Pergamon

Tetrahedron 55 (1999) 393–404

TETRAHEDRON

Selective Alkoxycarbonylation of 2,3-Dichloropyridines

Yves Bessard* and Jean Paul Roduit

Department of Process Research, LONZA LTD P.O. Box CH-3930 Visp, Switzerland.

Received 29 May 1998; revised 30 August 1998; accepted 31 August 1998

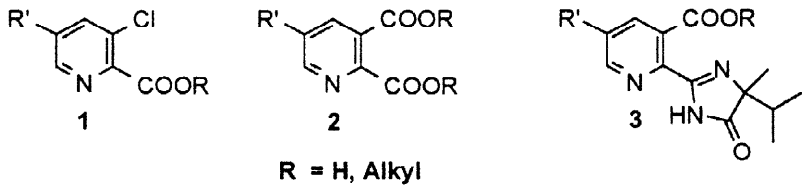
Abstract: 2,3-Dichloropyridines undergo a mono- or a dicarbonylation in the presence of carbon monoxide, an alcohol and a palladium catalyst, affording selectively either alkyl 3-chloropicolinates, or dialkyl pyridine-2,3-dicarboxylates in good yields, depending on the reaction conditions.

Keywords: Carbonylation reactions; Carboxylic acid esters; Heck type reactions; Pyridines.

Introduction

As part of a program directed towards the development of new synthetic technologies, we were interested in the preparation of esters of pyridinecarboxylic acids of general structure **1** or **2** as shown below (Figure 1). Chlorinated picolinic acids **1** can serve as intermediates for antifibrotics [1] or in agrochemistry as precursors for herbicides [2]. 5-Substituted pyridine-2,3-dicarboxylic acids **2** are useful as intermediates in the manufacture of a new class of imidazolinone herbicides [3-5] such as **3**. Compounds **1** and **2** are usually prepared by cyclocondensation reactions[1] [6,7] or by oxidation of 5-substituted quinolines with various oxidizing reagents [8]. However, when **2** is substituted with an alkoxymethyl group, the classical synthetic methods are unsatisfactory and a relatively complicated multistep synthesis is often required [9].

Figure 1.

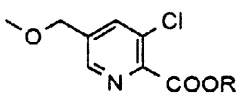


[1] The reaction of a ketoester (i.e. dialkyl oxalacetate) with an α,β-unsaturated aldehyde or ketone (i.e. 2-alkylacrolein) and 1 molar equivalent of ammonium salt in the presence of dehydrogenation catalyst (i.e. Pd/C) affords 5-alkyl-2,3-pyridinecarboxylates in moderate yields [10].

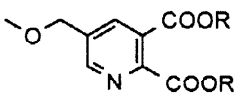
0040-4020/99/$ - see front matter
PII: S0040-4020(98)01037-0

We thought to take advantage of the particular reactivity of 2-halopyridines [11-15] in Heck type [16] reactions and speculated that the presence of a carboxylic group in the 2-position of a 3-halopyridine could provide sufficient activation [17] to allow for carbonyl insertion into the C-halogen bond. Following this reasoning, 2,3-dihalogenopyridines such as **4** could serve as convenient starting materials for the preparation of either **1** or **2** (Figure 2). We wish to report here on the successful application of this concept to the efficient preparation of 3-chloro-5-(methoxymethyl)pyridine-2-carboxylic acid derivatives (**1a,b**) or 5-(methoxymethyl)pyridine-2,3-dicarboxylic acid derivatives (**2a,b**). This was achieved by either a selective mono alkoxycarbonylation or a double alkoxycarbonylation of 2,3-dichloro-5-(methoxymethyl)pyridine (**4**). Dihalogenopyridine **4** is easily prepared from the readily available chlorinated pyridine **13**.

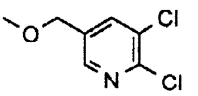
Figure 2.



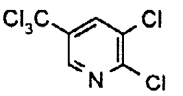
1a, R = Me
1b, R = Et



2a, R = Me
2b, R = Et



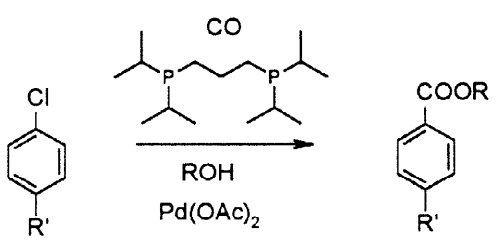
4



13

The carbonylation reaction concept

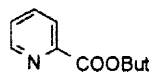
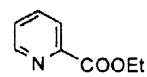
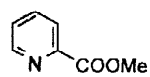
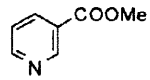
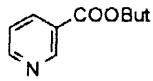
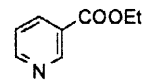
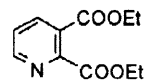
Palladium mediated coupling reactions have become important tools in synthetic organic chemistry [18,19]. The functionalization of aryl molecules with carbon monoxide to yield carbonyl compounds represents a rapidly growing area of investigation. Among the carboxylic acid derivatives accessible by this chemistry, esters are certainly the most reported in the literature. 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 [20] and coworkers recently obtained very good results (70 - 90% yield) for the carbonylation of *p*-substituted chlorobenzenes with active palladium complexes. (Scheme 1). As expected, electron withdrawing groups accelerated the reaction and electron donating groups inhibited it.



Scheme 1. **Alkoxycarbonylation of chloroaromatic rings.**

This concept has only 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 [21], pyrazine [22] or quinoline [23]. However, most procedures reported in recent years used expensive iodo- or bromoheterocyclic [24,25] as starting materials. Indeed, only a few examples of alkoxycarbonylation 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. **Selection of carbonylation reactions of chloropyridines reported in the literature.**

Entry	Chloropyridine	Ester	Solvent Base	Reaction conditions	Ligand[a]	Catalyst[b]	Yield [%]	Author
1			Butanol/Toluene Na_2CO_3	200°C/3h 50 atm CO	dppb	$PdCl_2$	54	Kudo [26]
2			Ethanol NEt_3	120°C/48h 66 atm CO	-	$(Ph_3P)_2PdCl_2$	51	Zhang [27]
3			Methanol NEt_3	150°C/16h 40 atm CO	Ph_3P	$Pd(dba)_2$	79	Takeuchi [17]
4			Methanol NEt_3	150°C/16h 40 atm CO	Ph_3P	$Pd(dba)_2$	No Reaction	Takeuchi [17]
5			Butanol/Toluene Na_2CO_3	200°C/3h 50 atm CO	dppb	$PdCl_2$	44	Kudo [26]
6			Ethanol/Benzene Na_2CO_3	250°C/3h 50 atm CO	dppb	$PdCl_2$	~20	Suto [28]
7			Ethanol/Benzene Na_2CO_3	250°C/3h 50 atm CO	dppb	$PdCl_2$	<5	Suto [28]

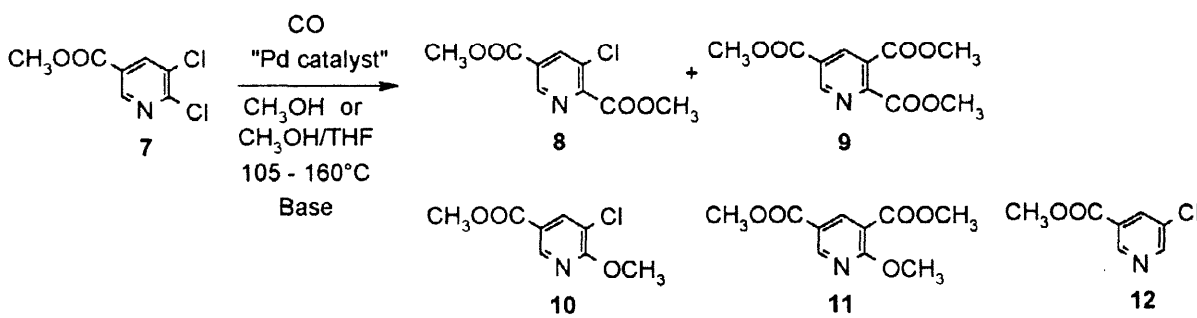
[a] Ligands: 1,4-bis(diphenylphosphino)butane (dppb); triphenylphosphine (Ph_3P).

[b] Catalyst: palladium bis(dibenzylideneacetone) $Pd(dba)_2$.

Results and discusssions

A. Preliminary experiments: alkoxycarbonylation of methyl 5,6-dichloropyridine-3-carboxylate

It was first decided to use methyl 5,6-dichloropyridine-3-carboxylate[1] (7) as a model system to determine the initial conditions for the carbonylation. Depending on the reaction conditions, several products can be formed in addition to the desired esters **8** and **9**. A competing substitution reaction can take place giving **10**. The latter can undergo a subsequent alkoxycarbonylation to **11**. The production of **12** may also be due to a reduction of the starting material 7 at the 2-position or to a decarboxylation of the monoester **8**. All of these products and side products (Scheme 2) were isolated by column chromatography and positively identified.



Scheme 2. **Alkoxycarbonylation of methyl 5,6-dichloropyridine-3-carboxylate showing main products and known side products.**

[1] Methyl 2,3-dichloro-5-pyridinecarboxylate was prepared by esterification of 5,6-dichloronicotinoyl chloride (obtained from 6-hydroxypicolinic acid [29]).

Carbonylation reactions were carried out in an autoclave on 10 mmol scale under 15 atm of carbon monoxide. The most interesting results are given in the table (Table 1), the values reported correspond to area % ratio (GC).

Table 2. **Comparison of reaction conditions for the carbonylation reaction.**

Entry	Solvent	Reaction conditions[a]	Ligand[b]	Base [equiv.]	**8** [%]	**9** [%]	**10** [%]	**11** [%]	**12** [%]	**7** [%]
1	CH_3OH	155°C/6h	dppb	Na_2CO_3 [2.2]	<1[c]	<1	63	34	1	1
2	CH_3OH	155°C/6h	dppb	CH_3COONa [3.0]	40	48	10	<1	2	<1
3	CH_3OH	105°C/16h	dppb	CH_3COONa [3.0]	27	<1	10	<1	<1	63
4	THF/CH_3OH	160°C/6h	dppb	CH_3COONa [3.0]	80	10	2	<1	5	1
5	THF/CH_3OH	155°C/24h	dppb	CH_3COONa [3.0]	71	7	2	<1	15	2
6	CH_3OH	155°C/6h	tmpp	CH_3COONa [3.0]	29	<1	26	3	<1	36

[a] Reaction conditions: the temperature given is the external temperature (internal temperature is 15-20°C less); catalyst: dichlorobis(triphenylphosphine)palladium.

[b] Ligands: 1,4-bis(diphenylphosphino)butane (dppb); tris(4-methoxyphenyl)phosphine (tmpp).

[c] <1% means: no GC signal or GC signal not integrated

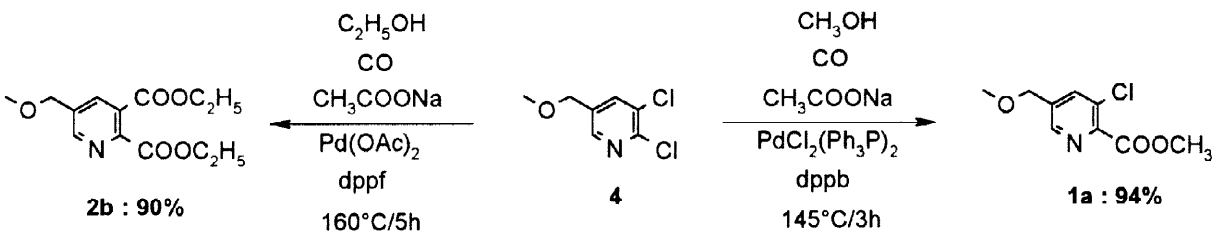
Choice of the base has a dramatic effect on the selection of a carbonylation reaction over a substitution reaction (Entries 1 and 2). When sodium carbonate was used (Entry 1), the major reaction pathway was substitution at the 2-position, giving methoxy substituted **10**, a portion of which underwent carbonylation at the 3-position to give **11**. When sodium carbonate was replaced by sodium acetate (Entry 2), other conditions being the same, the substitution reaction was drastically reduced. Carbonylation occurred at the 2-position followed by carbonylation at the 3-position, giving a mixture of monoester **8** and diester **9**. At lower temperatures and longer reaction time (Entry 3), the substitution reaction remained the same and a high proportion of starting material **7** was unchanged. When the reaction was carried out in tetrahydrofuran with 3 equiv. of methanol, the main reaction was carbonylation at the 2-position (80% of monoester **8** and 10% of diester **9**; GC area %), (Entry 4). After separation by chromatography, the monoester **8** was isolated in 73% yield and the diester **9** in 6% yield. A longer reaction time (Entry 5), did not increase the amount of diester **9**, but increased the amount of **12** most likely by decarboxylation of monoester **8**. At this preliminary stage we did not probe deeply the effect of the catalyst or the ligand, except for one attempt (Entry 6) in which a monophosphine was tested. With tris(4-methoxyphenyl)phosphine instead of 1,4-bis(diphenylphosphino)-butane, we once again observed an increasing amount of substitution product **10**.

Our primary conclusions from the initial phase of the project showed :

- the nature of the base is crucial for the ratio of carbonylation to substitution,
- the polarity of the solvent probably has an influence on the selectivity,
- a diphosphine is essential for an efficient carbonylation,
- the temperature should be higher than 150°C,
- long reaction times should be avoided due to the limited stability of the esters (decarboxylation).

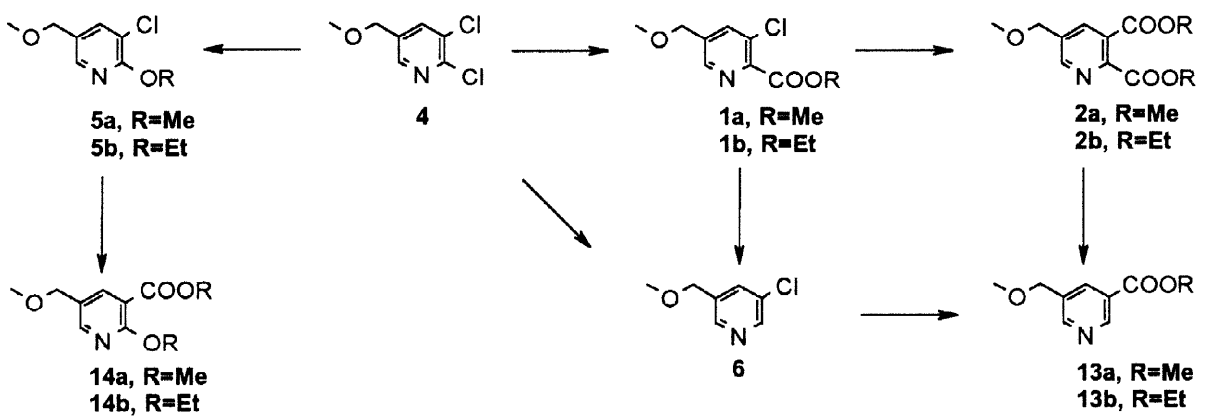
B. Mono- and bisalkoxycarbonylation of 2,3-dichloro-5-(methoxymethyl)pyridine (4).

Both mono- and bisalkoxycarbonylations of 2,3-dichloro-5-(methoxymethyl)pyridine (**4**) could be achieved in very good yields. One set of conditions was found to selectively prepare the methyl ester **1a** in 94% yield and another set was found to prepare the diethyl ester **2b** in 90% yield (Scheme 3). In this section the influence of the different reaction parameters on these two sequences will be discussed.



Scheme 3. **Mono- and bisalkoxycarbonylation of 2,3-dichloro-5-(methoxymethyl)pyridine (4).**

Based on our observations in the preliminary study (Part A), we expected the product mixture shown below (Scheme 4). In addition to the possible side products by the pathways already described, we also suspected that **13** might result via decarboxylation of diester **2**. Most of these side products were isolated by column chromatography and identified by spectroscopic methods (see Experimental Section). Various reaction parameters and their corresponding results on the product mixtures are shown in Table 2 and summarized thereafter.



Scheme 4. **Alkoxycarbonylation of 2,3-dichloro-5-(methoxymethyl)pyridine (4) showing main products and known side products.**

Table 3. **Comparison of reaction conditions for the carbonylation of 2,3-dichloro-5-(methoxymethyl)pyridine.**

Entry	Solvent	Reaction conditions[a]	Ligand[b]	Catalyst	**1a** [%]	**2a** [%]	**5a** [%]	**6** [%]	**13a** [%]	**4** [%]
1[c]	THF/CH_3OH	160°C/6h	dppb	$(Ph_3P)_2PdCl_2$	76	<1	<1	15	<1	7
2[c]	THF/CH_3OH	195°C/6h	dppb	$(Ph_3P)_2PdCl_2$	76	<1	1	19	<1	3
3	CH_3OH	210°C/3h	dppb	$(Ph_3P)_2PdCl_2$	<1	22	<1	64	<1	<1
4	CH_3OH	165°C/3h	dppb	$(Ph_3P)_2PdCl_2$	63	36	<1	<1	<1	<1
5	CH_3OH	160°C/22h	dppf	$(Ph_3P)_2PdCl_2$	6	83	3	8	<1	<1
6	CH_3OH	165°C/10h	josiphos	$(Ph_3P)_2PdCl_2$	45	49	4	2	<1	<1
7	CH_3OH	180°C/2h	dppf	$(Ph_3P)_2PdCl_2$	1	79	5	2	<1	<1
8	CH_3OH	170°C/4h	dppf	$Pd(OAc)_2$	4	90	2	2	<1	<1
9	**CH_3OH**	**145°C/3h**	**dppb**	**$(Ph_3P)_2PdCl_2$**	**96**	**3**	**<1**	**<1**	**<1**	**<1**
10	CH_3OH	165°C/6h	dppb	$Pd(OAc)_2$	31	64	1	4	<1	<1
11	CH_3OH	165°C/6h	dppb	$PdCl_2$	32	62	3	3	<1	<1
					1b [%]	**2b** [%]	**5b** [%]	**6** [%]	**13b** [%]	**4** [%]
12	C_2H_5OH	160°C/5h	dpppe	$Pd(OAc)_2$	52	<1	3	<1	<1	45
13	C_2H_5OH	160°C/5h	dpppr	$Pd(OAc)_2$	70	27	3	<1	<1	<1
14	C_2H_5OH	160°C/5h	josiphos	$Pd(OAc)_2$	39	61	<1	<1	<1	<1
15	C_2H_5OH	160°C/5h	dppb	$Pd(OAc)_2$	20	76	2	<1	<1	<1
16	**C_2H_5OH**	**160°C/5h**	**dppf**	**$Pd(OAc)_2$**	**5**	**95**	**<1**	**<1**	**<1**	**<1**
17	C_2H_5OH	160°C/5h	dppf	$Rh(OAc)_2$	37	<1	<1	4	<1	59
18	C_2H_5OH	160°C/5h	dppf	$Co(acac)_3$	43	<1	4	<1	<1	53
19	C_2H_5OH	175°C/4h	dppf	$(Ph_3P)_2PdCl_2$	14	79	<1	<1	<1	<1
20[d]	**C_2H_5OH**	**160°C/5h**	**dppf**	**$Pd(OAc)_2$**	**<1**	**99**	**<1**	**<1**	**<1**	**<1**

The values reported in Table 2 correspond to relative area % (GC); <1% means either no GC signal or GC signal not integrated.

[a] 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 and sodium acetate (3 equiv.) was used as base.

[b] Ligands: 1,4-bis(diphenylphosphino)butane (dppb); 1,1'-bis(diphenylphosphino)ferrocene (dppf); (±)-1-[2-(diphenylphosphino)-ferrocenyl]ethyl-di-*tert*-butylphosphine (josiphos); 1,4-bis(diphenylphosphino)propane (dpppr); 1,4-bis(diphenylphosphino)pentane (dpppe)

[c] Alcohol used as reagent in tetrahydrofuran.

[d] Double amount of catalyst was used in this attempt.

Influence of the base. In an alkoxycarbonylation reaction, the base is indispensable for neutralization of the hydrogen chloride generated during the reaction. As demonstrated in our preliminary work (Part A), a stronger base, i.e. sodium carbonate, favors substitution of the chlorine with the alcoholate. For this reason, we began our experiments with the weaker base sodium acetate. As a logical consequence, the proportion of side-products **5a** and **5b** remained low (always lower than 5%), moreover the side-products **14a** and **14b** from the subsequent alkoxycarbonylation of **5a** and **5b** were practically undetectable.

Influence of the solvent. The presence of 3-chloro-5-(methoxymethyl)pyridine (**6**) can be explained either by the reduction of 2,3-dichloro-5-(methoxymethyl)pyridine (**4**) or by decarboxylation of **1a** or **1b**. Indeed, this side-reaction must be considered since the presence of water cannot be excluded. Without rigorous exclusion of water in any reaction involving CO, there is always the possibility of hydrogen formation *via* the "water-gas" shift reaction. The decarboxylation of the monoester **1a** or **1b** can also give the side product **6**. These side reactions were observed when the reactions were carried out in tetrahydrofuran (influence on the reaction rate) as solvent and the alcohol as reagent (Table 2, Entry 1 and 2).

Influence of the nature of the alcohol. When we attempted to prepare diester **2a** with reactions carried out in methanol, the quantity of material isolated after the reaction was relatively low compared to the very good conversion observed (Entry 8). Indeed, only 62% of the diester **2a** could be isolated after chromatography though GC analysis of the crude reaction mixture indicated 90% conversion to **2a**. However, when the reactions were carried out in ethanol, a higher yield was obtained, presumably due to higher stability of the ethyl esters under the reaction conditions (Entry 16 and 20). Indeed the methyl esters are much more prone to decarboxylate than ethyl esters in presence of sodium chloride (*Krapcho conditions*).

Influence of the temperature. When the reaction was carried out at relatively high temperature (Table 2, entry 3), the product of reduction (**6**) was observed in high proportion. In fact, the temperature has a major impact both on the rate of the reaction and on the stability of the products. Since the carbonylation in 3-position requires more vigorous conditions, one would hope to control the selectivity of the reaction solely by temperature selection. In fact, this is not possible, because for any given set of conditions (ligand, alcohol, catalyst), the extent of the side reactions increases greatly with the temperature. As a result, the fate of the reaction can be governed only by the proper choice of the ligand/catalyst complex.

Influence of the ligand. Other conditions being the same, 1,4-bis(diphenylphosphino)butane (dppb) is the most selective ligand, allowing an efficient monocarbonylation reaction to proceed (Entry 9). By contrast, 1,1'-bis(diphenylphosphino)ferrocene (dppf) is the most active ligand, the only one capable of effecting a bis carbonylation (Entry 16 and 20) under relatively mild conditions. All of the other ligands tested (Entry 12 - 14) 1,4-bis(diphenylphosphino)pentane (dpppe), bis(diphenylphosphino)propane (dpppr) and (±)-1-[2-(diphenylphosphino)-ferrocenyl]ethyl-di-*tert*-butylphosphine (josiphos) were less selective than dppb and/or less active than dppf.

Influence of the metal catalyst. The activity of various catalysts (0.2 mol%) was tested (Entries 17 to 20) with 1,1'-bis(diphenylphosphino)ferrocene as ligand. Rhodium acetate and cobalt(III)acetoacetonate were not reactive enough to allow for good conversion (Entry 17 and 18). With dichlorobis(triphenylphosphine)-palladium, the conversion was complete but a mixture of monoester **1b** and diester **2b** was obtained (Entry 19). As already demonstrated (Entry 16), palladium acetate is the most effective catalyst for the formation of the

diester **2b**. We attempted not only to achieve a high conversion to the diester **2b** (Entry 20) but also to obtain a higher yield of product with double the amount of catalyst (0.4 mol%). Under these conditions we achieved 99% conversion and obtained a 90% isolated yield.

Conclusion

Palladium-catalyzed methoxy- and ethoxycarbonylation of dichloropyridines proceeded successfully, delivering the target products in high yields. Selectivity for monoalkoxycarbonylation was obtained by judicious choice of ligand. Indeed (Table 2, entry 9), methyl 3-chloro-5-(methoxymethyl)pyridine-2-carboxylate (**1a**) could be isolated in 94% yield under the correct conditions. The reaction was carried out in the presence of dichlorobis(triphenylphosphine)palladium, 1,4-bis(diphenylphosphino)butane and sodium acetate as acid acceptor with methanol as reagent and solvent at 145°C under 15 atm of carbon monoxide for 3h. Diethyl 5-(methoxymethyl)pyridine-2,3-dicarboxylate (**2b**) could also be isolated in 90% yield by choice of another set of catalyst and ligand (Table 2, entry 20). The reaction was carried out in the presence of palladium acetate and 1,1'-bis(diphenylphosphino)ferrocene and sodium acetate in ethanol at 160°C under 15 atm of carbon monoxide for 5h.

Experimental

Reagents and solvents were reagent grade and used as received. Melting points were determined on a Büchi 535 apparatus and were not corrected. ^{1}H NMR (400 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.

Selective mono-alkoxycarbonylation of methyl 5,6-dichloropyridine-3-carboxylate (7).

The reaction was carried out in a 100 mL stainless steel autoclave equipped with a magnetic stirring bar. The reagents were charged into a teflon liner in the following order : (1) tetrahydrofuran (20 mL), (2) methanol (686 mg, 21.4 mmol) (3) sodium acetate (1.76 g, 21.5 mmol), (4) methyl 5,6-dichloropyridine-3-carboxylate (**7**, 1.47 g, 7.1 mmol), (5) 1,4-bis(diphenylphosphino)butane (91 mg, 0.21 mmol [3 mol%]) and (6) dichlorobis(triphenylphosphine)palladium (10 mg, 0.014 mmol [0.2 mol%]). The air in the autoclave was replaced with carbon monoxide and the pressure adjusted to 15 bar. The reaction mixture was then heated to 160°C (jacket temperature; 150°C internal temperature) and the reaction was carried out with stirring. After 6h, the reaction mixture was cooled to room temperature and filtered through celite. GC analysis indicated that the mixter consisted of 80% of **8**, 10% of **9**, 2% of **10**, <1% of **11**; 5% of **12** and 2% of starting material **7**. The reaction mixture was concentrated under vacuum and the products were isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:4) affording 1.20 g of **8** (73%), 0.10 g of **9** (6%), 0.06 g of **10** (3%) and 0.09 g of **12** (8%).

Dimethyl 3-chloropyridine-2,5-dicarboxylate (8). White solid, mp 35.5 - 36.0°C. ^{1}H NMR ($CDCl_3$): δ 9.11 (1 H, d, J = 1.8); 8.41 (1H, d, J = 1.8); 4.03 (3 H, s); 4.00 (3 H, s). GC/MS (m/e) : 229 (M^+); 199; 171.

Trimethyl pyridine-2,3,5-tricarboxylate (9). Oil. ^{1}H NMR ($CDCl_3$): δ 9.32 (1 H, d, J = 2.0); 8.78 (1H, d, J = 2.0); 4.02 (3 H, s); 4.01 (3 H, s); 3.97 (3 H, s). GC/MS (m/e) : 254; 253 (M^+); 223; 222; 195; 194; 165; 137.

Methyl 5-chloro-6-methoxypyridine-3-carboxylate (10). White solid, mp 105.5 - 107.0°C. ^{1}H NMR ($CDCl_3$): δ 8.71 (1 H, d, J = 2.0); 8.22 (1H, d, J = 2.0); 4.09 (3 H, s); 3.92 (3 H, s). GC/MS (m/e) : 201 (M^+); 200; 199; 198; 173; 172; 171; 170; 140; 111.

Dimethyl 2-methoxypyridine-3,5-dicarboxylate (11). White solid, mp 117.5 - 118.5°C. ^{1}H NMR ($CDCl_3$): δ 8.94 (1 H, d, J = 2.3); 8.73 (1H, d, J = 2.3); 4.12 (3 H, s); 3.94 (3 H, s); 3.92 (3 H, s). GC/MS (m/e) : 225 (M^+); 194; 137.

Methyl 5-chloropyridine-3-carboxylate (12). White solid, mp 84.9 - 86.7°C. ^{1}H NMR ($CDCl_3$): δ 9.10 (1 H, d, J = 1.8); 8.75 (1 H, d, J = 2.4); 8.28 (1 H, m); 3.97 (3 H, s). GC/MS (m/e) : 174; 173; 172; 171 (M^+); 170; 140; 112; 85; 76.

Preparation of 2,3-dichloro-5-(methoxymethyl)pyridine (4).
Under an argon atmosphere, a 30% solution of sodium methoxide in methanol (4.14 g, 23 mmol) was added (5 min) to a solution of 5-(chloromethyl)-2,3-dichloropyridine[1] (4.11 g, 21 mmol) in methanol (40 mL) at room temperature. The reaction mixture was then heated to 60°C for 3h (the conversion was followed by TLC). After completion of the reaction the solvent was removed by distillation and the residue diluted with water (100 mL) and then extracted with dichloromethane (3 x 75 mL). After drying (magnesium sulfate) and evaporation of the solvent, 4.06 g (90.4%) of a yellow oil was obtained (GC analysis : 90.8% Area). (If necessary the product can be further purified by silica gel chromatography using hexane/EtOAc, 3:1).
^{1}H NMR ($CDCl_3$): δ 8.25 (1 H, d, J = 2.1); 7.79 (1H, d, J = 2.1); 4.45 (2 H, s); 3.43 (3 H, s). GC/MS (m/e) : 195; 194; 193; 192 (M^+); 191; 190; 176; 161; 148; 124; 112.

Selective mono-alkoxycarbonylation of 2,3-dichloro-5-(methoxymethyl)pyridine (4).

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 : (1) methanol (30 mL), (2) sodium acetate (2.46 g, 30 mmol), (3) 2,3-dichloro-5-(methoxymethyl)pyridine (**4**, 1.98 g [97 %], 10 mmol), (4) 1,4-bis(diphenylphosphino)butane (128 mg, 0.30 mmol [3 mol%]) and (5) dichlorobis(triphenylphosphine)-palladium (14.3 mg, 0.020 mmol [0.2 mol%]).

---

[1] 2,3-Dichloro-5-chloromethylpyridine was obtained by chlorination of 2,3-dichloro-5-hydroxymethylpyridine [30] with thionyl chloride. It can also be prepared by selective reduction of 2,3-dichloro-5-trichloromethylpyridine[31,32].

The air in the autoclave was replaced with carbon monoxide and the pressure adjusted to 15 bar. The reaction mixture was then heated to 145°C (jacket temperature) and the reaction was carried out with stirring. After 3h, the reaction mixture was cooled to room temperature, filtered through celite. GC analysis indicated that the mixter consisted of 97% of **1a**, 3% of **2a**. The reaction mixture was concentrated under vacuum and the products were isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:3) affording 2.03 g of **1a** (94%), 0.10 g of **2a** (4%).

Methyl 3-chloro-5-(methoxymethyl)pyridine-2-carboxylate (1a). Oil. ^{1}H NMR ($CDCl_3$): δ 8.51 (1 H, m); 7.83 (1H, m); 4.52 (2 H, s); 4.01 (3 H, s); 3.45 (3 H, s). GC/MS (m/e) : 218; 217; 216; 215 (M^+); 214; 185; 157.

Dimethyl 5-(methoxymethyl)pyridine-2,3-dicarboxylate (2a). Oil. ^{1}H NMR ($CDCl_3$): δ 8.70 (1 H, m); 8.13 (1H, m); 4.56 (2 H, s); 4.00 (3 H, s); 3.94 (3 H, s); 3.45 (3 H, s). GC/MS (m/e) : 239 (M^+); 209; 181; 151; 123.

Depending on the reaction conditions, **5a**, **6** and **13a** were also identifiable and could be isolated :

3-Chloro-2-methoxy-5-(methoxymethyl)pyridine (5a). Oil. ^{1}H NMR ($CDCl_3$): δ 8.00 (1 H, m); 7.65 (1H, m); 4.38 (2 H, s); 4.02 (3 H, s); 3.38 (3 H, s). GC/MS (m/e) : 190; 189; 188; 187 (M^+); 186; 171; 156; 142; 128; 87.

3-Chloro-5-(methoxymethyl)pyridine (6). Oil. ^{1}H NMR ($CDCl_3$): δ 8.51 (1 H, d, J = 2.4); 8.44 (1 H, d, J = 1.9); 7.70 (1H, m); 4.47 (2 H, s); 3.42 (3 H, s). GC/MS (m/e) : 159; 158; 157 (M^+); 156; 143; 127; 90.

Methyl 5-(methoxymethyl)pyridine-3-carboxylate (13a). Oil. ^{1}H NMR ($CDCl_3$): δ 9.15 (1 H, d, J = 1.9); 8.74 (1H, d, J = 2.1); 8.28 (1H, m); 4.53 (2 H, s); 3.96 (3 H, s); 3.44 (3 H, s). GC/MS (m/e) : 181 (M^+); 166; 150; 138; 122.

Bis-alkoxycarbonylation of 2,3-dichloro-5-(methoxymethyl)pyridine (4).

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 : (1) ethanol (15 mL), (2) sodium acetate (0.86 g, 10.5 mmol), (3) 2,3-dichloro-5-(methoxymethyl)pyridine (**4**, 1.00 g [96%], 5.0 mmol), (4) 1,1'-Bis(diphenylphosphino)ferrocene (83 mg, 0.15 mmol [3 mol%]) and (5) palladium acetate (5.6 mg, 0.025 mmol [0.5 mol%]). The air in the autoclave was replaced with carbon monoxide and the pressure adjusted to 15 bar. The reaction mixture was then heated to 160°C (jacket temperature; 146°C internal temperature) and the reaction was carried out with stirring. After 5h, the reaction mixture was cooled to room temperature, filtered through celite. GC analysis indicated that the mixture consisted of 99% of **2b** and <1% of **1b**. The mixture was concentrated under vacuum and the product was isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (2:3) affording 1.20 g of **2b** (90%).

Diethyl 5-(methoxymethyl)pyridine-2,3-dicarboxylate (2b). Oil. ^{1}H NMR ($CDCl_3$): δ 8.70 (1 H, m); 8.14 (1 H, m); 4.56 (2 H, s); 4.46 (2 H, q, J = 7.2); 4.40 (2 H, q, J = 7.2); 3.44 (3 H, s); 1.42 (3 H, t, J = 7.2); 1.38 (3 H, t, J = 7.2). GC/MS (m/e) : 269; 268; 267 (M^+); 266; 223; 194; 151; 123.

Depending on the reaction conditions, **1b**, **6** and **13b** were also identifiable and could be isolated :

Ethyl 3-chloro-5-(methoxymethyl)pyridine-2-carboxylate (1b). Oil. ^{1}H NMR ($CDCl_3$): δ 8.50 (1 H, m); 7.81 (1 H, m); 4.51 (2 H, s); 4.49 (2 H, q, J = 7.1); 3.44 (3 H, s); 1.44 (3 H, t, J = 7.1). GC/MS (m/e) : 232; 231; 230; 229 (M^+); 228; 186; 157.

Ethyl 5-(methoxymethyl)pyridine-3-carboxylate (13b). GC/MS (m/e) : 195 (M^+); 180; 150; 122.

Acknowledgment

The authors would like to thank their colleagues in the Chemical Research and Development department for their support and especially Dr. Andy Naughton for his valuable advice during the redaction of this manuscript as well as Dr. Michael Hauck for his valuable NMR assistance.

References

* [Phone: (41) 27 948 5800, Fax: (41) 27 948 6180, E-mail: yves.bessard@lonza.ch].

[1] Weidmann K, Bickel M, Guenzler-Pukall V. (Hoechst A.-G.) Eur. Pat. Appl. EP 673932 (Chem. Abstr. 1996;124:86819).
[2] Foster CJ, Gilkerson T, Stocker R, Gilmore IJ. (Shell Int. Res. Neth.) Eur. Pat. Appl. EP 488474 A1 (Chem. Abstr. 1992;117:131081).
[3] Waldner A. Helv. Chim.Acta 1988;71:486-497.
[4] Doehner RF, Ladner DW, Finn JM. (American Cyanamid Co.) Eur. Pat. Appl. EP 322616 (Chem. Abstr. 1990;112:35858).
[5] Szczepanski H, Dürr D. (Ciba-Geigy A.-G.) Eur. Pat. Appl. EP 233150 (Chem. Abstr. 1989;110:75491).
[6] Yamashita T, Kodama M. (Sugai Chem. Ind. Co. Ltd.) Int. Pat. Appl. WO 89/08645 (Chem. Abstr. 1990;112:118660).
[7] Cevasco AA, Chiarello GA, Riecker WF, Doehner RF. (American Cyanamid Co.) Eur. Pat. Appl. EP 461401 (Chem. Abstr. 1992;116:106102).
[8] Strong HL, Cortes AD, Ahmed Z. (American Cyanamid Co.) US. Pat. Appl. US 5281713 (Chem. Abstr. 1994;120:269655).
[9] Strong HL. (American Cyanamid Co.) US. Pat. Appl. US 5288866 (Chem. Abstr. 1994;120:270130).
[10] Gupton BF, Rea JH, Müller WH, Saukaitis J. (Hoechst Celanese Corp.) WO 89/08103 (Chem. Abstr. 1990;112:118658).
[11] Bessard Y, Stucky G, Roduit JP. (Lonza Ltd.) Eur. Pat. Appl. EP 820986 (Chem. Abstr. 1998;128:154017).

[12] Bessard Y, Stucky G, Roduit JP. (Lonza Ltd.) Eur. Pat. Appl. EP 820987 (Chem. Abstr. 1998;128:140617).
[13] Bessard Y, Stucky G. (Lonza Ltd.) Eur. Pat. Appl. EP 819679 (Chem. Abstr. 1998;128:140722).
[14] Bessard Y, Stucky G. (Lonza Ltd.) Eur. Pat. Appl. EP 819680 (Chem. Abstr. 1998;128:140723).
[15] Roduit JP, Kalbermatten G.(Lonza Ltd.) Eur. Pat. Appl. EP 806415 (Chem. Abstr. 1998;128:22817).
[16] Schoenberg A, Bartoletti I, Heck RF. J. Org. Chem. 1974;39:3318.
[17] Takeuchi R, Suzuki K, Sato N. J. Mol. Catal. 1991;66:277-288.
[18] For a review of carbonylations, see : Colquhoun DM, Thompson DJ, Twigg MV. Carbonylation, Direct Synthesis of Carbonyl Compounds, Plenum Press: New York, 1991.
[19] Beller M, Cornils B, Frohning CD, Kohlpaintner CW. J. Mol. Catal. 1995;104:17-85.
[20] Ben-David Y, Portnoy M, Milstein D. J. Am. Chem. Soc. 1989;111:8742.
[21] Murata N, Sugihara T, Kondo Y, Sakamoto T. Synlett 1997;298-300.
[22] Takeuchi R, Suzuki K, Sato N. Synthesis 1990;923-924.
[23] Ciufolini MA, Mitchell JW, Roschangar F. Tetrahedron Lett. 1996;37:8281-8284.
[24] Chambers RJ, Marfat A. Synth. Commun. 1997;27:515-520.
[25] Heck RF. (University of Delaware) US. Pat. Appl. US 4128554 (Chem. Abstr. 1979;90:103676).
[26] Kudo M. Shokubai (catalysts) 1994;36:580-584.
[27] Zhang TY, Scriven EFV. (Reilly Industries, Inc.) Int. Pat. Appl. WO 93/18005 (Chem. Abstr. 1994;120:106784).
[28] Suto K, Kudo M, Yamamoto M. (Nihon Nohyaku CO., LTD) Eur. Pat. Appl. EP 282266 (Chem. Abstr. 1989;111:133974).
[29] Quarroz D. (Lonza Ltd.) Swiss Pat. Appl. 664754A (Chem. Abstr. 1989;110:7953).
[30] Roduit JP. unpublished results.
[31] Katsuhiro I. (Koei Chemical Co) Jpn. Kokai Tokkyo Koho JP 5320132 (Chem. Abstr. 1994;120:217307).
[32] Humphries PL, Ditsche TJ, Bixby JL. (Dow Chemical Co.) U.S.S.R. SU 1787156 (Chem. Abstr. 1993;119:225839).