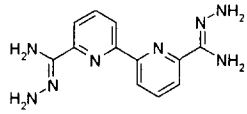
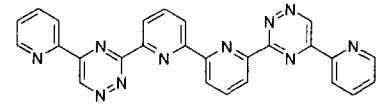
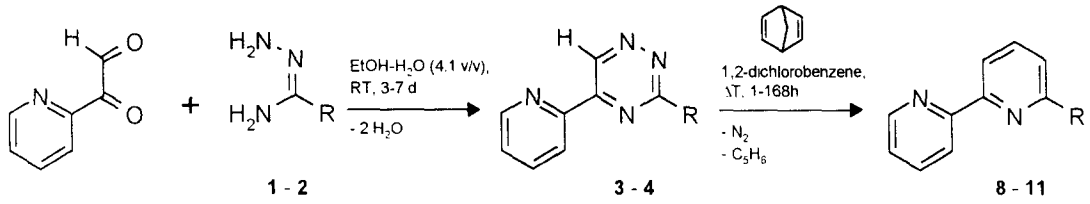
The concentration of 2-pyridylglyoxal was determined by ^{1}H NMR spectroscopy of its aqueous solution with 3-trimethylsilyl-(2,2,3,3-d_4)-propionic-acid-sodium salt as internal and integral standard.

Table 1. Mono-, bi- and bis-[1,2,4]-triazines synthesized according to Scheme 1

Carboxmidrazone [Ref]		Triazine		Reaction Times and Conditions	Yield [%]	M P [°C]
1a [15]		**3a**		1 d, r t.	49	162-165
1b [16]		**3b**		2 d, r t.	85	220-222
2a [17]		**4a**		3 d, r.t.; 2 h 100°C in DMF	85	336-339
1c analogue to [16]		**3c**		2 d, r.t.	72	246-248
2b [18]		**4b**		3 d, r.t.	67	293-298
2c analogue to [18]		**4c**		8 d, r.t. 2 h 100°C in DMF	60	303-308
2d [19], analogue to [16]		**4d**		9 d, r.t.; 2 h 100°C in DMF	71	395-398

Typical procedure for the preparation of 1,2,4-triazines **3** - **4**: **1b** (1.58 g, 7.40 mmol) and 2-pyridylglyoxal (1.00 g, 7.40 mmol, c = 33.3 µmol/l) in 222 ml ethanol-water (4:1 v/v) were stirred at ambient temperature. After 3 days the resulting yellow precipitate (**3b**) was collected by suction filtration, washed several times with water and ethanol and dried for 16 hours at 80°C/0.01 Torr. No further purification was necessary. Analytical data for **3b**: IR (KBr): ν = 3080, 3060, 3000, 1570, 1550, 1525, 1505, 1460, 1420, 1350, 1235, 1030, 980, 755, 725 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (ddd, 1 H, J = 7.5 Hz, J = 4.8 Hz, J = 1.2 Hz), 7.53 (ddd, 1 H, J = 7.6 Hz, J = 4.7 Hz, J = 1.2 Hz), 7.90 (ddd, 1 H, J = 8.0 Hz, J = 7.5 Hz, J = 1.8 Hz), 8.00 (ddd, 1 H, J = 7.8 Hz, J = 7.7 Hz, J = 1.8 Hz), 8.09 (dd, 1 H, J = 7.8 Hz, J = 7.8 Hz), 8.66 (dd, 1 H, J = 7.9 Hz, J = 1.1 Hz), 8.70 (dd, 1 H, J = 7.8 Hz, J = 1.0 Hz), 8.73 (ddd, 1 H, J = 4.8 Hz, J = 1.8 Hz, J = 0.9 Hz), 8.77 (ddd, 1 H, J = 8.0 Hz, J = 1.2 Hz, J = 0.9 Hz), 8.81 (ddd, 1 H, J = 7.8 Hz, J = 1.2 Hz, J = 0.9 Hz), 8.83 (ddd, 1 H, J = 4.7 Hz, J = 1.8 Hz, J = 0.9 Hz), 10.34 (s, 1 H) ppm; EI-MS (70eV): m/z (%) 312 (35) [M$^+$], 284 (78) [M$^+$ - N_2], 236 (4) [M$^+$ - C_5H_2N], 206 (5) [M$^+$ - C_5H_2N - N_2], 181 (100) [M$^+$ - C_5H_4N - N_2], 155 [$C_{10}H_7N_2$] 128 (11) [C_9H_6N], 103 (95) [C_7H_4N], 78 (20) [C_5H_4N]; $C_{18}H_{12}N_6$ (312.3): calcd. C 69.22, H 3.87, N 26.91; found C 69.13, H 4.01, N 26.80. All other 1,2,4-triazines were characterized by the same analytical methods.

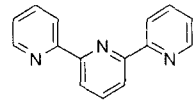
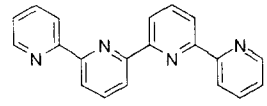
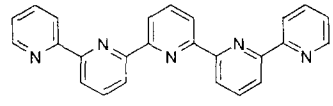
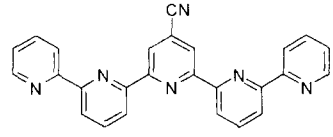
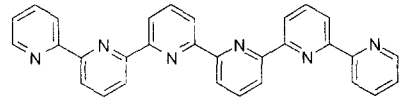
1,2,4-Triazines are known to participate as electron poor dienes in inverse-type Diels-Alder reactions with electron rich and angle strained dienophiles to yield dihydropyridine and pyridine derivatives after extrusion of molecular nitrogen [13,20].



Scheme 1. Reaction sequence for the synthesis of pyridines via 1,2,4-triazines

Acetylene as dienophile is too unreactive, unpracticable and dangerous. Therefore, we used bicyclo[2.2.1]hepta-2,5-diene (10 fold excess) in refluxing 1,2-dichlorobenzene as a synthetic equivalent for acetylene (Scheme 1).

Table 2. Synthesis of 2,6-oligopyridines according to Scheme 1.

Triazine	Oligopyridine		Reaction Conditions and Times	Yield [%]	M.P [°C]	Reference
3a	**8**		140°C, 1h	50	87-88	[7]
4a	**9a**		140°C, 1h	79	208-210	[8]
4b	**10a**		140°C, 3h	60	261-263	[8]
4c	**10b**		ΔT, 14 h	77	219-221	-
4d	**11**		ΔT, 168 h	78	326-329	[8]

Typical procedure for the preparation of oligopyridines **8 - 11**: **4a** (236 mg, 750 µmol) and bicyclo[2.2.1]hepta-2,5-diene (1.38 g, 15.0 mmol) were heated at 140°C under an inert atmosphere in 15 ml 1,2-dichlorobenzene for 1 hour. The reaction mixture was cooled and the resulting precipitate was collected by suction filtration, washed with 2 ml 1,2-dichlorobenzene and 40 ml petroleum ether 40/60. Recrystallization from benzene yielded **9a** as colorless crystals. Analytical data for **9a**: IR (KBr): ν = 3040, 3000, 1575, 1560, 1550, 1455, 1430, 1410, 1250, 1095, 1060, 755 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (ddd, 2 H, J = 7.5 Hz, J = 4.8 Hz, J = 1.3 Hz), 7.87 (ddd, 2 H, J = 8.0 Hz, J = 7.5 Hz, J = 1.8 Hz), 8.01 (dd, 2 H, J = 7.9 Hz, J = 7.8 Hz), 8.48 (dd, 2 H, J = 7.8 Hz, J = 1.1 Hz), 8.67 (ddd, 2 H, J = 8.0 Hz, J = 1.3 Hz, J = 0.9 Hz), 8.68 (dd, 2 H, J = 7.8 Hz, J = 1.1 Hz), 8.72 (ddd, 2 H, J = 4.8 Hz, J = 1.8 Hz, J = 0.9 Hz) ppm. All other oligopyridines were characterized in the same way

The NMR spectra of 1,2,4-triazines **3** and **4** exhibit in each case one singlet for the expected triazine-H^6 and the corresponding pyridines are confirmed by the expected coupling constants for 2,6-oligopyridines (footnote Table 2).

Recent investigations have shown that 1,2,4-triazines undergo [4+2] cycloaddition with ethynyltributyltin to furnish 4-tributylstannyl-pyridines [21,22], which lead to a variety of 4-functionalized pyridines. Further work on this topic with 1,2,4-triazines **3** - **4** is in progress.

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