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Synthesis of Multitopic Bidentate Ligands Based on Alternating Pyridine and Pyridazine Rings

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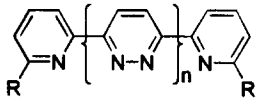
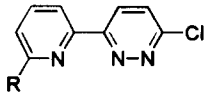
Abstract: A synthetic route based on Stille coupling between tributyltinpyridyl derivatives and chloropyridazines is used for the synthesis of ditopic bidentate ligands **8**, **9** and **10**. This methodology can be extended for the synthesis of a linear tetradentate ligand **11** with four pyridine and two pyridazine rings.

Polyheterocyclic molecules based on pyridine and pyridazine rings play a very important role as ligands in coordination and supramolecular chemistry. In fact, ligands **1** and **2** were used for constructing grid-like architectures through self-assembly processes with metal ions such as Cu(I) and Ag(I).[1-3] Type **1** ligands can be synthesized from tetrazines obtained by condensation of 2-cyanopyridines and hydrazine.[4] Type **2** ligands have been obtained from **3** by a homocoupling reaction catalyzed by Ni^0 complexes.[3] In general, both routes lead to symmetrical ring systems. Herein, we report a procedure for the synthesis of functionalized pyridine-pyridazine-pyridine derivatives, and related extended systems, which are potentially versatile ligands for coordination chemistry.



1: n=1; **2**: n=2



3

A convenient starting material for the synthesis of 2,5-substituted pyridines is the commercially available 2,5-dibromopyridine. This compound can be selectively lithiated in position 5 and after quenching with dimethylformamide it is transformed into the 2-bromo-5-pyridinecarboxaldehyde (Scheme 1). The protection of this group was accomplished by formation of the corresponding dioxolane; the use of Amberlyst-15 as acid catalyst gave the best results. Typical lithium exchange and quenching with Bu_3SnCl leads to the 2-(2-tributylstannyl-5-pyridyl-)-1,3-dioxolane, which can be used for Stille coupling reaction with compound **3**.

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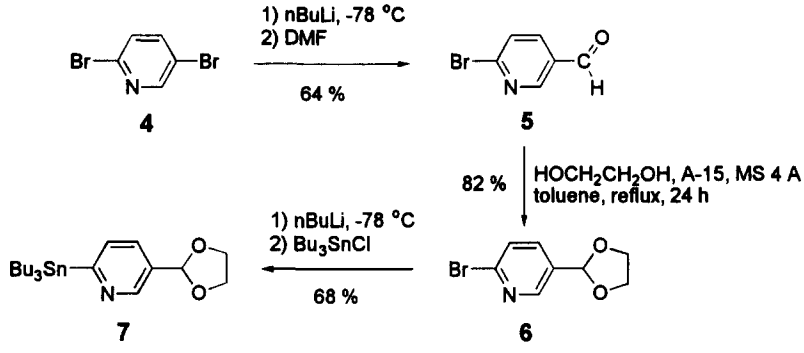
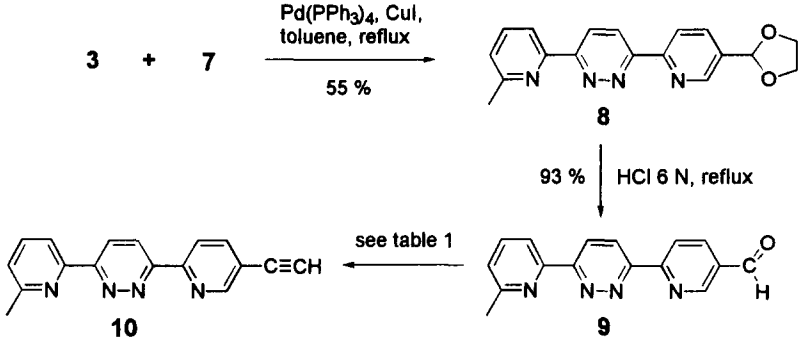


Scheme 1

The best conditions found for the coupling between compounds **3** and **7** are described in Scheme 2. By using an excess of **3** (1.8 equiv.) with respect to 7 and CuI (2.2 equiv.), as well as $Pd[P(C_6H_5)_3]_4$ (10 % mol) as catalyst, compound **8**[5] was obtained, after refluxing for 36 h, in moderate yield (55 %). The reaction mixture was treated with KCN, in order to destroy the complexes between **8** and copper ions. The deprotection of the aldehyde group was carried out under strong acid conditions in excellent yield (93 %).[6]

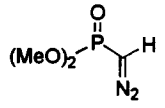
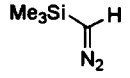
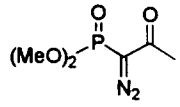


Scheme 2

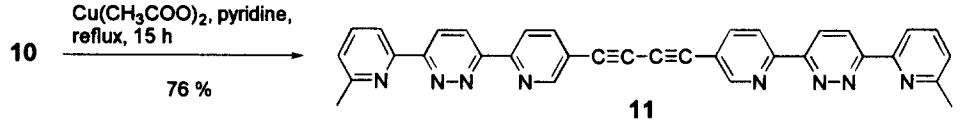
Although several procedures have been described for the transformation of aldehydes into acetylenes,[7] we found that in our case the one-pot procedure using different diazocompound reagents was the simplest in order to avoid a difficult work-up. However, the use of dimethyl (diazomethyl)phosphonate[8] and the commercially available trimethylsilyldiazomethane[9] led to poor yields (table 1). We suspected that the main reasons were the high insolubility of the aldehyde (making the reaction heterogeneous) and the strong basic conditions in the reaction medium. Therefore, we decided to use the dimethyl-(1-diazo-2-

oxopropyl)phosphonate,[10] which generates dimethyl (diazomethyl)phosphonate by methanolysis under mild conditions, with K_2CO_3 as base at O °C. Effectively, **10**[11] was obtained in good yield (73 %).

Table 1. Results obtained for the one pot transformation of **9** into **10** with several diazocompounds

Diazocompound	Conditions	Yield (%)
	^{t}BuOK, THF, -78 °C	20
	nBuLi, THF, -78 °C	15
	K_2CO_3, MeOH, 0 °C	73

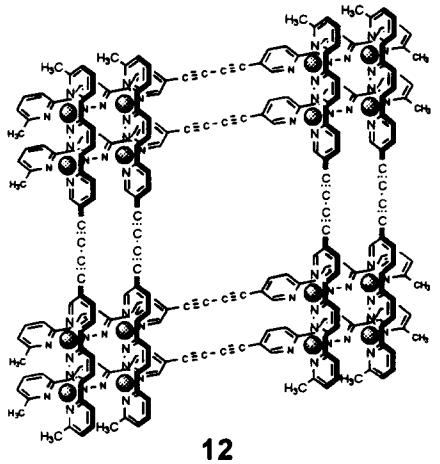
Finally, the ligand **11**[12] was synthesized by coupling of **10** under conditions similar to the Eglinton procedure[13] in 76 % yield, as shown below.



11

Ligand **11** is highly insoluble in organic solvents. In fact, it was purified by trituration and washing with several organic solvents.

Ligand **11** possesses two metal coordination subunits of the type known to form [2x2] grid-type complexes with metal ions of tetrahedral coordination geometry. It could thus yield in principle an area of sixteen ions arranged in a grid-of-grids type geometry consisting in a [2x2] grid of four [2x2] subunits as represented schematically by **12**.



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Acknowledgements:

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5. Data for 2-[2-[6-[2-(6-methylpyridyl)]-3-pyridazinyl]-5-pyridyl)]-1,3-dioxolane (**8**): ^{1}H NMR ($CDCl_3$), δ (ppm): 2.66 (s; 3 H), 4.13 (m; 1 H), 5.96 (s; 1 H), 7.26 (d; J= 7.5 Hz, 1 H), 7.78 (t; J= 7.8 Hz, 1 H), 8.00 (dd ; J= 8.2 Hz, 2.2 Hz, 1 H), 8.55 (d ; J= 7.8 Hz, 1 H), 8.69 (AB_q ; J= 8.9 Hz, Δν= 8.7 Hz, 2 H), 8.78 (d ; J= 8.4 Hz, 1 H), 8.82 (d ; J= 1.9 Hz, 1 H). ^{13}C NMR : 24.6, 65.5, 101.8, 118.7, 121.2, 124.3, 125.1, 134.7, 135.4, 137.3, 148.0, 152.7, 154.3, 157.7, 158.5. FAB : 321.1 (M+1, 100 %). Anal. calcd. for $C_{18}H_{16}N_4O_2$: C 67.49, H 5.03, N 17.49 ; found : C 67.28, H 4.90, N 17.63.
6. Data for 2-[6-[2-(6-methylpyridyl)]-3-pyridazinyl]-5-pyridinecarboxaldehyde] (**9**): ^{1}H-NMR ($CDCl_3$), δ (ppm): 2.67 (s ; 3 H), 7.28 (d ; J= 7.9 Hz, 1 H), 7.80 (t ; J= 7.7 Hz, 1 H), 8.37 (d ; J= 8.2 Hz, 1 H), 8.57 (d ; J= 7.8 Hz, 1 H), 8.75 (AB_q ; J= 9.0 Hz, Δν= 5.4 Hz, 2 H), 8.96 (d ; J= 8.2 Hz, 1 H), 9.18 (s ; 1 H), 10.21 (s ; 1 H). ^{13}C NMR : 24.6, 118.9, 121.8, 124.6, 125.3, 125.8, 137.3, 137.4, 151.5, 158.5, 190.4. Anal. calcd. for $C_{18}H_{16}N_4O_2$: C 69.55, H 4.38, N 20.28 ; found : C 69.56, H 4.55, N 20.30.
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10. (a) Ohira, S. *Synth. Commun.*, **1989**, *19*, 561. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett.*, **1996**, 521.
11. Data for 2-[6-[2-(6-methylpyridyl)]-3-pyridazinyl]-5-pyridylethyne] (**10**): ^{1}H-NMR ($CDCl_3$), δ (ppm): 2.66 (s ; 3 H), 3.34 (s ; 1 H), 7.27 (d ; J= 7.8 Hz, 1 H), 7.79 (t ; J= 7.8 Hz, 1 H), 7.98 (dd ; J= 8.3 Hz, 2.1 Hz, 1 H), 8.55 (d ; J= 7.8 Hz, 1 H), 8.69 (AB_q ; J= 8.9 Hz, Δν= 13.6 Hz, 2 H), 8.74 (dd ; J= 8.3 Hz, 0.8 Hz, 1 H), 8.82 (dd ; J= 2.1 Hz, 0.7 Hz, 1 H). ^{13}C NMR : 24.6, 82.0, 118.8, 120.8, 124.4, 125.2, 137.3, 140.2, 152.4. Anal. calcd. for $C_{17}H_{12}N_4$: C 74.98, H 4.44, N 20.57 ; found : C 74.72, H 4.40, N 20.50.
12. Data for 1,4-bis[2-[6-[2-(6-methylpyridyl)]-3-pyridazinyl]-5-pyridyl]-1,3-butadiyne (**11**): ^{1}H-NMR (CD_3CN/ CF_3COOD), δ (ppm): 2.97 (s; 6 H), 8.04 (d; J= 8.0 Hz, 2 H), 8.54 (d; J= 7.8 Hz, 2 H), 8.64 (t; J= 7.8 Hz, 2 H), 8.75 (AB_q; J= 9.0 Hz, Δν= 25.1 Hz, 4 H), 8.80 (d; J= 8.4 Hz, 2 H), 8.89 (dd; J= 8.7 Hz, 1.4 Hz, 2 H), 9.2 (d; J= 1.3 Hz, 2 H). ^{13}C NMR : 20.9, 78.8, 125.2, 125.6, 127.8, 129.8, 130.0, 132.1, 146.2, 148.5, 149.6, 152.4, 153.5. MS *m/z*+ (FAB): 543.1 (M+1, 100 %). HRMS calcd. for $C_{34}H_{23}N_8$ (MH^+): 543.2046; found: 543.2059.
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