Pergamon

Tetrahedron Letters 40 (1999) 3719–3722

TETRAHEDRON
LETTERS

Selective Palladium-Catalysed Carbonylations of Dichloroquinoline and Simple Dichloropyridines

Douja Najiba, Jean-François Carpentier,* Yves Castanet,*
Christophe Biot, Jacques Brocard and André Mortreux

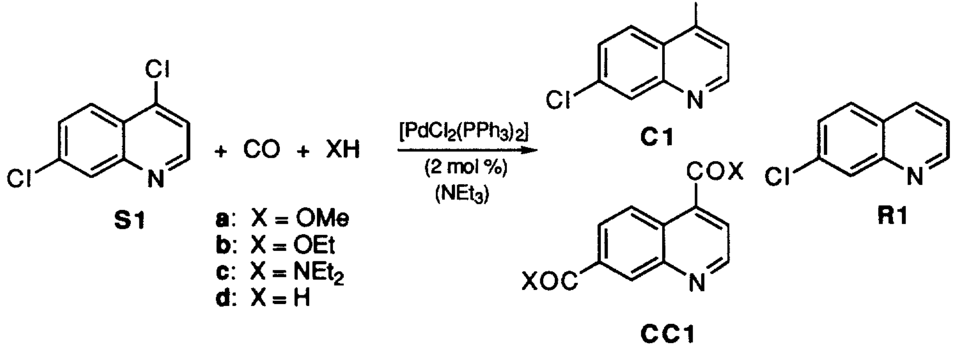
Laboratoire de Catalyse associé au CNRS, Groupe de Chimie Organique Appliquée,
Ecole Nationale Supérieure de Chimie de Lille, B.P. 108 - 59652 Villeneuve d'Ascq, France

Received 23 February 1999; accepted 16 March 1999

Abstract : Dichloroquinoline and some dichloropyridines undergo selective alkoxycarbonylation in the presence of carbon monoxide, an alcohol and $PdCl_2(PPh_3)_2$ as a catalyst, affording chloro-monoester and/or diesters in good yields under selected reaction conditions. © 1999 Elsevier Science Ltd. All rights reserved.

As part of a program directed towards the development of new anti-malarial agents,[1] we required compounds of type **C1** (Scheme 1) bearing a carbonyl function at the 4-position, e.g. an alkoxycarbonyl moiety or a carbaldehyde group. We envisioned to prepare compounds **C1** via palladium-catalysed aryl halide carbonylation, which has become in recent years an important tool in synthetic organic chemistry.[2] For this purpose, 4,7-dichloroquinoline (**S1**) is a readily available and cheap starting material. Although carbonylations are generally carried out with [expensive] aryl bromides or iodides since aryl chlorides are much less reactive,[2,3] recent reports have shown that the presence of a heteroatom can activate sufficiently the C–Cl bond.[4,5] The first example of regioselective carbonylation of a heteroaryl dichloride appeared very recently.[6] We now report that alkoxycarbonylation of **S1** and of other simple dichloropyridines can take place selectively to afford mono- and/or diesters in high yields. These esters offer an efficient entry towards the corresponding alcohols by reduction with $NaBH_4$ and to the aldehydes by subsequent Swern oxidation or direct reduction.[6]

Scheme 1



---

* email: carpentier@ensc-lille.fr; fax: +33 (0)320 436 585

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00597-3

Table 1 summarises the representative results of the carbonylation reactions of **S1**. Attempts to synthesize 7-chloro-quinoline-4-carbaldehyde (**C1d**) by direct hydrocarbonylation of **S1** under a variety of reaction conditions led systematically to poor selectivities and/or yields, because of competitive hydrogenolysis of the C–Cl function and/or inherent low activity (entry 1).[7-9] The formation of the *N,N*-diethylamido derivative **C1c**, which is by the way not such a versatile intermediate for further organic synthesis, gave intermediary results; in fact, amidocarbonylation using $HNEt_2$ as the nucleophile and the base proceeds selectively as just a small amount of the nucleophilic substitution product (7-chloro-4-*N,N*-diethylaminoquinoline) is formed besides **C1c**; however, the palladium catalyst is rather unstable under these conditions ($HNEt_2$ solvent), leaving some unreacted starting material despite a 2 mol% charge (entry 2). Alkoxycarbonylation proved to be an efficient alternative for the synthesis of compounds of type **C1**. Methyl and ethyl esters **C1a,b** are obtained in high yields, provided triethylamine concentration, temperature and reaction time are adequately adjusted.

Table 1. Palladium-catalysed carbonylation of 4,7-dichloroquinoline and its derivatives[a]

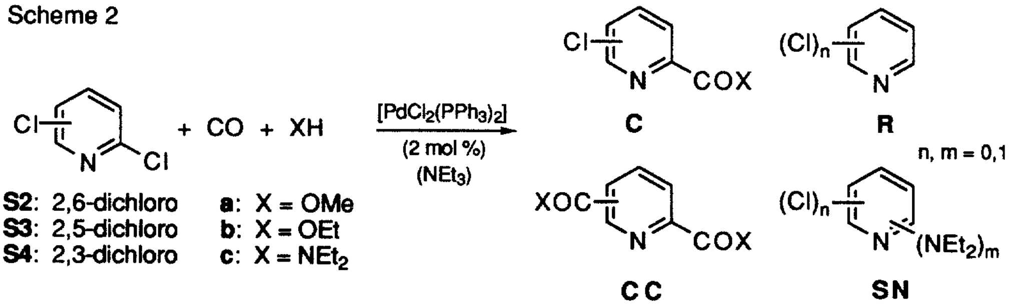
Entry	Subst.	XH	*T* (° C)	Time (h)	S conv (%)	C sel (%)	CC sel (%)	R sel (%)
1[b]	**S1**	H_2 (**d**)	140	10	51	30	<<	70
2[c]	**S1**	$HNEt_2$ (**c**)	140	16	72[c]	95	<<	<<
3	**S1**	MeOH (**a**)	130	10	38	92	2	3
4	**S1**	MeOH (**a**)	155	1	97	**96** (85)	4	<<
5	**S1**	EtOH (**b**)	130	8	91	**99** (82)	<<	<<
6	**S1**	MeOH (**a**)	140	17	99	60	40	<<
7	**C1a**	MeOH (**a**)	145	16	71	29	**71** (60)	<<

[a] Reaction conditions as described below in the typical experiment; selectivities and conversion were determined by quantitative GLC; data into brackets are isolated yields. [b] 60 bar CO/H_2 (1:1), toluene. [c] $HNEt_2$ solvent, no NEt_3 added.

A typical procedure is as follows (entry 4): a mixture of 4,7-dichloroquinoline (**S1**, 2.40 g, 12.1 mmol), methanol (15 mL), triethylamine (2.1 mL, 15 mmol), $PdCl_2(PPh_3)_2$ (170 mg, 0.24 mmol), and PPh_3 (0.31 g, 1.2 mmol) was charged under nitrogen into a 50 mL-stainless steel autoclave equipped with a magnetic stirrer bar. After sealing, the reactor was pressurised to 50 bar with carbon monoxide and heated to 150 °C for one hour. After cooling to room temperature, the solution was concentrated under vacuum. The crude product was chromatographed on silica using $CHCl_3$/heptane (4:1) as eluant to give 7-chloro-4-methoxycarbonylquinoline as an off-white powder (**C1a**, 2.25 g, 85% yield).

Carbonylation in ethanol occurs also selectively at the 4-position and no diester was detected in the experiments. In methanol, some diester progressively appears, even at relatively low temperature, the optimal reaction conditions for **C1a** being a high temperature for a short time. A longer reaction time increases the amount of diester **CC1a** to some extent but further reaction is limited by the amount of triethylamine; higher amounts of base led to increased amounts of reduction products and formation of a yet unidentified product. Diester **CC1a** can be obtained in moderate yield by methoxycarbonylation of **C1a**.

Scheme 2



Simple dichloropyridines are also cheap and available, and constitute thus interesting starting materials for the elaboration of more complex molecules via this procedure (Scheme 2). The most interesting results are given in Table 2. Thus, 2,6-dichloropyridine is converted to dimethyl diester **CC2a** in ca. 90% yield, provided a minimal amount of triethylamine is used. Although the reaction of **S2** in ethanol proceeds more slowly, it turned out impossible to produce selectively monoester **C2b**, in contrast to the reaction using 2,6-dibromopyridine.[6] Amidocarbonylation of **S2** and of 2,5-dichloropyridine (**S3**) with $HNEt_2$ led to unsatisfactory results because of large amounts of substitution products. Effective methoxycarbonylation of dichloropyridine **S3** at the 2-position gives monoester **C3a** in good yield. The reaction of 2,3-dichloropyridine (**S4**) under similar conditions proceeds in the same way, but significant amounts of 3-chloropyridine (**R4**) progressively form during the reaction course,[11] hampering the final yields.

Table 2. Palladium-catalysed carbonylation of dichloropyridines[a]

Entry	Subst.	X	*T* (° C)	Time (h)	S conv (%)	C sel (%)	CC sel (%)	R[f] sel (%)	SN[f] sel (%)
8[b]	**S2**	**a**	140	6	100	1	**90** (81)	9	-
9[c]	**S2**	**a**	140	6	93	1	37	62	-
10[c]	**S2**	**b**	110	2	20	88	12	<<	-
				4	35	69	31	<<	-
				20	88	20	79	<1	-
11[c]	**S2**	**b**	140	1	50	70	30	<<	-
				4	88	42	57	<<	-
				16	95	11	**88**	<1	-
12	**S2**	**c**	140	18	100	6	66	<1	27
13[b]	**S3**	**a**	140	7	95	**93** (76)[d]	7	<<	-
14	**S3**	**c**	150	24	67	58[d]	<<	3	39
15[b]	**S4**	**a**	140	1.5	40	91[e]	<<	9	-
				7	99	56	1	43	-
16[b]	**S4**	**a**	110	5	40	98[e]	<<	2	-
				23	69	**88**	<<	12	-

[a] See Table 1. [b] NEt_3 = 1.5 eq vs. S. [c] NEt_3 = 3 eq vs. S. [d] **C3a,b** = 5-chloro-2-(carboxy)pyridine. [e] **C4a** = 3-chloro-2-(methoxycarbonyl)pyridine. [f] Total amount of reduction or substitution by-products.

In conclusion, we have developed an effective access to some heteroaryl esters. This method is based on cheap and readily available starting materials and a simple catalytic system, and allows to isolate esters in high yields provided reactions are carried out under the correct conditions.

References and Notes

1. (a) Biot, C.; Glorian, G.; Maciejewski, L. A.; Brocard, J. S.; Domarle, O.; Blampain, G.; Millet, P.; Georges, A. J.; Abessolo, H.; Dive, D.; Lebibi, J. *J. Med. Chem.* **1997**, *40*, 3715. (b) Brocard, J.; Lebibi, J.; Maciejewski, L. WO PCT 00721, **1996**.
2. (a) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. "*Carbonylation: Direct Synthesis of Carbonyl Compounds*" Plenum, New York, 1991. (b) Beller, M. in "*Applied Homogeneous Catalysis with Organometallic Compounds*" Cornils, B.; Herrmann, W. A. Eds, VCH, Weinheim, 1996, p148.
3. (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Bartoletti, I. *J. Org. Chem.* **1974**, *39*, 3327.
4. (a) Takeuchi, R.; Suzuki, K.; Sato, N. *Synthesis* **1990**, 923. (b) ibid *J. Mol. Catal.* **1991**, *66*, 277. (c) Murata, N.; Sugihara, T., Kondo, Y., Sakamoto, T. *Synlett* **1997**, 298. (d) For palladium-mediated substitution reactions of chlorine in 2-chloroquinolines, see: Ciufolini, M. A.; Mitchell, J. W.; Roschangar, F. *Tetrahedron Lett.* **1996**, *37*, 8281.
5. Mono and dialkoxycarbonylation of 2,3-dichloro-5-(methoxymethyl)pyridine: Bessard, Y.; Roduit, J.-P. *Tetrahedron* **1999**, *55*, 393.
6. Dialkoxycarbonylation of 2,7-dichloro-1,8-naphtyridin to 2,7-di-(n-butoxycarbonyl)-1,8-naphtyridin was also reported recently: El-ghayoury, A.; Ziessel, R. *Tetrahedron Lett.* **1998**, *39*, 4473.
7. Use of HCOONa as the hydrogen source (DMF, 10 atm CO, 140 °C, 10 h) was also inefficient.
8. Hydrocarbonylation is usually performed with aryl iodides or bromides. To the best of our knowledge, no efficient synthesis of aldehyde via aryl chloride hydrocarbonylation has been reported.
9. Metallation of **S1** and subsequent formylation is a tedious and low efficient synthesis of aldehyde **C1d**. Another indirect and problematic [Se contamination] route implies SeO_2 oxidation of chlorolepidines: Bender, D. R.; Coffen, D. L. *J. Het. Chem.* **1971**, *8*, 937.
10. All products were characterized by GC-MS, ^1H and $^{13}C\{^1H\}$ NMR and are consistent with literature data or the proposed structures. 4,7-dimethoxycarbonylquinoleine (**CC1a**) is a new product: Off-white solid. ^1H NMR: δ 9.11 (d, J = 4.4, 1H, H-2), 8.88 (d, J = 9.0, 1H, H-5), 8.87 (d, J = 1.6, 1H, H-8), 8.25 (dd, J = 9.1 and 1.0, 1H, H-6), 8.01 (d, J = 4.4, 1H, H-3), 4.07 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3). $^{13}C\{^1H\}$ NMR: δ 166.4 (COO), 166.1 (COO), 150.8 (C-2), 148.6 (C-9), 134.6 (C-4), 132.4 (CH), 131.1 (C-7), 127.4 (CH), 126.1 (CH), 123.8 (C-3), 52.8 (OCH_3), 52.5 (OCH_3). MS (EI): 245 (M^+, 70%), 214 (M^+ – OMe, 100%), 186 (M^+ – CO_2Me, 40%). Anal. calculated for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71; found: C, 63.92; H, 4.28; N, 5.60. IR (KBr): ν 1735 (vs), 1728 (vs).
11. 3-chloropyridine may form either through direct, selective hydrogenolysis of 2,3-dichloropyridine, or more likely via decarbonylation of ester **C4a**; see ref 5.