HETEROCYCLES, Vol. 63, No. 2, 2004, pp. 411 - 417
Received, 31st October, 2003, Accepted, 12th December, 2003, Published online, 15th December, 2003

PALLADIUM-CATALYZED CARBONYLATION OF POLYCHLORINATED PYRIDINES. A SIMPLE LABORATORY APPROACH TO METAL CATALYZED CARBONYLATION REACTIONS

John W. Hull, Jr.* and Chen Wang

The Dow Chemical Company, Chemical Sciences Process R&D, 1707 Building,
Midland, MI 48674, USA. E-mail: JWHull@dow.com

Abstract – The palladium-catalyzed carbonylation reactions of pentachloropyridine and 2,3,4,5-tetrachloropyridine were investigated in alcoholic or aqueous solvent. The high boiling alcohol 2-ethyl-1-hexanol was an effective carbonylation solvent above 100 °C at 1 atm of CO, representing a convenient and simple method for carrying out transition metal catalyzed carbonylation reactions using standard laboratory glassware.

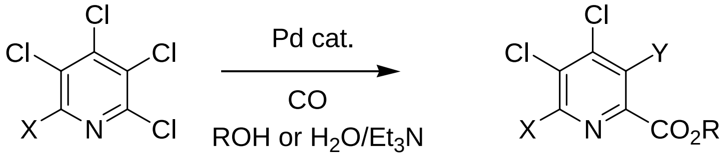
INTRODUCTION

Chlorinated pyridines exhibit a rich chemistry, including a wide range of known biological activity.[1,2] Since Milstein's seminal publication of the palladium-catalyzed carbonylation of aryl chlorides promoted by chelating phosporous ligands in 1989,[3] a number of investigators have reported the carbonylation of various substituted chlorinated pyridines,[4-7] including the important work of Beller and co-workers in which the palladium catalyzed carbonylation of simple chloropyridines was reported with high catalyst turnover numbers (TON).[5] No studies to date have reported the carbonylation of the polychlorinated systems 2,3,4,5-tetrachloropyridine (**1**) or pentachloropyridine (**2**). Since the halogenated pyridines are available commercially,[8] efficient methods of carbonylation of **1** or **2** would represent a potential low-cost preparation of pyridines having a high degree of functionalization.

RESULTS AND DISCUSSION

Carbonylation of pentachloropyridine (**2**) under CO pressure in ethanol solvent in the presence of base and a diphosphine ligand,[4-7] gave predominantly the known 2,6 diester (**4a**) (Scheme 1). The initially formed monoester intermediate (**3a)** could be observed by GC analysis, but was rapidly converted to **4a**. By using more forcing reaction conditions of extended reaction time and the ligand 1,3-bis(diphenylphosphino)propane (DPPP) in place of the butane analogue gave higher levels of a triester carbonylation product that was isolated and purified by flash chromatography. This product was readily identified by its ^{13}C NMR spectrum as the 2,3,6-triester (**5**). The deactivated nature of the 3-position relative to the 2-position for chloropyridine carbonylation reactions has been reported.[4,5] The facile formation of a 2,6-dicarbonylation product likely results from coordination of palladium with the ring nitrogen, rendering the adjacent 2- and 6-positions favored for metal insertion, with subsequent insertion of CO. The lack of products observed at the ring 4-position argues against a purely electronic effect whereby an electron-rich metal center attacks the most electrophilic 2-, 4-, or 6-position of the pyridine ring.

Carbonylation of **2** under CO pressure in aqueous Et_3N as the solvent medium, resulted in rapid consumption of CO at 80 °C, and gave the picolinic acids directly. These conditions favored the monocarbonylation product (**6)** as the main reaction product in a 59% isolated yield, along with an 8% yield of the reduction/carbonylation product (**7**). The formation of **7** likely arises from prior reduction of **2** to **1** *in-situ via* the water gas shift reaction (WGSR),[12] followed by carbonylation of **1** to form **7**. This reduction was not observed under non-aqueous conditions using alcoholic solvents. Only low levels of the 2,6-diacid (**8)** were observed when the reaction was carried out in a basic aqueous medium. This may be due to a more tightly bound catalyst metal center to the initially formed carboxylate anion of **6**, rendering a second carbonylation at the 6-position less favored than that observed in alcoholic solvents.



1: X=H
2: X=Cl

	X	Y	R
3a:	Cl	Cl	Et
3b:	Cl	Cl	C_8H_{17}
4a:	CO_2Et	Cl	Et
4b:	$CO_2C_8H_{17}$	Cl	C_8H_{17}
5:	CO_2Et	CO_2Et	Et
6:	Cl	Cl	H
7:	H	Cl	H
8:	CO_2H	Cl	H

Scheme 1. Carbonylation of Polychlorinated Pyridines (1) and (2)

With the H_2O/Et_3N solvent system, black palladium catalyst solids could be isolated from the reaction medium by acetone washing of the initial filtered catalyst. This may be helpful for the recovery of precious metal in an industrial process. Metals analysis of the recovered black solids was not attempted. The re-use of the catalyst solids in the carbonylation reaction was also not attempted, but represents a future opportunity for development of a robust commercial process.

Beller and co-workers have reported the use of neat alcohol solvent at low CO pressures as a medium for carbonylation reactions.[5,13] In the course of our work, we sought to develop a general laboratory method for performing metal catalyzed carbonylation reactions under atmospheric conditions using standard laboratory glassware. Since the solubility of CO in alcohol is known to increase with increasing chain length,[14] we chose to investigate the high-boiling and inexpensive alcohol 2-ethyl-1-hexanol, which has excellent physical properties (mp –76 °C, bp 182-186 °C, flashpoint 77 °C) for consideration in an industrial as well as laboratory process. Although no CO solubility data have been published for this alcohol, we anticipated that the solubility of CO should be sufficiently high to effect carbonylation reactions at atmospheric pressure at the temperatures above 100 °C typically required for rapid reaction rates.[5]

The carbonylation of **2** at atmospheric pressure was effected by sparging CO into a 2-ethyl-1-hexanol solution at 125-140 °C with the $Pd(OAc)_2$/DPPP catalyst system in the presence of Na_2CO_3 base. After 3 h > 90% of **2** had been consumed, and the 2,6-diester (**4b)** was the predominant product, with lesser amounts of the monoester (**3b)** present. With extended reaction times and higher temperatures small amounts of a triester was observed by GC but was not isolated. The products (**3b)** and (**4b)** were readily isolated by filtration of the reaction mixture, followed by removal of solvent *in-vacuo* and purified by flash chromatography. A CO sparge rate of 0.08 mol/h was used, and a total of 3 molar equivalents were sparged into the reaction relative to **2**. Thus, it would appear that a high efficiency of CO use is possible with this method due to adequate solubility of CO under the reaction conditions. Finally, the 2-mono- and 2,6-diesters (**3**) and (**4)** obtained by this method were readily saponified to the corresponding known acids (**6**) and (**8)** using standard conditions.[19]

Likewise, the carbonylation of tetrachloropyridine (**1)** was effected at atmospheric pressure to give a 56% isolated yield of 3,4,5-trichloro-2-picolinic acid (**7)** after LiOH saponification of the unisolated intermediate ester. The saponification step was carried out after salt removal by filtration, and utilized the 2-ethyl-1-hexanol phase as the organic solvent. With this approach, recycle of the alcohol phase back to a carbonylation reactor after extraction of the picolinic acid esters into the basic aqueous phase presents an opportunity for an industrially useful process.

In conclusion, we report here a simplified approach to laboratory scale carbonylation reactions with carbon monoxide under atmospheric conditions in the solvent 2-ethyl-1-hexanol. This method can be used to effect metal catalyzed carbonylation reactions in standard laboratory glassware without the need for more expensive pressure equipment. The reactions can be carried out in a standard well-ventilated laboratory hood, with the critical proviso that readily available electronic carbon monoxide detector and alarm systems are used in the immediate vicinity.

EXPERIMENTAL

Note: *Carbon monoxide should only be used in a well ventilated area, and the use of readily available electronic detection systems designed to alarm well below the lethal limit of 300 ppm CO is highly recommended*. Reactions with CO pressure were carried out in a well-ventilated explosion proof cubicle with a CO detection and alarm system. Reaction vessels were standard Parr pressure reactors of 316 SS or Hastelloy construction. Reactions using CO under atmospheric conditions were carried out in a well-ventilated fume hood using hand-held electronic CO detector systems in the vicinity. Polychlorinated pyridines (**1**) and (**2**) were obtained from Dow AgroSciences and Aldrich, respectively. Solvents, palladium catalysts, and phosphine ligands were obtained from Aldrich. Reverse phase gradient HPLC (CH_3CN/H_2O) analyses of pyridine and picolinic acid derivatives were carried out using an Rx C8 column and *o*-toluic acid as internal standard. Chlorinated pyridines and picolinic acid esters were also analyzed by megabore GC using a DB-5 column.

Pressure Carbonylation of 2 in Ethanol – Preparation of 3,4,5-Trichloropyridine-2,6-dicarboxylic Acid Diethyl Ester (4a)[15] and 4,5-Dichloro-2,3,6-tripicolinic Acid Triethyl Ester (5). Pentachloropyridine (**2**) (5.35 g, 0.021 mol), $Pd(OAc)_2$ (0.3054 g, 0.00136 mol), 1,4-bis(diphenylphosphino)butane (DPPB, 0.5971 g, 0.0014 mol), and Na_2CO_3 (2.27 g, 0.0214 mol) were placed into a 100 mL pressure reactor with 50 mL dry EtOH, purged with N_2 then pressurized to 21 bar CO. The reactor was stirred and heated to 100 ^{o}C for 20 h. During this time a small pressure drop was observed. The reactor was cooled and vented and the contents filtered through Celite to give 6.84 g of light orange oil after solvent evaporation. Analysis by GC showed complete conversion of **2** and a GC area % purity of 88% diester (**4a**).[15] The product was purified by flash chromatography (90/10 hexane/EtOAc) to give a colorless oil; ^{13}C NMR ($CDCl_3$) δ 163.1, 147.5, 144.3, 131.2, 62.9, 14.1 ppm; mass spectrum showed the highest fragment of *m/z* 281 (parent ion minus ethoxy radical). In a similar manner, pressure carbonylation of **2** was carried out as above but using the ligand 1,3-bis(diphenylphosphino)propane (DPPP) and an extended reaction time gave a product containing higher levels of triester (**5**). The product was purified by flash chromatography as above, and **5** was obtained as a viscous colorless oil; ^{13}C NMR ($CDCl_3$) δ 163.3, 163.1, 162.6, 150.2, 143.5, 142.5, 133.6, 132.1, 63.1, 63.0, 62.7, 14.0, 13.9 ppm; ^{1}H NMR ($CDCl_3$) δ 4.44 (m, 6 H), 1.38 (m, 9 H); mass spectrum showed the highest fragment of *m/z* 319 (parent ion minus EtO radical).

Pressure Carbonylation of 2 Under Aqueous Conditions – Preparation of 3,4,5,6-Tetrachloro-2-picolinic Acid (6).[16] Pentachloropyridine (**2**) (42.13 g, 0.1676 mol), Pd(OAc)$_2$ (0.6764 g, 0.003 mol), 1,3-bis(diphenylphosphino)propane (DPPP, 1.2189 g, 0.003 mol), hydroquinone (1.1389 g, 0.010 mol), Et$_3$N (76 mL, 0.545 mol), and 77 mL of water were weighed into a 450 mL Hastaloy C pressure reactor, purged with N$_2$ and pressurized to 27 bar CO. The reactor was stirred and heated to 80 ^{o}C for 3 h. After 45 min the reactor pressure had dropped to 20 bar, and the reactor was re-pressurized to 27 bar with additional CO. After 3 h at 80 ^{o}C, consumption of CO had ceased. The reactor was cooled and vented to give a dark homogeneous solution with a small amount of black insoluble catalyst fines. The solution was diluted with water and filtered to remove catalyst solids, which were obtained as a black tar-like material. The aqueous filtrate was acidified with conc. HCl to give a white precipitate of crude **6**. The white solid was collected on a funnel and rinsed with an excess of water and vacuum dried to give 33.71 g of dry white solid. Product analysis with HPLC using *o*-toluic acid as an internal standard showed 77% 3,4,5,6-tetrachloropicolinic acid (**6**)[16] (25.96 g, 59% yield) and 8% of the reduction product 3,4,5-trichloro-2-picolinic acid (**7**).[17] This product also contained some Et$_3$N•HCl salt, observed by NMR. The black tar-like catalyst material isolated above was dissolved in acetone and filtered to give 0.19 g of black Pd solid. Evaporation of the acetone filtrate gave 1.97 g of a brown oily residue.

In a similar manner, the same reaction was carried out with 5% Pd/C catalyst[20] (5.15 g, 0.002 mol) and DPPP (1.002 g, 0.002 mol) at 80 ^{o}C and 29 bar CO pressure for 17 h. The reaction was worked up as above to give 6.47 g of recovered black catalyst solids after drying, and 39.57 g of crude **6** as a white solid. Product analysis by HPLC using *o*-toluic acid as internal standard showed 60.8% **6** (24.06 g, 55% yield) and 15% reduction/carbonylation product (**7**) (5.94 g, 15% yield).

Carbonylation of 2 at Atmospheric Pressure in 2-Ethyl-1-hexanol. Pentachloropyridine (**2**) (20.30 g, 0.0808 mol), Pd(OAc)$_2$ (0.3429, 0.0015 mol), 1,3-bis(diphenylphosphino)propane (DPPP, 1.0199 g, 0.0025 mol), Na$_2$CO$_3$ (10.36 g, 0.098 mol) and 250 mL of 2-ethyl-1-hexanol were weighed into a 1 L three-necked glass round bottom flask fitted with a Teflon inlet sparge tube, an overhead stirrer, and a cold water condenser. The stirring reactor was heated to 125 ^{o}C with a heating mantle and controller. During heat up CO gas was sparged below the liquid surface at a rate of 0.08 mol/h. The stirring slurry remained colorless throughout the reaction. After 2.5 h at 125 ^{o}C, the reactor temperature was raised to 140 ^{o}C for another 30 min, then the heat was removed and the CO sparge stopped. The slurry was cooled, filtered, and evaporated under vacuum to give a viscous oil consisting of a mixture of 15.1% monoester (**3b**), 68.4% 2,6-diester (**4b**), and 9.6% unreacted **2** by area % GC analysis. The products were purified by flash chromatography (80/20 toluene/hexane). Monoester (**3b**): ^{13}C NMR (CDCl$_3$) δ 163.0, 147.9, 146.7, 144.5, 132.4, 128.6, 69.3, 38.3, 30.4, 28.9, 23.8, 23.0, 14.0, 11.0 ppm. Anal. Calcd for $C_{14}H_{17}NO_2Cl_4$: C, 45.07; H, 4.59; N, 3.75; Cl, 38.01. Found: C, 45.31; H, 4.74; N, 3.77; Cl, 36.94. 2,6-

Diester (**4b**): ^{13}C NMR ($CDCl_3$) δ 163.5, 147.8, 144.1, 130.9, 69.1, 38.8, 30.3, 28.9, 23.7, 23.0, 14.0, 11.0 ppm. Anal. Calcd for $C_{21}H_{34}NO_4Cl_3$: C, 55.82; H, 6.93; N, 2.83; Cl, 21.49. Found: C, 56.03; H, 7.11; N, 2.88; Cl, 21.19.

Carbonylation of 1 at Atmospheric Pressure in 2-Ethyl-1-hexanol – Preparation of 3,4,5-Trichloro-2-picolinic acid (7). To a 50-mL flask purged with N_2 were added 2,3,4,5-tetrachloropyridine (**1**)[18] (4.30 g, 0.020 mol), Na_2CO_3 (2.60 g, 0.025 mol), and 2-ethyl-1-hexanol (30 mL). The mixture was heated to 80 °C. To a separate 25-mL flask purged with N_2 were added $Pd(OAc)_2$ (340 mg, 1.5 mmol), 1,3-bis(diphenylphosphino)propane (0.770 g, 0.00187 mol), and 2-ethyl-1-hexanol (8 mL). The catalyst mixture was heated to 60 °C and was stirred for 30 min. This dark brown catalyst solution was transferred to the chloropyridine mixture through a syringe. CO gas was bubbled into the reaction mixture through a needle with its tip subsurface. The reaction mixture was heated to 120-130 °C and CO was added until GC analysis showed all of **1** was converted to the ester. The yellow reaction slurry was cooled to 80 °C and filtered. The filtrate was added to the original flask. $LiOH{\cdot}H_2O$ (1.20 g, 29 mmol) and water (10 mL) were added. The reaction was heated to 90 °C, held for 1 h, and cooled to rt. Water (10 mL) and hexanes (10 mL) were added to the mixture. The phases were separated and the aqueous phase was further extracted with hexanes (20 mL x 2). To the aqueous phase was added concentrated HCl aqueous solution until pH was about 1. The resulting white precipitate was collected by filtration, washed with cold water, and dried in an oven to give 3,4,5-trichloro-2-picolinic acid (**7**) as a white powder (2.50 g, 56%). This product has the same ^{1}H and ^{13}C NMR spectra as that of an authentic sample: mp 173-175 °C (decomp, lit.,[17] 161 ^{o}C); ^{1}H NMR (300 MHz, $DMSOd_6$) δ 8.77 (s, 1 H), 14.0 (br s, 1 H); ^{13}C NMR (75 MHz, $DMSOd_6$) δ 127.6, 131.9, 141.2, 147.4, 149.4, 165.0.

ACKNOWLEDGEMENTS

Thanks to Mike Gullo for performing HPLC analyses. Thanks to Alex Fung for analytical standards of chlorinated pyridines. Thanks to Pat Kastl for GC/MS analyses.

REFERENCES AND NOTES

1. H. Suschitzky, ‘Polychloroaromatic Compounds’, Plenum Press, London and New York, 1974, and references cited therein.
2. A. Tiwari, J.M. Riordan, W.R. Waud, and R.F. Struck, *J. Med. Chem.*, 2002, **45**, 1079.
3. Y. Ben-David, M. Portnoy, and D. Milstein, *J. Am. Chem. Soc.*, 1989, **111**, 8742.
4. R. Crettaz, J. Waser, and Y. Bessard, *Org. Proc. Res. & Dev.*, 2001, **5**, 572.
5. M. Beller, W. Magerlein, A.F. Indolese, and C. Fischer, *Synthesis*, 2001, 1098.
6. D. Najiba, J.F. Carpentier, Y. Castanet, C. Biot, J. Brocard, and A. Mortreux, *Tetrahedron Lett.*,

1999, **40**, 3719.

7. H.U. Blaser, M. Diggelmann, H. Meier, F. Naud, E. Scheppach, A. Schnyder, and M. Studer, *J. Org. Chem.,* 2003, **68**, 3725.
8. Pentachloropyridine (**2)** has been known for over a century (see ref. 1 p. 221) and can be prepared in a high yield by chlorination of pyridine (see ref. 1 p. 225 and refs. 9-11).
9. R.C. Chambers, J. Hutchinson, and W.K.R. Musgrave*, J. Chem. Soc*., 1964, 3573.
10. R.E. Banks, R.N. Haszeldine, J.V. Latham, and I.M. Young, *J. Chem. Soc*., 1965, 594.
11. H. Bender, H. Eilingsfeld, and P. Neumann, Ger. Pat. DE 3306905 (*Chem. Abstr*., 1985, **102**, 45784).
12. F.A. Cotton and G. Wilkinson, ‘Advanced Inorganic Chemistry’, 5th Ed., John Wiley and Sons, Inc., New York, 1988, pp. 1226-1227.
13. W. Magerlein, M. Beller, and A. Indolese, *J. Mol. Cat. A: Chem.*, 2000, **156**, 213.
14. R.W. Cargill, *Solubility Data Series* **1990**, *(43 Carbon Monoxide)*, 152; Kirk-Othmer, ‘Encyclopedia of Chemical Technology’, 4th Ed., John Wiley and Sons, Inc., New York, 1993, Vol. 5, p. 100.
15. M. Dohrn and P. Diedrich, *Ann.*, 1932, **494**, 284.
16. R.M. Bimber and P.H. Schuldt, U.S. Pat. 3,766,195 (*Chem. Abstr*., 1974, **80**,14855).
17. R. Graf, *J. Prakt. Chem*., 1937, **148**, 13.
18. W.J. Sell and F.W. Dootsen, *J. Chem. Soc*., 1899, **75**, 979.
19. Diesters (**4)** could be readily hydrolyzed to the known diacid (**8)** with 3 molar equivalents of 50% NaOH in aqueous MeOH at 68 ^{o}C for 1 h. The solution was acidified with 37% HCl and concentrated to give **8** as a white crystalline solid, which could be further recrystallized from warm water and dried; mp 162 ^{o}C (decomp, lit.,[16] 167-168 ^{o}C).
20. For a discussion on the use of Pd/C catalysts as effective substitutes for soluble Pd catalysts, see: A. Standler, B.H. Yousefi, D. Dallinger, P. Walla, E. Van der Eycken, N. Kaval, and C.O. Kappe, *Org. Proc. Res. Dev.,* 2003, **7**, 707 and references therein.