Organic Process Research & Development **2001**, *5*, 572–574

Synthetic Process Development and Scale Up of Palladium-Catalyzed Alkoxycarbonylation of Chloropyridines

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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-chloropyridine-2-carboxylates or dialkyl pyridine-2,3-dicarboxylates in good yields, depending on the reaction conditions. For instance, the process could be scaled up for the monoalkoxycarbonylation of 2,3-dichloro-5-(trifluoromethyl)pyridine, affording in high yield and selectivity the corresponding 3-chloro-5-(trifluoromethyl)pyridine-2-carboxylate.

Introduction

Chlorinated picolinic acids and pyridine-2,3-dicarboxylic acids are useful intermediates[1−3] to the agrochemical industry as precursors for herbicides such as **3**.[4] In continuation of our program directed to the development of synthetic methods in heterocyclic chemistry,[5] we were interested in the preparation of esters of pyridinecarboxylic acids of structure **1** or **2** by alkoxycarbonylation of the dichloropyridine **4** (Figure 1).

We aimed to take advantage of the particular reactivity of 2-halopyridines in *Heck*-type reactions[6] and speculated that the presence of a carboxylic group in the 2-position of a 3-halopyridine could provide sufficient activation[7] to allow for carbonyl insertion into the carbon−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 1). We wish to report here the application of this concept to the efficient preparation of 3-chloro-5-(trifluoromethyl)pyridine-2-carboxylic acid derivatives **1** and 5-(trifluoromethyl)pyridine-2,3-dicarboxylic acid derivatives **2**, achieved by selective mono- or double-

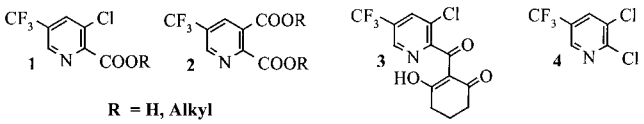

Figure 1.

alkoxycarbonylation of 2,3-dichloro-5-(trifluoromethyl)pyridine (**4**) using previously developed reaction conditions.[8] Furthermore, the process could be successfully scaled up from mmol routine labscale to molar scale.

The Carbonylation Reaction Concept

Palladium-mediated coupling reactions have become important tools in synthetic organic chemistry.[9,10] 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.

Nevertheless, this concept has only been seldom applied to heteroaryl molecules, although the carbonylation of heterocyclic halides could provide an attractive method for the synthesis of esters and amides of heterocyclic carboxylic acids derived from pyridine,[11] pyrazine,[12] or quinoline.[13] However, most procedures reported in recent years used expensive iodo- or bromoheterocycles[14,15] 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 are relatively harsh.[16−18]

Results and Discussion

On the basis of knowledge gained from previous findings,[8a] the reactivity of a monochloropyridine was first tested at 10 mmol scale with 2-chloro-5-(trifluoromethyl)pyridine (**5**) to

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 10.1021/op010012k CCC: $20.00
Published on Web 11/16/2001

Scheme 2

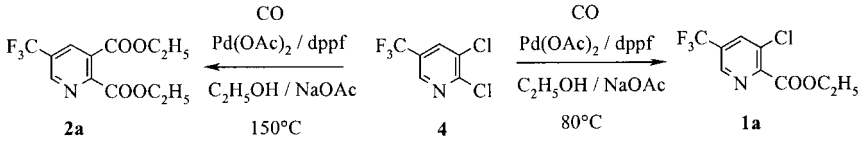


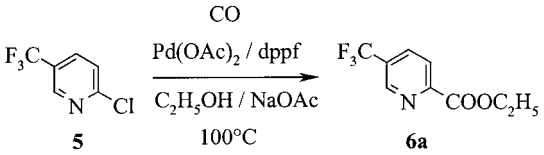
Table 1. **Effect of temperature on the carbonylation reaction**[a]

entry	reaction conditions[b]	ligand/catalyst	**4** [%]	**1a** [%]	**2a** [%]	yield[c] [%]
1	120 °C/2 h	dppb/$PdCl_2(Ph_3P)_2$	59	32	9	–
2	80 °C/2 h	dppf/Pd(II)Ac	32	68	–	–
3	100 °C/2 h	dppf/Pd(II)Ac	–	97	3	–
4	80 °C/5 h	dppf/Pd(II)Ac	–	99	1	92 (**1a**)
5	150 °C/2 h	dppf/Pd(II)Ac	–	–	>99	92 (**2a**)

[a] The values reported correspond to relative GC (crude reaction mixture) integration results. [b] Reaction conditions: 3 mol % of ligand (dppf: 1,1′-bis(diphenylphosphino)ferrocene; dppb: 1,4-bis(diphenylphosphino)butane) and 0.5 mol % of catalyst (Pd(II)Ac: palladium acetate); ethanol; 15 atm CO. The temperature given is the bath temperature (internal temperature is ~15 °C less). [c] Isolated yield after flash chromatography.

set up the preliminary reaction conditions. The reaction was carried out in ethanol under 15 atm of carbon monoxide, in the presence of palladium acetate (0.5 mol %) and 1,1′-bis-(diphenylphosphino)ferrocene (3 mol %) using sodium acetate as a base (2 equiv) (Scheme 1).

Scheme 1



GC analysis of the reaction mixture showed that the conversion was complete in 2 h at 100 °C. Following isolation and chromatographic purification, ethyl 5-(trifluoromethyl)-pyridine-2-carboxylate (**6a**) was obtained in 93% yield.

In the case of 2,3-dichloro-5-(trifluoromethyl)pyridine (**4**), both the mono- and the dicarboxylate could be expected (Scheme 2). The carbonylation occurring first at the 2-position,[8a] the selectivity could be directed by controlling the temperature and the reaction time.

Even at relatively low temperature, the dichloropyridine **4** was totally transformed to the monocarboxylate **1a**. Selectivity was also high since less than 1% of dicarboxylate **2a** could be detected by GC analysis. Indeed, after 5 h at 80 °C, ethyl 3-chloro-5-(trifluoromethyl)-pyridine-2-carboxylate (**1a**) could be isolated in 92% yield after flash chromatography. Logically, a higher temperature was necessary for the exclusive formation of the dicarboxylate **2a**. In this case, after 2 h at 150 °C, diethyl 5-(trifluoromethyl)pyridine-2,3-dicarboxylate (**2a**) could be isolated by flash chromatography also in 92% yield. In both cases, the reaction was carried out on a 10 mmol scale in ethanol under 15 atm of carbon monoxide, in the presence of palladium acetate (0.5 mol %) and 1,1′-bis(diphenylphosphino)ferrocene (3 mol %) using sodium acetate as a base (2 equiv). Table 1 shows a summary of reaction conditions and the corresponding results.

Using these reaction conditions, ethyl 3-chloro-5-(trifluoromethyl)pyridine-2-carboxylate (**1a**) was then prepared on a 0.5 mol scale by alkoxycarbonylation of 2,3-dichloro-5-(trifluoromethyl)pyridine (**4**). To test its robustness, the process was repeated three times, and in each case GC analysis of the reaction mixture showed complete conversion of the starting material **4** after 5 h at 80 °C. Very good selectivity was also obtained, with only 1% of diethyl 5-(trifluoromethyl)pyridine-2,3-dicarboxylate (**2a**) present in the reaction mixture. After filtration of insoluble salts, ethyl 3-chloro-5-(trifluoromethyl)pyridine-2-carboxylate was isolated with 94% yield by high vacuum distillation (see Experimental Section).

Conclusions

A process has been developed to prepare pyridine mono- and dicarboxylates by alkoxycarbonylation of 2,3-dichloropyridines. The process was scaled up from 10 mmol (routine laboratory experiments) to 0.5 mol, affording ethyl 3-chloro-5-(trifluoromethyl)pyridine-2-carboxylate with high selectively and yield.

Experimental Section

General Procedures. Reagents and solvents were reagent grade and used as received. All reactions were conducted under nitrogen. Melting points were determined on a Büchi 535 apparatus and have not been corrected. ^{1}H NMR (400 MHz) spectra were recorded on a VARIAN spectrometer. Chemical shifts are reported as parts per million relative to tetramethylsilane. Coupling constants (*J*) are given in hertz.

Alkoxycarbonylation of 2-Chloro-5-(trifluoromethyl)-pyridine (5). Synthesis of Ethyl 5-(trifluoromethyl)-pyridine-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 into a Teflon liner in the following order: ethanol (20 mL), sodium acetate (1.70 g, 20 mmol), 2-chloro-5-(trifluoromethyl)-

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pyridine (**5**) (1.80 g [97 area %], 10 mmol), 1,1′-bis-(diphenylphosphino)ferrocene (166 mg, 0.30 mmol [3 mol %]), and palladium acetate (12 mg, 0.05 mmol [0.5 mol %]). The air in the autoclave was replaced with carbon monoxide and the pressure adjusted to 15 atm. The reaction mixture was then heated to 100 °C (jacket temperature), and the reaction was carried out with stirring. After 2 h, the reaction mixture was cooled to room temperature and filtered through Celite. GC analysis indicated that the mixture consisted of >99 area % of **6a**. The mixture was concentrated under vacuum, and the product was isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:4) affording 2.04 g (>99% GC area %) of **6a** (93%). At higher scale (>50 mmol scale), after filtration through Celite, the mixture was concentrated under vacuum and the product was isolated by high vacuum distillation (bp 50 °C/0.1 mmHg, sublimation).

$C_9H_8F_3NO_2$ [219.17]. Appearance: white solid, mp 45−48 °C.

^{1}H NMR ($CDCl_3$): δ 9.01 (1H, s); 8.27 (1H, d, $J = 8.1$); 8.10 (1H, dd, $J = 8.1, 2.3$); 4.52 (2H, q, $J = 7.1$); 1.45 (3H, t, $J = 7.1$).

GC/MS (*m*/*e*): 219 (M^+); 200; 175; 147; 126.

Bis-alkoxycarbonylation of 2,3-Dichloro-5-(trifluoromethyl)pyridine (4). Synthesis of Diethyl 5-(trifluoromethyl)pyridine-2,3-dicarboxylate (2a). 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: ethanol (20 mL), sodium acetate (1.70 g, 20 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine (**4**) (2.16 g [97 area %], 10 mmol), 1,1′-bis(diphenylphosphino)ferrocene (166 mg, 0.30 mmol [3 mol %]), and palladium acetate (12 mg, 0.05 mmol [0.5 mol %]). The air in the autoclave was replaced with carbon monoxide and the pressure adjusted to 15 atm. The reaction mixture was then heated to 150 °C (jacket temperature), and the reaction was carried out with stirring. After 2 h, the reaction mixture was cooled to room temperature and filtered through Celite. GC analysis indicated that the mixture consisted of >99 area % of **2a**. The mixture was concentrated under vacuum, and the product was isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:4) affording 2.68 g (>99% GC area %) of **2a** (92%). At higher scale (>50 mmol scale), after filtration through Celite, the mixture was concentrated under vacuum, and the product was isolated by high-vacuum distillation (bp 80 °C/0.02 mmHg).

$C_{12}H_{12}F_3NO_4$ [291.23]. Appearance: colourless oil.

^{1}H NMR ($CDCl_3$): δ 9.00 (1H, s); 8.47 (1H, s); 4.50 (2H, q, $J = 7.1$); 4.42 (2H, q, $J = 7.1$); 1.43 (3H, t, $J = 7.1$); 1.40 (3H, t, $J = 7.1$).

GC/MS (*m*/*e*): 292; 291 (M^+); 246; 218; 174; 147.

Mono-alkoxycarbonylation of 2,3-Dichloro-5-(trifluoromethyl)pyridine (4). Synthesis of Ethyl 3-chloro-5-(trifluoromethyl)pyridine-2-carboxylate (1a). 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: ethanol (20 mL), sodium acetate (1.70 g, 20 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine (**4**) (2.16 g [97 area %], 10 mmol), 1,1′-bis(diphenylphosphino)ferrocene (166 mg, 0.30 mmol [3 mol %]), and palladium acetate (12 mg, 0.05 mmol [0.5 mol %]). The air in the autoclave was replaced with carbon monoxide and the pressure adjusted to 15 atm. The reaction mixture was then heated to 80 °C (jacket temperature), and the reaction was carried out with stirring. After 5 h, the reaction mixture was cooled to room temperature and filtered through Celite. GC analysis indicated that the mixture consisted of 98 area % of **1a**. The mixture was concentrated under vacuum, and the product was isolated by flash chromatography on silica gel eluting with ethyl acetate/hexane (1:4) affording 2.34 g (>99% GC area %) of **1a** (92%). At higher scale (>50 mmol scale), after filtration through Celite, the mixture was concentrated under vacuum and the product was isolated by high-vacuum distillation (bp 50 °C/0.02 mmHg).

$C_9H_7ClF_3NO_2$ [253.61]. Appearance: colourless oil.

^{1}H NMR ($CDCl_3$): δ 8.82 (1H, s); 8.06 (1H, s); 4.52 (2H, q, $J = 7.1$); 1.45 (3H, t, $J = 7.1$).

GC/MS (*m*/*e*): 254; 253 (M^+); 234; 208; 181.

Large-Scale Synthesis of Ethyl 3-Chloro-5-(trifluoromethyl)pyridine-2-carboxylate (1a). The reaction was carried out in a 2000-mL stainless steel autoclave (Büchi BEP, max pressure 100 atm, max temp 250 °C) equipped with a mechanical stirrer. The reagents were charged in the following order: ethanol (600 mL), anhydrous sodium acetate (75.5 g, 920 mmol), 2,3-dichloro-5-(trifluoromethyl)pyridine (**4**) (100.0 g [97 area %], 449 mmol), 1,1′-bis(diphenylphosphino)ferrocene (7.4 g, 13.3 mmol [3 mol %]), and palladium acetate (530 mg, 2.4 mmol [0.5 mol %]). The air in the autoclave was replaced with carbon monoxide and the pressure adjusted to 15 atm. The reaction mixture was then heated to 80 °C (jacket temperature), and the reaction was carried out with stirring. After 5 h, the reaction mixture was cooled to room temperature and filtered through Celite. GC analysis indicated that the mixture consisted of 99 area % of **1a** and 1 area % of **2a**. The mixture was concentrated under vacuum to about 120 g of crude material.

The reaction was repeated two more times in the same conditions giving always the same mixture of 99% of **1a** and 1% of **2a**.

The concentrated reaction mixtures of the three experiments were then together distilled under vacuum (68−70 °C/0.05 mmHg) affording, as a main fraction, 331.9 g of 3-chloro-5-(trifluoromethyl)pyridine-2-carboxylate (**1a**, 94% yield, based on the three experiments) with a purity of 99.6% (GC area %).

Acknowledgment

We thank our colleagues in the Chemical Research and Development department for their support and especially Dr. D. Michel as well as Dr. G. Paddon-Jones for their valuable advice during the preparation of this manuscript.

Received for review February 6, 2001.

OP010012K