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The New and Simple 'LEGO' System for the Synthesis of Thienyl Substituted 2,6-Oligopyridines

Oliver C. Pfüller and Jürgen Sauer*,[1]

Institut für Organische Chemie der Universität Regensburg, D-93040 Regensburg, Germany

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Abstract

Carboxamidrazones **1-3** were condensed with thienylglyoxal hydrates **5** to form thienyl substituted 1,2,4-triazines **6-8**. The 1,2,4-triazines are easily transformed to pyridines **9-11** in a [4+2] cycloaddition. This reaction sequence offers a new and simple access to thienyl substituted 2,6-oligopyridines with defined regiochemistry.

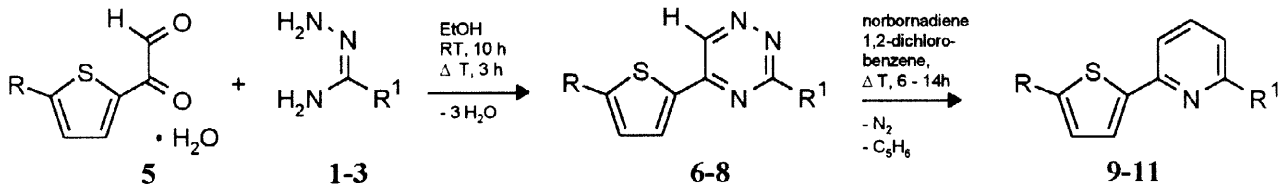
Keywords: *Cycloadditions; Oligomers; Pyridines; Triazines*

In this communication we extend our new 'LEGO' system [1,2], a new and simple route to pyridines via 1,2,4-triazines, to the generation of thienyl substituted 2,6-oligopyridines. The central point of our strategy is the regiospecific condensation of carboxamidrazones **1-3** (Table 1) with thienylglyoxal hydrates **5** (Table 2) to form 1,2,4-triazines **6-8** [3,4,5] (Table 3).

Table 1. Carboxamidrazones used for the condensation with glyoxals **5**.

Carboxamidrazones [Ref.]		
1 dicarboxbisamidrazone [6]	**2** pyridine-2-carboxamidrazone [7]	**3** pyridine-2,6-dicarboxamidrazone [8]

The 1,2,4-triazines **6-8** are easily transformed to pyridines **9-11** in a Diels-Alder reaction with 2,5-norbornadiene followed by extrusion of nitrogen and 1,3-cyclopentadiene (Scheme 1) [9].



5 **1-3** **6-8** **9-11**

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

[1] E-mail: elisabeth.liebl@chemie.uni-regensburg.de

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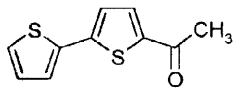
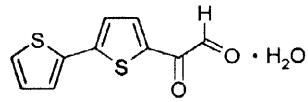
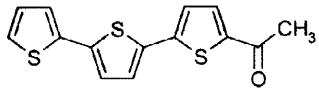
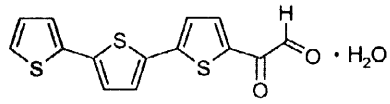
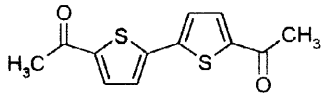
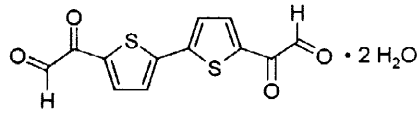
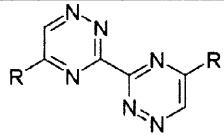
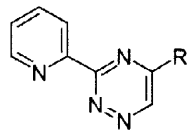
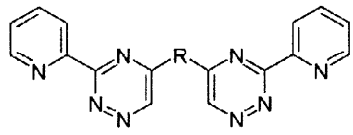
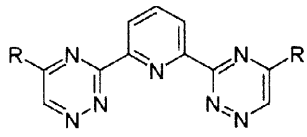
Thienylglyoxal hydrates **5** were prepared by SeO_2 oxidation of the corresponding acetylthiophene derivatives **4** [10,11] in a dioxane / water mixture [12].

Table 2. Preparation of glyoxal hydrates **5** from the corresponding ethanones **4**

Ethanone [Ref.]	Glyoxal hydrate [Ref.]	Conditions	Yield [%]	M.P. [°C]
4a [10] 	**5a** [13] 	100 °C, 18 h	80	126-128
4b [11] 	**5b** 	100°C, 34 h	75	158-160
4c [11] 	**5c** 	100°C, 3d	48	210-212

Typical procedure for the preparation of glyoxal hydrates **5**: **4b** (1.40 g, 4.82 mmol) was added to a solution of SeO_2 (0.54 g, 4.82 mmol) in 100 ml 1,4-dioxane and 10 ml water at 50 °C and heated to reflux for 1d. After addition of further SeO_2 (0.30 g, 2.70 mmol) and 10 h reflux the reaction mixture was filtered hot to separate from selenium. After cooling, the filtrate was diluted with 200 ml of water. The precipitate was collected by suction filtration and washed with water. Recrystallization from acetic acid / water (10 : 1, v/v) yielded **5b** (1.17 g, 3.62 mmol, 75%). Analytical data for **5b**: IR (KBr): $\tilde{\nu}$ = 3440, 3380, 3100, 3060, 1670, 1460, 1440, 1420, 1240, 1130, 1070, 1020, 820, 790 cm^{-1}. ^1H NMR (250 MHz, DMSO-d_6): δ = 5.51 (t, 1 H, J = 7.0 Hz), 6.88 (d, 2 H, J = 7.0 Hz), 7.13 (dd, 1H, J = 5.10 Hz, J = 3.62 Hz), 7.35 (d, 1 H, J = 3.81 Hz), 7.42 (dd, 1 H, J = 3.62 Hz, J = 1.19 Hz), 7.47 (d, 1 H, J = 4.01 Hz), 7.53 (d, 1H, J = 3.81 Hz), 7.59 (dd, 1H, J = 5.10 Hz, J = 1.19 Hz), 7.98 (d, 1 H, J = 4.01 Hz) ppm. EI-MS (70eV); m/z (%): 304 (57) [M^+ - H_2O], 276 (20) [M^+ - H_2O - CO], 275 (100) [M^+ - H_2O - CHO], 248 (6) [M^+ - H_2O - 2 CO], 247 (13) [M^+ - H_2O - CHO - CO], 204 [M^+ - H_2O - 2 CO - CS], 203 (55) [M^+ - H2O - CHO -CO -CS], 138 (8) [M^{2+} - H_2O - CO], 102 (6) [M^{2+} - H_2O - 2CO - 2CS]. $C_{14}H_{10}O_3S_3$ (322.4): calcd. C 52.15, H 3.13; found C 52.59, H 3.20. All other glyoxal hydrates were characterized by the same analytical methods.

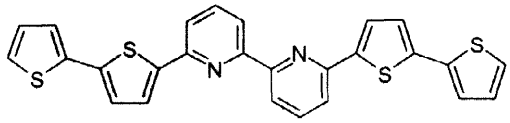
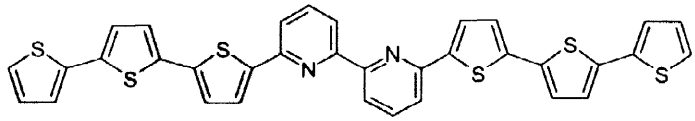
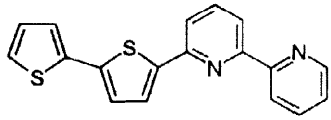
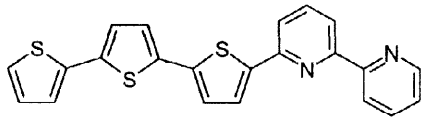
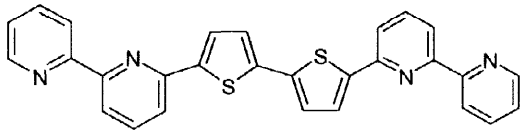
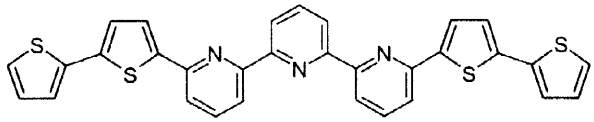
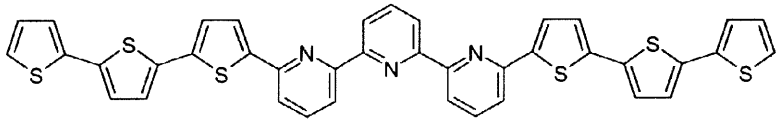
Table 3. 1,2,4-Triazines **6-8** obtained from thienylglyoxal hydrates **5** and carboxamidrazones **1-3**.

Amidrazone	Glyoxal	Triazine		R	Yield [%]	M.P. [°C]
1	**5a**	**6a**		[2,2′]bithiophene-5-yl	97	238-240
1	**5b**	**6b**		[2,2′;5′,2″]terthiophene-5-yl	81	281-284
2	**5a**	**7a**		[2,2′]bithiophene-5-yl	64	179-181
2	**5b**	**7b**		[2,2′;5′,2″]terthiophene-5-yl	60	198-200
2	**5c**	**7c**		[2,2′]bithiophene-5,5′-diyl	63	330-335
3	**5a**	**8a**		[2,2′]bithiophene-5-yl	81	283-285
3	**5b**	**8b**		[2,2′;5′,2″]terthiophene-5-yl	70	269-272

Typical procedure for the preparation of triazines **6-8**: To a solution of **2** (283 mg, 2.08 mmol) in 15 ml ethanol a solution of **5a** (500 mg, 2.08 mmol) in 20 ml ethanol was added and stirred for 24 h at ambient temperature. The mixture was then heated to reflux for 1h. After cooling the yellow precipitate was collected by suction filtration, washed with 15 ml of cold ethanol and dried for 24 h at 60°C/0.01 Torr to yield **7a** (429 mg, 1.33 mmol, 64%). No further purification was necessary. Analytical data for **7a**: IR (KBr): $\tilde{\nu}$ = 3060, 1550, 1530, 1490, 1450, 1390, 1330, 1280, 1240, 1110, 1010, 960, 840, 820, 770, 700 cm^{-1}. ^1H NMR (250 MHz, DMF-d_7): δ = 7.24 (dd, 1H, J = 5.1 Hz, J = 3.7 Hz), 7.63 (d, 1 H, J = 4.1 Hz), 7.65 (dd, 1 H, J = 3.6 Hz, J = 1.2 Hz), 7.67 (ddd, 1 H, J = 7.6 Hz, J = 4.7 Hz, J = 1.2 Hz), 7.74 (dd, 1 H, J = 5.1 Hz, J = 1.2 Hz), 8.13 (ddd, 1 H, J = 7.9 Hz, J = 7.6 Hz, J = 1.8 Hz), 8.48 (d, 1 H, J = 4.1 Hz), 8.56 (ddd, 1 H, J = 7.9 Hz, J = 1.2 Hz, J = 1.0 Hz), 8.90 (ddd, 1 H, J = 4.7 Hz, J = 1.8 Hz, J = 1.0 Hz), 10.08 (s, 1H) ppm. EI-MS (70eV); m/z (%): 322 (20) [M^+], 190 (20) [M^+ - $C_{10}H_6S_2$]. $C_{16}H_{10}N_4S_2$ (322.4): calcd. C 59.60, H 3.13, N 17.38; found C 59.34, H 3.29, N 17.07. All other 1,2,4-triazines were characterized by the same analytical methods.

To prepare the pyridines **9-11** (Table 4) we used a 10 fold molar excess of bicyclo[2.2.1]hepta-2,5-diene (norbornadiene) as synthetic equivalent for acetylene and 1,2-dichlorobenzene as solvent. The structures of pyridines **9-11** are confirmed by the observed coupling constants for 2,6-disubstituted pyridines.

Table 4. Synthesis of 2,6-oligopyridines **9-11** according to Scheme 1.

Triazine	Oligopyridine		Reaction conditions	Yield [%]	M.P. [°C]
6a	**9a**		170°C, 6h	83	264-266
6b	**9b**		150°C, 6h	79	302-305
7a	**10a**		140°C, 6h	85	117-120
7b	**10b**		160°C, 14h	72	198-199
7c	**10c**		180°C, 6h	83	274-277
8a	**11a**		190°C, 9h	80	222-225
8b	**11b**		150°C, 12h	80	328-331

Typical procedure for the preparation of oligopyridines **9 - 11**: **6a** (200 mg, 409 μmol) and bicyclo[2.2.1]hepta-2,5-diene (754 mg, 8.18 mmol) were heated at 170°C under an inert atmosphere in 5 ml 1,2-dichlorobenzene for 6 hours. The reaction mixture was

cooled and the resulting precipitate was collected by suction filtration, washed with 5 ml diethyl ether and 20 ml petroleum ether 40/60. Recrystallization from dimethylsulfoxide yielded **9a** (157 mg, 323 µmol, 79%). Analytical data for **9a**: IR (KBr): $\tilde{\nu}$ = 3100, 3060, 1550, 1450, 1420, 1410,1300, 1270, 1250, 1210, 1190, 1140 cm^{-1}. ^1H NMR (400 MHz, DMF-d_7, 100°C): δ = 7.13 (dd, 2 H, J = 5.1 Hz, J = 3.6 Hz), 7.35 (d, 2 H, J = 3.8 Hz), 7.41 (dd, 2 H, J = 3.6 Hz, J = 1.1 Hz), 7.50 (dd, 2 H, J = 5.1 Hz, J = 1.1 Hz), 7.80 (d, 2 H, J = 3.9 Hz), 7.93 (dd, 2 H, J = 7.9 Hz, J = 1.0 Hz), 8.03 (dd, 2 H, J = 7.8 Hz, J = 7.7 Hz), 8.42 (dd, 2H, 7.7 Hz, 1.0 Hz) ppm. EI-MS (70eV); m/z (%): 484 (100) [M^+], 451 (6) [M^+ - SH), 439 (1), [M^+ - CSH), 242 (16) [M^{2+}]. $C_{26}H_{16}N_2S_4$ (484.7): calcd. C 64.43, H 3.33, N 5.78; found C 64.12, H 3.55, N 5.61. All other pyridines were characterized by the same analytical methods.

With our 'LEGO' System we provide an efficient and versatile method for the synthesis of oligopyridines, which are of great importance as polydentate ligands in metallosupramolecular chemistry [14,15]. As well as thiophene, other heterocycles may be inserted into the linear chains. Actual investigations have shown interesting fluorescence and pH sensitive properties both of the ligands **6-11** and their Ru^{II}-, Ag^{I}-, and Cu^{I} complexes. Further work using symmetrically substituted 1,2-diones in 1,2,4-triazine synthesis as well as conversions of 1,2,4-triazines with ethinyltributyltin via [4+2] cycloadditions to form stannylated pyridines [16], which are synthetically valuable intermediates, are in progress.

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