

## THE PREPARATION OF PYRIDINECARBOXYLATES FROM CHLOROPYRIDINES BY THE PALLADIUM-CATALYZED ALKOXYCARBONYLATION

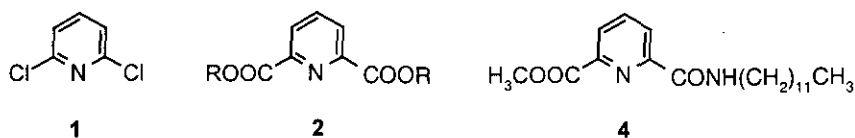
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**Abstract** - The preparation of pyridinecarboxylates and pyridinedicarboxylates by alkoxy carbonylation of chloropyridines with carbon monoxide in the presence of palladium acetate and 1,1'-bis(diphenylphosphino)ferrocene is described. The process uses readily available starting materials and affords pyridinecarboxylates in good to very good yields.

### INTRODUCTION

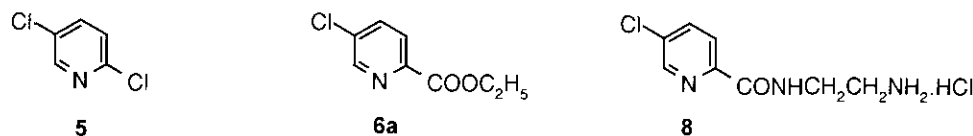
Pyridinecarboxylic acids and their derivatives are highly useful in many organic synthetic applications and represent an important class of agricultural and pharmaceutical intermediates. For instance, pyridine-2,6-dicarboxylates (**2**), accessible by alkoxy carbonylation of 2,6-dichloropyridine (**1**), have been used as intermediates for the preparation of phospholipase inhibitors <sup>1</sup> of structure type (**4**) (Figure 1) or for the preparation of 2,6-bis(hydroxymethyl)pyridine, another common pharmaceutical intermediate.<sup>2</sup> There is also a growing number of applications for pyridine-2,6-dicarboxylates, as building block for the preparation of macrocycles <sup>3</sup> with complexation properties.



**Figure 1.** Pyridinecarboxylic derivatives from 2,6-dichloropyridine

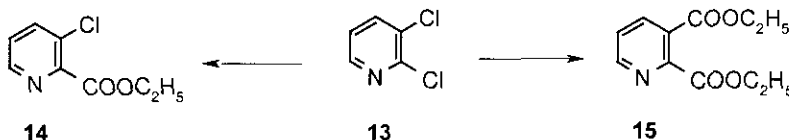
A very smart application of the carbonylation reaction is the extremely short route <sup>4</sup> to the pharmaceutical *lazabemide* (**8**) (Figure 2), an anti-Parkinson drug developed by Hoffmann-La Roche.<sup>5</sup> The original synthesis involved eight steps, starting from 2-methyl-5-ethylpyridine, and afforded *lazabemide* in 8%

overall yield. In their new process, *lazebamide hydrochloride* could be obtained in 65% yield in one step by amidocarbonylation of 2,5-dichloropyridine (**5**). This led to a drastic reduction in both costs and environmental impact of the production process.



**Figure 2.** Pyridinecarboxylic derivatives from 2,5-dichloropyridine

In continuation of our programme directed to the development of synthetic methods in heterocyclic chemistry,<sup>6</sup> we report here the successful use of the carbonylation reaction concept for the synthesis of pyridinecarboxylates. For example, the monoester (**6a**), a potential precursor of **8**, was prepared in 86% yield using the reaction conditions we previously developed.<sup>7</sup> Another interesting aspect of the carbonylation reaction is the possibility to develop selective conditions for the mono- and biscarbonylations of dichloropyridines. As shown below (Scheme 1), both the monoester (**14**) and the diester (**15**) could be selectively prepared, in high yields, from 2,3-dichloropyridine (**13**), using well defined reaction conditions.

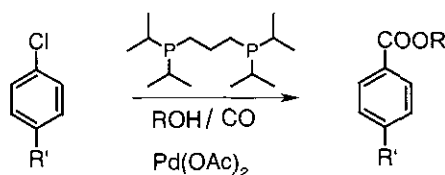


**Scheme 1.** Selectivity in the alkoxy carbonylation reaction

## THE CARBONYLATION REACTION CONCEPT

Palladium mediated coupling reactions have become important tools in synthetic organic chemistry.<sup>8</sup> The functionalization of aryl molecules with carbon monoxide to yield carbonyl compounds<sup>9</sup> represents a rapidly growing area of investigation. Among the carboxylic acid derivatives accessible by this chemistry, esters are certainly most reported in the literature<sup>10-14, 16-19</sup>. Primarily this is due to experimental convenience, the alcohol can be often used as solvent and the ester formed is sufficiently stable for isolation and purification purposes. In general, these transformations are successful with aryl bromides or iodides. The aryl chlorides are much less reactive, though encouraging results have been recently reported. For instance, Milstein<sup>10</sup> and coworkers recently obtained very good results (70 - 90% yield) for

the carbonylation of *p*-substituted chlorobenzenes with active palladium complexes (Scheme 2). As expected, electron withdrawing groups accelerated the reaction and electron donating groups inhibited it.



**Scheme 2.** Alkoxy carbonylation of chloroaromatic rings

This concept has been seldom applied to heteroaryl molecules. However, the carbonylation of heterocyclic halides could provide an attractive method for the synthesis of esters and amides of heterocyclic carboxylic acids derived from pyridine,<sup>11</sup> pyrazine<sup>12</sup> or quinoline.<sup>13</sup> However, most procedures reported in recent years used expensive iodo- or bromoheterocyclic compounds<sup>14,15</sup> as starting materials. Indeed, only a few examples of alkoxy carbonylation of chloropyridines can be found in the literature and the yields are usually fairly low and the reaction conditions relatively harsh (Table 1).

**Table 1.** Comparison of a selection of alkoxy carbonylation reactions of chloropyridines reported in the literature

Entry	Chloropyridine	Ester	Solvent Base	Reaction conditions	Ligand <sup>a</sup>	Catalyst <sup>b</sup>	Yield [%]	Author
1			Butanol/Toluene Na <sub>2</sub> CO <sub>3</sub>	200°C / 3 h 50 atm CO	dppb	PdCl <sub>2</sub>	54	Kudo <sup>16</sup>
2			Ethanol NEt <sub>3</sub>	120°C / 48 h 66 atm CO	-	(Ph <sub>3</sub> P) <sub>2</sub> PdCl 2	51	Zhang <sup>17</sup>
3			Methanol NEt <sub>3</sub>	150°C / 16 h 40 atm CO	Ph <sub>3</sub> P	Pd(dba) <sub>2</sub>	79	Takeuchi <sup>18</sup>
4			Methanol NEt <sub>3</sub>	150°C / 16 h 40 atm CO	Ph <sub>3</sub> P	Pd(dba) <sub>2</sub>	No Reaction	Takeuchi <sup>18</sup>
5			Butanol/Toluene Na <sub>2</sub> CO <sub>3</sub>	200°C / 3 h 50 atm CO	dppb	PdCl <sub>2</sub>	44	Kudo <sup>16</sup>
6			Ethanol/Benzene Na <sub>2</sub> CO <sub>3</sub>	250°C / 3 h 50 atm CO	dppb	PdCl <sub>2</sub>	~20	Suto <sup>19</sup>
7			Ethanol/Benzene Na <sub>2</sub> CO <sub>3</sub>	250°C / 3 h 50 atm CO	dppb	PdCl <sub>2</sub>	<5	Suto <sup>19</sup>

<sup>a</sup> Ligands: 1,4-bis(diphenylphosphino)butane (dppb); triphenylphosphine (Ph<sub>3</sub>P).

<sup>b</sup> Catalyst: palladium bis(dibenzylideneacetone) (Pd(dba)<sub>2</sub>).

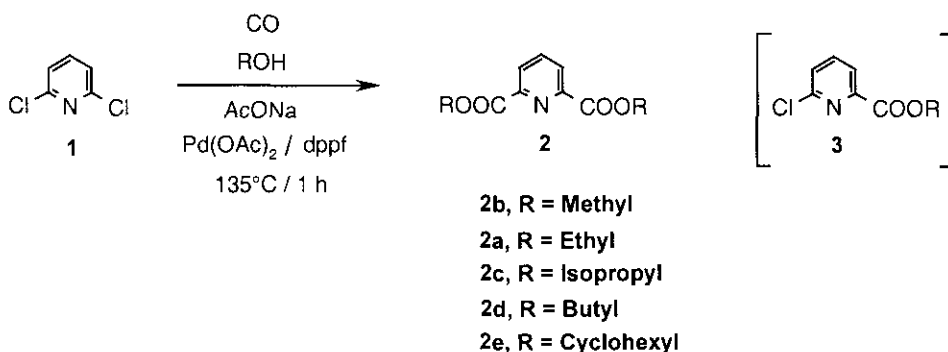
## RESULTS AND DISCUSSIONS

### 1.- Bisalkoxycarbonylation of 2,6-dichloropyridine

The alkoxy carbonylation of 2,6-dichloropyridine has already been reported by Zhang *et al.*<sup>17</sup> The reaction was carried out in a 5:2 mixture of ethanol/triethylamine under 65 atm of carbon monoxide, using dichlorobis(triphenylphosphine)nickel as catalyst. After 48 h at 160°C, the GC analysis of the reaction mixture indicated a ratio of 5.9:5.3:10.4 for the 2,6-dichloropyridine (1), the monoester (3a) and the diester (2a), respectively.

We have found the reaction conditions to form exclusively the diester (2a). Indeed, analysis of the reaction mixture (GC, area%) indicated more than 99% of the diester (2a) which was isolated by flash chromatography in 88% yield (Table 2). The reaction (Scheme 3) was carried out in the presence of palladium acetate, 1,1'-bis(diphenylphosphino)ferrocene (dppf) and sodium acetate as acid acceptor in ethanol as reagent and solvent at 135°C under 15 atm of carbon monoxide for 1 h.

A series of other esters were also prepared under the same conditions. In spite of the fact that practically only the dicarboxylates (2) were formed (monoesters (3) could hardly be detected), yields were somehow slightly lower: the dimethyl ester (2b) (78% yield), the diisopropyl ester (2c) (48% yield), the dibutyl ester (2d) (85% yield) and the dicyclohexyl ester (2e) (51% yield).



#### Scheme 3. Alkoxy carbonylation of 2,6-dichloropyridine

A detailed study of the influence of the reaction parameters for the alkoxy carbonylation of 5-substituted 2,3-chloropyridines has been discussed in our previous article.<sup>7a</sup> The optimal reaction conditions for the alkoxy carbonylation of 2,3-dichloropyridine were very close to those which were developed. Indeed, the

catalyst/ligand couple palladium acetate and 1,1'-bis(diphenylphosphino)ferrocene (dppf) (Entry 5; Table 2) proved to be the best. The use of 1,4-bis(diphenylphosphino)butane (dppb) required more forcing reaction conditions (higher reaction temperature and longer reaction time) to get complete conversion (Entries 10, 11). This led to a lower isolated yield because of stability problems. With tetrahydrofuran as a solvent, the reactivity dramatically dropped (Entries 8, 9), a good conversion could be obtained by increasing the temperature (Entry 9) but, as already shown, this was detrimental to the yield (25%). The nature of the base also played an important role. The use of sodium acetate gave very good results, the higher yields being obtained with 4 equiv. of the base (Entry 5). The reaction could be successfully reproduced (Entry 6). The use of a stronger base such as sodium carbonate (Entry 7) drastically reduced the yield of isolated product.

**Table 2. Comparison of reaction conditions for the carbonylation of 2,6-dichloropyridine**

Entry	Solvent	Base [equiv.]	Reaction conditions <sup>a</sup>	Ligand <sup>b</sup>	Catalyst	1* [%]	3a* [%]	2a* [%]	2a, Yield [%] <sup>c</sup>
1	C <sub>2</sub> H <sub>5</sub> OH	AcONa [2]	120°C/1 h	dppf	Pd(OAc) <sub>2</sub>	<1	<1	>99	74
2	C <sub>2</sub> H <sub>5</sub> OH	AcONa [2]	135°C/1 h	dppf	Pd(OAc) <sub>2</sub>	<1	<1	>99	79
3	C <sub>2</sub> H <sub>5</sub> OH	AcONa [2]	150°C/1 h	dppf	Pd(OAc) <sub>2</sub>	<1	<1	>99	71
4	C <sub>2</sub> H <sub>5</sub> OH	AcONa [3]	175°C/2 h	dppf	(Ph <sub>3</sub> P) <sub>2</sub> PdCl <sub>2</sub>	<1	<1	>99	69
5	C <sub>2</sub> H <sub>5</sub> OH	AcONa [4]	135°C/1 h	dppf	Pd(OAc) <sub>2</sub>	<1	<1	>99	88
6	C <sub>2</sub> H <sub>5</sub> OH	AcONa [4]	135°C/1 h	dppf	Pd(OAc) <sub>2</sub>	<1	<1	>99	87
7	C <sub>2</sub> H <sub>5</sub> OH	Na <sub>2</sub> CO <sub>3</sub> [2]	135°C/1 h	dppf	Pd(OAc) <sub>2</sub>	<1	<1	>99	45
8	THF/C <sub>2</sub> H <sub>5</sub> OH <sup>d</sup>	AcONa [4]	135°C/1 h	dppf	Pd(OAc) <sub>2</sub>	97	3	<1	-
9	THF/C <sub>2</sub> H <sub>5</sub> OH <sup>d</sup>	AcONa [4]	150°C/3 h	dppf	Pd(OAc) <sub>2</sub>	<1	<1	>99	25
10	C <sub>2</sub> H <sub>5</sub> OH	AcONa [4]	135°C/1 h	dppb	Pd(OAc) <sub>2</sub>	85	15	5	-
11	C <sub>2</sub> H <sub>5</sub> OH	AcONa [4]	150°C/3 h	dppb	Pd(OAc) <sub>2</sub>	<1	<1	>99	74

The values reported in Table 2 correspond to GC (crude reaction mixture) ratio (area %); <1% means: no GC signal or GC signal not integrated.

<sup>a</sup> Reaction conditions: The temperature given is the external temperature (internal temperature is 15-20°C less); the reactions were carried out under 15 atm of CO.

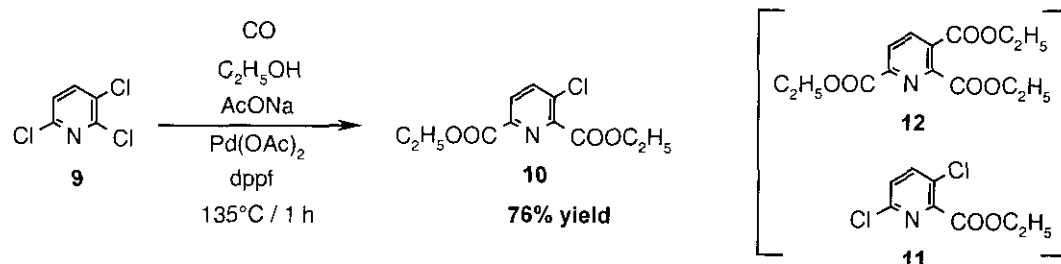
<sup>b</sup> Ligands: 1,4-bis(diphenylphosphino)butane (dppb); 1,1'-bis(diphenylphosphino)ferrocene (dppf).

<sup>c</sup> Isolated yield after flash chromatography.

<sup>d</sup> The alcohol was used only as reagent (3 equiv.).

## 2.- Alkoxy-carbonylation of 2,3,6-trichloropyridine

Using the same approach, we wanted to prepare selectively the diester (**10**) from the trichloropyridine (**9**). The alkoxy-carbonylation of 2,3,6-trichloropyridine (**9**) was carried out for 1 h at 135°C and 15 atm of carbon monoxide, in the presence of palladium acetate and 1,1'-bis(diphenylphosphino)ferrocene (dppf) using ethanol as reagent and solvent and sodium acetate as acid acceptor (Scheme 4).



**Scheme 4.** Alkoxy-carbonylation of 2,3,6-trichloropyridine

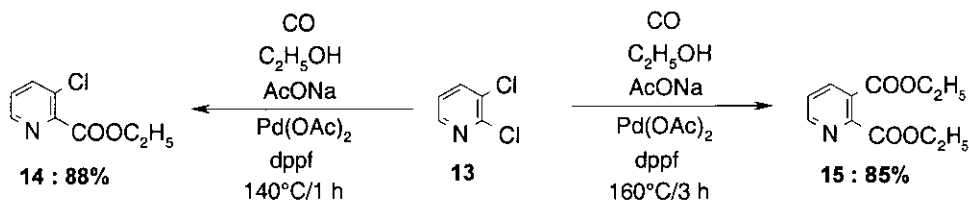
Under the reaction conditions mentioned above, the diester (**10**), was predominantly formed. Analysis of the reaction mixture (GC, area%) showed 87% of the diester (**10**), 5% for the monoester (**11**) and 8% for the triester (**12**). The desired diester (**10**) was isolated in 76% yield by flash chromatography.

## 3.- Alkoxy-carbonylation of 2,3-dichloropyridine

The alkoxy-carbonylation of 2,3-dichloropyridine (**13**) was reported by Suto<sup>19</sup> in only 2-3% yield to **15**. The reaction was carried out for 3 h at 250°C and 50 atm of carbon monoxide in the presence of palladium dichloride and diphenylphosphinobutane using benzene as solvent and ethanol as reagent and with sodium carbonate as acid acceptor.

We were able to control the selectivity of the reaction only by controlling the temperature and the reaction time. The monoester (**14**) was selectively formed at 140°C (1 h) with a ratio >95% (GC) and was isolated by flash chromatography in 88% yield. The diester (**15**) was efficiently produced at 160°C (3 h) (>95%, GC) and was isolated by flash chromatography in 85% yield.

In both cases (Scheme 5), the reaction was carried out in ethanol under 15 atm of carbon monoxide, in the presence of palladium acetate and 1,1'-bis(diphenylphosphino)ferrocene (dppf) using sodium acetate as a base.



#### Scheme 5. Alkoxy carbonylation of 2,3-dichloropyridine

At temperatures lower than 140°C, the conversion to the monoester (**14**) was not complete. At temperatures between 140 and 160°C, a mixture of monoester (**14**) and diester (**15**) was obtained.

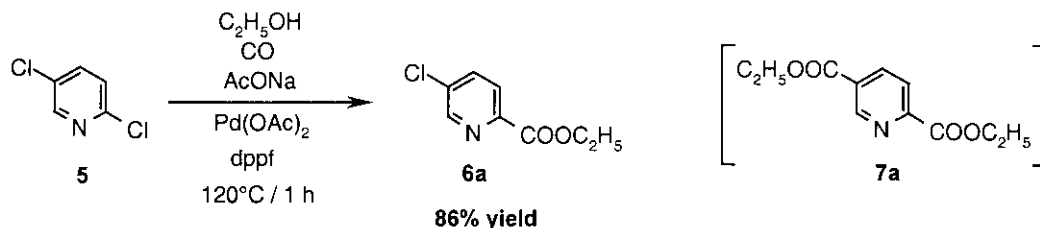
#### 4.- Alkoxy carbonylation of 2,5-dichloropyridine

In an alkoxy carbonylation described by Hoffmann-La Roche,<sup>4</sup> the methyl 5-chloropyridine-2-carboxylate was obtained in 49% yield, as crude material after extraction. Their reaction was carried out for 24 h at 110°C and 10 atm of carbon monoxide, in the presence of bis(triphenylphosphine)palladium dichloride in methanol/triethylamine.

A similar selective alkoxy carbonylation has been recently published by Pfizer,<sup>14</sup> starting from 2,5-dibromopyridine. The ethyl 5-bromopyridine-2-carboxylate was obtained in 65% yield. The reaction was carried out for 6 h at 50°C and 30 atm of carbon monoxide, in the presence of palladium acetate (3 mol%) and 1,1'-bis(diphenylphosphino)ferrocene (dppf, 6 mol%) using a 3:3:1 ethanol/DMF/triethylamine mixture.

When we carried out the alkoxy carbonylation of 2,5-dichloropyridine (**5**), we rapidly obtained with a good selectivity the monoester (**6a**) (Scheme 6) only by controlling the temperature and the reaction time. Indeed, after 1 h at 120°C, the monoester (**6a**) was the only product formed and was isolated by flash chromatography in 86% yield. The diester (**7a**) was present only at higher temperature (Table 3).

The reaction was carried out in ethanol with 15 atm of carbon monoxide, in the presence of palladium acetate and 1,1'-bis(diphenylphosphino)ferrocene (dppf) using sodium acetate as a base.



**Scheme 6.** Alkoxy-carbonylation of 2,5-dichloropyridine

**Table 3.** Effect of temperature on the carbonylation reaction

Entry	Reaction conditions <sup>a</sup>	Base [equiv.]	5* [%]	6a* [%]	7a* [%]	6a, Yield <sup>b</sup> [%]
1	110°C / 1 h	AcONa [4]	25	75	<1	65
2	110°C / 4 h	AcONa [4]	-	95	5	85
3	120°C / 1 h	AcONa [2]	-	97	3	77
4	120°C / 1 h	AcONa [4]	-	95	5	86
5	135°C / 1 h	AcONa [4]	-	85	15	77

\* The values reported in table 3 correspond to GC (crude reaction mixture) ratio (area %); <1% means: no GC signal or GC signal not integrated.

<sup>a</sup> Reaction conditions : 3 mol% of ligand (dppf) and 0.2 mol% of catalyst (palladium acetate); ethanol; 15 atm CO.

The temperature given is the bath temperature (internal temperature is 15 - 20°C less).

<sup>b</sup> Isolated yield after flash chromatography.

## EXPERIMENTAL

Reagents and solvents were reagent grade and used as received. Melting points were determined on a Büchi 535 apparatus and have not been corrected. <sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) spectra were recorded on a VARIAN spectrometer. Chemical shifts are reported as parts per million. Tetramethylsilane was used as internal standard. Coupling constants *J* are given in Hertz.



## 1.- Alkoxy carbonylation of 2,6-dichloropyridine

### Diethyl pyridine-2,6-dicarboxylate (2a)<sup>17</sup>

The reaction was carried out in a 100 mL stainless steel autoclave equipped with a magnetic stirring bar. The reagents were charged in a teflon liner in the following order : ethanol (30 mL), sodium acetate (3.28 g, 40 mmol), 2,6-dichloropyridine (1.48 g, 10 mmol), 1,1'-bis(diphenylphosphino)ferrocene (166 mg, 0.3 mmol [3%mol]) and palladium acetate (4.3 mg, 0.02 mmol [0.2%mol]). The air in the autoclave was replaced with carbon monoxide (this air/carbon monoxide exchange was repeated two more times) and the pressure adjusted to 15 bar. The reaction mixture was then heated to 135°C (bath temperature) and the reaction was carried out thereon with stirring. After 1 h, the reaction mixture was cooled to rt and concentrated under vacuum. The products were isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:1) giving 1.96 g (88% yield) of white powder, mp 41.5 - 42.8°C (lit.,<sup>21</sup> mp 41 - 42°C). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.29 (2 H, d, *J* = 7.9); 7.99 (1 H, t, *J* = 7.9); 4.50 (4 H, q, *J* = 7.1); 1.45 (6 H, t, *J* = 7.1). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 164.7 (C [C=O]); 148.8 (C); 138.2 (=CH); 127.8 (=CH); 62.3 (CH<sub>2</sub>); 14.2 (CH<sub>3</sub>). GC/MS (*m/z*) : 224; 223 (M<sup>+</sup>); 208; 179; 151; 123; 105.

### Ethyl 6-chloropyridine-2-carboxylate (3a)<sup>17</sup>

Compound **3a** can be found, under certain reaction conditions as by-product of the alkoxy carbonylation of 2,6-dichloropyridine in ethanol. It was isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:1) as colorless oil.<sup>20</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.05 (1 H, dd, *J* = 7.8, 1.1); 7.82 (1 H, t, *J* = 7.8); 7.52 (1 H, dd, *J* = 7.8, 1.1); 4.48 (2 H, q, *J* = 7.1); 1.42 (3 H, t, *J* = 7.1). GC/MS (*m/z*) : 185 (M<sup>+</sup>); 141; 113; 76. HRMS (EI) (*m/z*) : 185.0245 (185.0244 calc for C<sub>8</sub>H<sub>8</sub>NO<sub>2</sub>Cl).

### Dimethyl pyridine-2,6-dicarboxylate (2b)

Same procedure as for diethyl pyridine-2,6-dicarboxylate (**2a**).

T(135°C; bath); t(1 h). Yield 78%; white powder, mp 120.8 - 122.5°C (lit.,<sup>22</sup> mp 121 - 124°C). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.31 (2 H, d, *J* = 7.9); 8.02 (1 H, t, *J* = 7.9); 4.02 (6 H, s). GC/MS (*m/z*) : 195 (M<sup>+</sup>); 165; 137; 105.

### Diisopropyl pyridine-2,6-dicarboxylate (2c)

Same procedure as for diethyl pyridine-2,6-dicarboxylate (**2a**).

T(135°C; bath); t(1 h). Yield 48%; white powder, mp 59.4 - 59.6°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.24 (2 H, d, *J* = 7.9); 7.97 (1 H, t, *J* = 7.9); 5.32 (2 H, hept, *J* = 6.3); 1.43 (12 H, d, *J* = 6.3). GC/MS (*m/z*): 251 (M<sup>+</sup>); 236; 210; 192; 165; 123; 94; 77. HRMS (EI) (*m/z*): 251.1152 (251.1158 calc for C<sub>13</sub>H<sub>17</sub>NO<sub>4</sub>).

### Dibutyl pyridine-2,6-dicarboxylate (2d)

Same procedure as for diethyl pyridine-2,6-dicarboxylate (2a).

T(135°C; bath); t(1 h). Yield 85%; white powder, mp 65.5 - 65.9°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.28 (2 H, d, *J* = 7.9); 7.98 (1 H, t, *J* = 7.9); 4.42 (4 H, t, *J* = 7.1); 1.82 (4 H, pent, *J* = 7.1); 1.47 (4 H, hex, *J* = 7.1); 0.98 (6 H, t, *J* = 7.1). GC/MS (*m/z*): 280; 279 (M<sup>+</sup>); 236; 224; 206; 179; 150; 123; 105; 78. HRMS (EI) (*m/z*): 279.1458 (279.1471 calc for C<sub>15</sub>H<sub>21</sub>NO<sub>4</sub>).

### Dicyclohexyl pyridine-2,6-dicarboxylate (2e)

Same procedure as for diethyl pyridine-2,6-dicarboxylate (2a).

T(135°C; bath); t(1 h). Yield 50%; white powder, mp 111.6 - 112.3°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.22 (2 H, d, *J* = 7.9); 7.97 (1 H, t, *J* = 7.9); 5.10 (2 H, m); 2.1-1.3 (20 H, m). GC/MS (*m/z*): 331 (M<sup>+</sup>); 287; 250; 219; 205; 168; 150; 123. HRMS (EI) (*m/z*): 331.1777 (331.1784 calc for C<sub>19</sub>H<sub>25</sub>NO<sub>4</sub>).

## 2.- Alkoxyacylation of 2,3,6-trichloropyridine

### Diethyl 3-chloropyridine-2,6-dicarboxylate (10)

The reaction was carried out in a 100 mL stainless steel autoclave equipped with a magnetic stirring bar. The reagents were charged in a teflon liner in the following order: ethanol (30 mL), sodium acetate (3.28 g, 40 mmol), 2,3,6-trichloropyridine (1.82 g, 10 mmol), 1,1'-bis(diphenylphosphino)ferrocene (166 mg, 0.3 mmol [3%mol]) and palladium acetate (4.4 mg, 0.02 mmol [0.2%mol]). The air in the autoclave was replaced with carbon monoxide (this air/carbon monoxide exchange was repeated two more times) and the pressure adjusted to 15 bar. The reaction mixture was then heated to 135°C (bath temperature) and the reaction was carried out thereon with stirring. After 1 h, the reaction mixture was cooled to rt and concentrated under vacuum. The products were isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:2) giving 1.98 g (76% yield) of colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.14 (1 H, d, *J* = 8.4); 7.93 (1 H, d, *J* = 8.4); 4.49 (2 H, q, *J* = 7.1); 4.47 (2 H, q, *J* = 7.1); 1.44 (3 H, t, *J* = 7.1); 1.43 (3 H, t, *J* = 7.1). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 164.0 (C=O); 163.9 (C=O); 149.0 (=C); 146.3 (=C); 139.3 (=CH); 133.6 (=C); 127.1 (=CH); 62.6 (CH<sub>2</sub>); 62.4 (CH<sub>2</sub>); 14.3 (CH<sub>3</sub>); 14.1 (CH<sub>3</sub>). GC/MS (*m/z*): 257 (M<sup>+</sup>); 213; 185; 139; 113. HRMS (EI) (*m/z*): 257.0450 (257.0455 calc for C<sub>11</sub>H<sub>12</sub>NO<sub>4</sub>Cl).

**Triethyl pyridine-2,3,6-tricarboxylate (12)**<sup>7a</sup>

Compound **12** can be found, under certain reaction conditions as by-product of the alkoxycarbonylation of 2,3,6-trichloropyridine in ethanol. It was isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:2) as colorless oil.<sup>20</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.34 (1 H, d, *J* = 8.1); 8.23 (1 H, d, *J* = 8.1); 4.50 (2 H, q, *J* = 7.1); 4.48 (2 H, q, *J* = 7.1); 4.42 (2 H, q, *J* = 7.1); 1.44 (3 H, t, *J* = 7.1); 1.42 (3 H, t, *J* = 7.1); 1.39 (3 H, t, *J* = 7.1). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 165.7 (C=O); 164.5 (C=O); 164.0 (C=O); 151.8 (=C); 150.2 (=C); 139.0 (=CH); 128.5 (=C); 125.7 (=CH); 62.6 (CH<sub>2</sub>); 62.5 (CH<sub>2</sub>); 62.4 (CH<sub>2</sub>); 14.3 (CH<sub>3</sub>); 14.1 (CH<sub>3</sub>); 14.0 (CH<sub>3</sub>). GC/MS (*m/z*): 296; 295 (M<sup>+</sup>); 280; 251; 223; 177; 151; 120; 105. HRMS (EI) (*m/z*): 295.1041 (295.1056 calc for C<sub>14</sub>H<sub>17</sub>NO<sub>6</sub>).

**3.- Alkoxycarbonylation of 2,3-dichloropyridine**<sup>19</sup>**Diethyl pyridine-2,3-dicarboxylate (15)**

The reaction was carried out in a 100 mL stainless steel autoclave equipped with a magnetic stirring bar. The reagents were charged in a teflon liner in the following order: ethanol (15 mL), sodium acetate (0.86 g, 10 mmol), 2,3-dichloropyridine (0.76 g, 5 mmol), 1,1'-bis(diphenylphosphino)ferrocene (83 mg, 0.15 mmol [3%mol]) and palladium acetate (11 mg, 0.05 mmol [1.0%mol]). The air in the autoclave was replaced with carbon monoxide (this air/carbon monoxide exchange was repeated two more times) and the pressure adjusted to 15 bar. The reaction mixture was then heated to 160°C (bath temperature) and the reaction was carried out thereon with stirring. After 3 h, the reaction mixture was cooled to rt and concentrated under vacuum. The products were isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:3) giving 0.95 g (85% yield) of colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.76 (1 H, dd, *J* = 4.8, *J* = 1.6); 8.19 (1 H, dd, *J* = 7.9, *J* = 1.6); 7.48 (1 H, dd, *J* = 7.9, *J* = 4.8); 4.47 (2 H, q, *J* = 7.1); 4.40 (2 H, q, *J* = 7.1); 1.43 (3H, t, *J* = 7.1); 1.38 (3 H, t, *J* = 7.1). GC/MS (*m/z*): 224; 223 (M<sup>+</sup>); 179; 150; 122; 107; 79.

**Ethyl 3-chloropyridine-2-carboxylate (14)**

The reaction was carried out in a 100 mL stainless steel autoclave equipped with a magnetic stirring bar. The reagents were charged in a teflon liner in the following order: ethanol (15 mL), sodium acetate (0.86 g, 10 mmol), 2,3-dichloropyridine (0.76 g, 5 mmol), 1,1'-bis(diphenylphosphino)ferrocene (83 mg, 0.15 mmol [3%mol]) and palladium acetate (2.2 mg, 0.01 mmol [0.2%mol]). The air in the autoclave was replaced with carbon monoxide (this air/carbon monoxide exchange was repeated two more times) and

the pressure adjusted to 15 bar. The reaction mixture was then heated to 140°C (bath temperature) and the reaction was carried out thereon with stirring. After 1 h, the reaction mixture was cooled to rt and concentrated under vacuum. The products were isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:3) giving 0.83 g (88% yield) of colorless oil.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.58 (1 H, dd,  $J = 4.7, J = 1.6$ ); 7.81 (1 H, dd,  $J = 8.1, J = 1.6$ ); 7.38 (1 H, dd,  $J = 8.1, J = 4.7$ ); 4.49 (2 H, q,  $J = 7.1$ ); 1.44 (3 H, t,  $J = 7.1$ ). GC/MS ( $m/z$ ): 188; 187; 186; 185 ( $\text{M}^+$ ); 143; 142; 141; 140; 113; 85; 76.

#### 4.- Alkoxy-carbonylation of 2,5-dichloropyridine <sup>4,5</sup>

##### Ethyl 5-chloropyridine-2-carboxylate (6a)

The reaction was carried out in a 100 mL stainless steel autoclave equipped with a magnetic stirring bar. The reagents were charged in a teflon liner in the following order : ethanol (30 mL), sodium acetate (3.28 g, 40 mmol), 2,5-dichloropyridine (1.51g, 10 mmol), 1,1'-bis(diphenylphosphino)ferrocene (166 mg, 0.3 mmol [3%mol]) and palladium acetate (4.3 mg, 0.02 mmol [0.2%mol]). The air in the autoclave was replaced with carbon monoxide (this air/carbon monoxide exchange was repeated two more times) and the pressure adjusted to 15 bar. The reaction mixture was then heated to 120°C (bath temperature) and the reaction was carried out thereon with stirring. After 1 h, the reaction mixture was cooled to rt and concentrated under vacuum. The products were isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:2) giving 1.59 g (86% yield) of white powder, mp 57.5 - 57.7°C.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.70 (1H, d,  $J = 2.2$ ); 8.09 (1H, d,  $J = 8.2$ ); 7.82 (1H, dd,  $J = 8.2, 2.2$ ); 4.48 (2H, q,  $J = 7.1$ ); 1.43 (3H, t,  $J = 7.1$ ). GC/MS ( $m/z$ ): 186; 185 ( $\text{M}^+$ ); 141; 113; 85; 76. HRMS (EI) ( $m/z$ ): 185.0245 (185.0244 calc for  $\text{C}_8\text{H}_8\text{NO}_2\text{Cl}$ ).

##### Diethyl pyridine-2,5-dicarboxylate (7a)

Compound(7a) can be found, under certain reaction conditions as by-product of the alkoxy-carbonylation of 2,5-dichloropyridine in ethanol. It was isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:2) as white powder, <sup>20</sup> mp 43.6 - 43.8°C (lit., <sup>23</sup>mp 42 - 44°C)..  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  9.32 (1 H, dd,  $J = 2.1, 0.8$ ); 8.45 (1 H, dd,  $J = 7.9, 2.1$ ); 8.21 (1 H, dd,  $J = 7.9, 0.8$ ); 4.52 (2 H, q,  $J = 7.1$ ); 4.46 (2 H, q,  $J = 7.1$ ); 1.47 (3 H, t,  $J = 7.1$ ); 1.44 (3 H, t,  $J = 7.1$ ). GC/MS ( $m/z$ ): 224; 223 ( $\text{M}^+$ ); 196; 178; 151; 123; 106. HRMS (EI) ( $m/z$ ): 223.0841 (223.0845 calc for  $\text{C}_{11}\text{H}_{13}\text{NO}_4$ ).

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