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LETTERS

A Convenient Synthetic Route to Polypyridine-esters by Palladium-promoted Carboalkoxylation

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Abstract: Pyridine and oligopyridines bearing halide or triflate groups react smoothly with CO (1 atm) and *n*-butanol in the presence of a tertiary amine and a catalytic amount of bis(triphenylphosphine)palladium dichloride to afford the corresponding esters. When ethanol and a disubstituted substrate are used under milder conditions, selective mono-carboalkoxylation occurs. Amidation is effected using a primary amine as nucleophile. © 1998 Elsevier Science Ltd. All rights reserved.

Pyridine, oligopyridines and their derivatives play a central role in coordination[1] and supramolecular chemistry.[2,3] Functionalization of bipyridine (bpy), phenanthroline (phen), terpyridine (terpy), or naphtyridine (napht) usually demands many tedious steps. A smart way to insert useful functions into these scaffolds is to first graft carbaldehyde functions which open the way to bis-imino multitopic ligands and bis-nitronyl-nitroxide pincer molecules. These are versatile compounds for the selective preparation of double stranded Cu(I) helicates[4] and discrete complexes exhibiting ferromagnetic interactions.[5]

Symmetrical dicarbaldehydes are normally obtained by formylation[6] of the metallated compounds, by SeO_2[7] or tertiobutyliodine[8] oxidation of the methyl substituted derivatives or more recently, by way of enamine oxidation.[9] These methods suffer from serious drawbacks associated with the reactivity of the metallated species, the difficulty to prepare selenium-free derivatives, and [to some extent] the cost of the reagents. The synthesis of such mono- or bis-carbaldehyde derivatives continues to be a topical issue for the chemistry community. In an ongoing project aimed at illustrating the potentiality of palladium-promoted formation of carbon-carbon bonds, we report here a useful route which allows one to obtain oligopyridines bearing ester groups. This represents a new entry to the preparation of unknown carbaldehyde derivatives, a class of compounds which continues to gain interest in view of their appealing chemical versatility. Examples of palladium-catalyzed aryl halide carboalkoxylation have previously been reported.[10,11]

$$\text{Oligopy-X} + CO + {}^{n}BuOH + {}^{n}Bu_3N \xrightarrow{\text{"Pd"}} \text{Oligopy-COO}^{n}Bu + {}^{n}Bu_3NH^{+}X^{-} \quad (1)$$
$$X = Cl, Br \text{ or } OTf$$

We now report that $[Pd(PPh_3)_2Cl_2]$ efficiently catalyzes reaction of carbon monoxide (1 atm), at 120 ° C, with mono- or di-halogenated oligopyridines and with terpyridine triflate, in the presence of *n*-butanol as nucleophile and a tertiary amine as base (eq. 1). Ligands were typically prepared on a 0.5 g scale by reaction of

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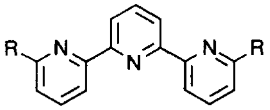
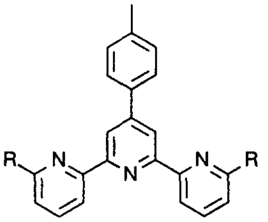
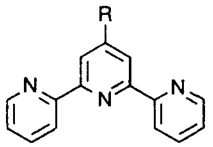
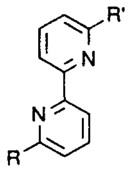
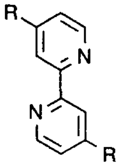
mono- or di-halide substituted starting compounds[12] in *n*-butanol (10 mL) containing tri-*n*-butylamine (2 mL), and under continuous CO flow, using $[Pd(PPh_3)_2Cl_2]$ (2 mol%). After heating for 20 hours, excess amine was neutralized and the crude product was chromatographed on triethylamine-deactivated silica with *n*-hexane/CH_2Cl_2 as eluent. The desired products were obtained in satisfactory yields and were characterized by ^1H, ^{13}C {^1H}-NMR, mass, UV-Vis, IR spectroscopies and elemental analysis. All products were consistent with the proposed structures (see Table for selective data). The generality of this synthetic protocol is illustrated in the Chart, where a variety of mono- and di-substituted oligopyridines were successfully prepared. The same reactivity was obtained with bromide, chloride or triflate functionalized derivatives.

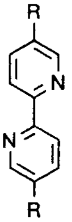

1a : R = Br
1b : R = $CO_2C_4H_9$
1c : R = CH_2OH
1d : R = CHO

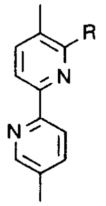

2a : R = Br
2b : R = $CO_2C_4H_9$

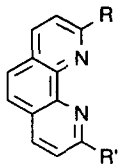

3a : R = OTf
3b : R = $CO_2C_4H_9$

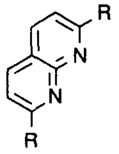

4a : R = R' = Br
4b : R = R' = $CO_2C_4H_9$
4c : R = Br ; R' = $CO_2C_2H_5$
4d : R = R' = $CONH(C_3H_7)$

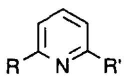

5a : R = Br
5b : R = $CO_2C_4H_9$


6a : R = Br
6b : R = $CO_2C_4H_9$

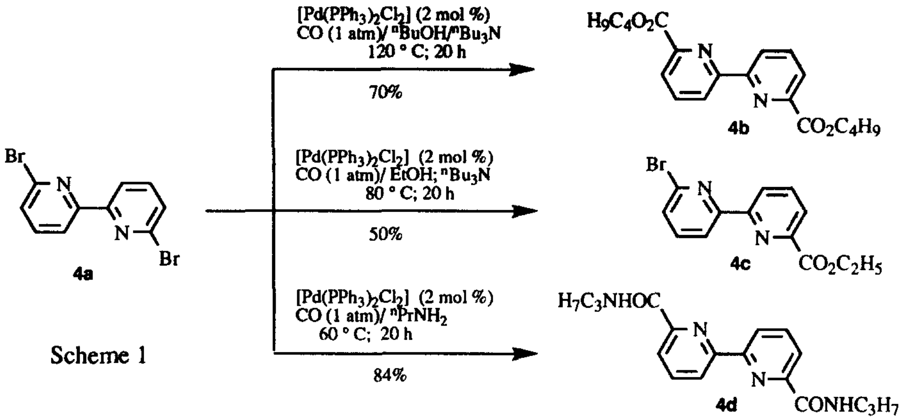

7a : R = Br
7b : R = $CO_2C_4H_9$


8a : R = Br ; R' = Cl
8b : R = R' = Cl
8c : R = R' = $CO_2C_4H_9$


9a : R = Cl
9b : R = $CO_2C_4H_9$


10a : R = R' = Br
10b : R = R' = $CO_2C_4H_9$
10c : R = Br ; R' = $CO_2C_2H_5$

It is noteworthy that when reaction was carried out at 80 °C in ethanol with 2,6-dibromopyridine or 6,6'-dibromo-2,2'-bipyridine as substrate mono-carboalkoxylation occured (Scheme 1). In this way it becomes possible to prepare ligands bearing two different functions. Such derivatives are of primary importance for the construction of supramolecular scaffoldings such as helicates, knots, cages, rings, grids, rotaxanes and more specifically polycatenated multi-dimensional networks.[2,13]



Scheme 1

When a primary amine, such as *n*-propylamine, is used as nucleophile in place of *n*-butanol, straightforward amidation occurs giving the amide compound in excellent yield, as outlined in eq. 2.

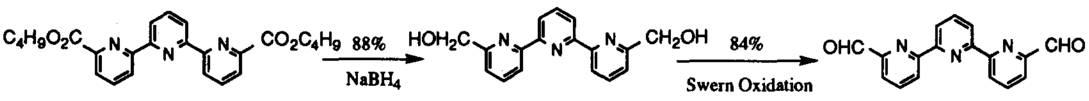
$$\text{Oligopy-X} + \text{CO} + 2\,{}^{n}\text{PrNH}_2 \xrightarrow{\text{"Pd"}} \text{Oligopy-CONH}{}^{n}\text{Pr} + {}^{n}\text{PrNH}_3{}^{+}\text{X}^{-} \quad (2)$$

Table. Selected data for novel compounds prepared during this program

Product	Isolated Yield (%)	IR ($\nu_{C=O}$, cm^{-1}) [a)]	UV-Vis [b)] λ nm (ε, M^{-1}cm^{-1})	m.p. (°C)	^{13}C-NMR [c)] (C=O) ppm	Mass spectrum [d)]
1b	50	1738	282 (26 000)	121/2	165.3	433
1c	88	-	284 (28 300)	142/3	-	293
1d	84	1721	285 (17 200)	230 (dec.)	-	289
2b	52	1715	276 (30 900)	90/1	165.4	523
3b	76	1716	271 (21 400)	68/9	165.5	333
4b	70	1731	278 (18 200)	92/3	165.1	356
4c	50	1739	286 (23 800)	106/7	165.0	306/308
4d	84	1663	283 (16 000)	260/1	-	326
5b[14]	50	1720	294 (13 600)	108/9	165.2	356
6b	90	1713	294 (18 200)	131/2	165.1	356
7b	60	1725	281 (30 300)	33/4	166.9	284
8c	60	1609	279 (40 800)	oil	162.6	380
9b	40	1610	298 (13 600)	33/4	165.2	330
10b	80	1741	264 (3 200)	63/4	164.6	279
10c	41	1723	271 (4 600)	40/1	163.8	229/231

a) $\nu_{C=O}$ stretching vibration measured in KBr pellets; b) π-π* absorption band measured in CH$_2$Cl$_2$; c) Chemical shift for C=O are reported relative to the solvent CDCl$_3$ (77.0 ppm); d) EI-MS, *m/e* [M].

Formyl substituted oligopyridines are extremely important building blocks and can be obtained by reduction of the esters to the alcohols with NaBH$_4$, followed by subsequent Swern oxidation to the aldehydes. This is illustrated in Scheme 2 for the synthesis of the hitherto unknown 6,6"-dicarbaldehyde-2,2':6',6"-terpyridine which is a promising synthon for the preparation of multitopic ligands.[15]



1b Scheme 2 **1c** **1d**

In summary, we have developed a flexible approach to the synthesis of oligopyridine esters and amides through a protocol that facilitates large-scale preparation. The relatively mild reaction conditions and the impressive overall yields make this sequence a novel and convenient route to this class of molecules. It also opens-up the preparation of ester derivatives from which new aldehydes such as **1d** could be obtained either by direct reduction or by a sequence of reactions such as the one presented in Scheme 2. Further elaboration of this strategy toward the synthesis of derivatives bearing multiple functionalities and segmented modules is currently under way in our laboratory.

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