SHORT PAPER

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A facile preparation of pyridine- and quinoline-carboxaldehydes by palladium catalysed carbonylation†

Cedric W. Holzapfel,* Alta C. Ferreira and Wilhelmina Marais

Department of Chemistry and Biochemistry, Rand Afrikaans University, P.O. Box 524, Auckland Park, 2006, South Africa

A range of pyridine and quinoline carboxaldehydes have been prepared by palladium catalysed carbonylation from the corresponding bromides and triflates.

Keywords: carbonylation, aldehydes, lavendamycin, palladium catalysis, pyridines, quinolines

Our initial approach[1] to the synthesis of the antitumour antibiotic lavendamycin[2] was based on a facile preparation of a key amide intermediate by a one-pot aminocarbonylation of a suitably substituted 2-chloroquinoline derivative with tryptophan methyl ester. The subsequent Bischler–Napieralski cyclisation to furnish the corresponding pentacyclic lavendamycin synthon following described methods[3] unexpectedly turned out to be problematic. The difficulty in obtaining a cyclisation product in good yield was in line with observations by a French group[4] who reported similar shortcomings with the Bischler–Napieralski cyclisation in the synthesis of lavendamycin analogues. They eventually opted for the alternative Pictet–Spengler reaction of quinoline-2-carboxaldehydes and tryptophan methyl ester to furnish pentacyclic precursors to lavendamycin analogues. However, their preparation of quinoline-2-carboxaldehydes requires oxidation of 2-methylquinolines with the toxic selenium dioxide with the additional drawback that it is difficult to separate the prepared aldehydes from selenium and its derivatives. Therefore, we now report the synthesis of quinoline-2-carboxaldehyde (**1**), an appropriate lavendamycin precursor in the Pictet-Spengler reaction, as well as several other pyridine and quinoline derivatives by employing palladium catalysed carbonylation (formylation).[5]

In our initial evaluation of the available literature procedures[5] on the palladium catalysed formylation of aromatic halides involving carbon monoxide and a suitable hydrogen donor we utilised iodobenzene as substrate. The reactions were carried out in acetonitrile at 80°C under CO (5 bar) using 1 mole % $Pd(PPh_3)_4$ as catalyst in the presence of 4 – 20% equivalents of Et_3N. Although relatively good yields of benzaldehyde (> 75% on conversion, GC analysis) were obtained with CO (5 bar) together with the hydrogen donors Me_2PhSiH and Bu_4NCHO_2, detection of benzene indicated that reductive deiodination was also taking place. Significantly poorer results were obtained with other hydrogen donors such as Bu_3SnH,[5d] poly(methylhydrosiloxane) (PMHS),[5b] *etc*. Furthermore, the reaction employing the formate salt Bu_4NCHO_2 was incomplete due to catalyst decomposition and precipitation of palladium. This problem was exacerbated in the case of the slower reacting bromobenzene, requiring long reaction times and higher reaction temperatures. Catalyst decomposition is often encountered in palladium catalysed reactions including the Heck, cross-coupling and carbonylation reactions. The inclusion of certain additives such as pyridine have been claimed[5b] to improve catalyst stability. We have found consistently good results with 1.0 equivalent of 2,4,6-trimethylpyridine. However, this and other additives deactivated the catalyst and reaction times as long as 18 hours at 80°C were required to effect complete reaction.

When subjecting 2-bromopyridine to formylation under these conditions, in the presence of added 2,4,6-trimethylpyridine, the required pyridine-2-carboxaldehyde was obtained in a yield of 80 % together with pyridine. While the $Pd(PPh_3)_4$ could be replaced with $Pd(OAc)_2$ and 4-5 mole equivalents of PPh_3, other ligands, particularly bidentate phosphines, gave poor results.

In an attempt to solve the problem of competing reductive dehalogenation, the above hydride donors were replaced with hydrogen.[5a] Carbonylation of iodobenzene was thus achieved using syngas (1 : 1 CO/H_2, 30 bar) under otherwise identical conditions to furnish benzaldehyde as the only product. Application of the optimal conditions for the conversion of iodobenzene using syngas to 2-bromopyridine (**2a**) as substrate furnished **3a** in a yield of only 30%, but by increasing the temperature to 120°C the yield of **3a** was improved to 80%. Although reductive dehalogenation to pyridine was minimal (≤ 5%), other reaction products included 2,2′-bipyridyl and 2-picolinic acid.

Various other quinoline- and pyridinecarboxaldehydes (see Table 1) were prepared successfully using syngas. Both bromides and triflates appeared to be suitable leaving groups for this particular transformation. It is of interest to note that formylation of the simple aryl triflate **6** to furnish **7** gave comparable results. However, 2-bromo-8-methoxyquinoline (**4c**), appropriately substituted to furnish a lavendamycin precursor, required a CO/H_2 pressure of 40 bar to furnish the aldehyde **1** in a yield of 60%. This observation was in line with our results[1] obtained when aminocarbonylating a suitably substituted 2-chloroquinoline derivative with tryptophan methyl ester to give the required amide intermediate, which also required a higher pressure (10 bar) compared to 5 bar in the case of 2-chloroquinoline.

The carbonylation reaction using syngas was successfully repeated with another electron-rich quinoline derivative, **4d,** resulting in the isolation of **5d**. The use of syngas was preferred over the other methods from a cost perspective and ease of work-up.

Experimental

All reactions were performed under positive nitrogen or argon pressure with dry solvents, in flamed-out glass apparatus, unless otherwise specified. The carbonylation reactions under pressure (5 – 40 bar) were carried out in a Parr reactor; the necessary safety precautions were taken. All reagents were obtained from commercial suppliers and used without purification unless otherwise indicated. 2-Bromo-8-methoxyquinoline was readily prepared from the com-

* To receive any correspondence. E-mail cwh@na.rau.ac.za

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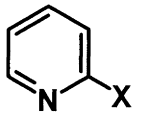
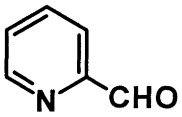
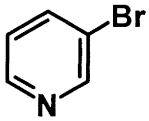
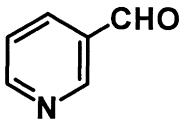
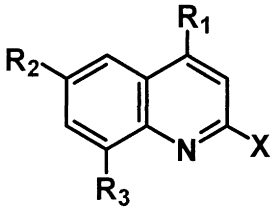
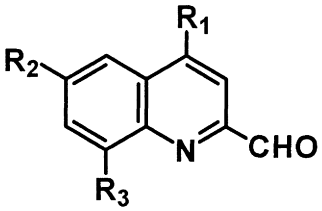
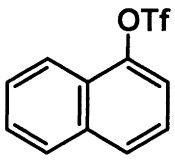
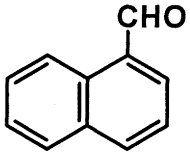
Table 1 Formylation with syngas (1:1 CO: H_2)

Substrate	Pressure /bar	Product	Yield /%
	30		80*
2a X - Br or OTf		**3a**	
	30		74[a]
2b		**3b**	
			
4a R_1=R_2=R_3=H, X=Br or OTf	30	**5a**	(88 or 60)[b]
4b R_1=Me,R_2=R_3=H, X=Br	30	**5b**	76[b]
4c R_1=R_2=H,R_3=OMe, X=Br	30 40	**1**	30[b] 60[b]
4d R_1=R_3=H,R_2=OMe, X-Br	30	**5d**	60[b]
	30		59[b]
6		**7**	

[a] GC-yield

[b] Isolated yield

mercially available 8-hydroxyquinoline involving the following sequence of reactions: protection of the hydroxyl group, *N*-oxidation with *m*-CPBA[6] and rearrangement utilising phosphorus oxybromide.[7] Solvents were purified and distilled prior to use according to standard procedures.[8] Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60 F_{254}) plates precoated (0.25 mm) with fluorescent indicator. "Flash chromatography" refers to column chromatography on Merck Kieselgel 60 (230–400 mesh) using v/v mixtures of the indicated eluents under a positive nitrogen pressure. GC analysis was performed on a Varian 3400 GC equipped with a FID using a DB-1 column (30 m) and toluene as internal standard. NMR spectra (^{1}H at 300 MHz and ^{13}C at 75.46 MHz)) were recorded on a Varian Gemini-300 spectrometer. NMR spectra were obtained as solutions in deuterochloroform ($CDCl_3$) and are reported in parts per million (ppm) from TMS. Electron-impact mass spectra were recorded on a Finnigan-MAT 8200 spectrometer at 70 eV. Accurate masses of key compounds were recorded on a VG70-70E double focusing magnetic sector mass spectrometer using a VG 11-250J data system. Melting points were recorded on a Reichert Kofler hot-stage apparatus.

General formylation procedure: A 50 ml Parr reactor equipped with an overhead stirrer bar was charged with: the 2-bromoquinoline derivative (0.63 mmol), CH_3CN (10 ml), $Pd(OAc)_2$ (0.0312 mmol), PPh_3 (0.126 mmol), tributylamine (0.882 mmol) and 2,4,6-trimethylpyridine (0.063 mmol). The bomb was flushed with argon, sealed and pressurised with syngas to 30 bar or as indicated in Table 1. The mixture was heated to 120°C for 18 hours. After cooling to room temperature the solvent was removed *in vacuo*. Flash chromatography of the residue on silica with hexane : EtOAc (1 : 1) afforded the product.

Quinoline-2-carboxaldehyde (**5a**): White crystals (60–88 %). m.p. 59 °C (lit.[9a] 50–57 °C).

4-Methylquinoline-2-carboxaldehyde (**5b**): Colourless crystals (76 %). m.p. 72 °C (lit.[9b] 76–77 °C).

8-Methoxyquinoline-2-carboxaldehyde (**1**): Colourless crystals (60 %). m.p. 101 °C (lit.[9c] 103 °C). ^{1}H NMR: δ 4.12 (3H, s), 7.06 (1H, dd J = 7.5 Hz, J, = 0.9 Hz), 7.43 (1H, dd J = 8.4 Hz, J = 0.9 Hz), 7.58 (1H, dd J = 8.4 Hz, J = 8.4 Hz), 8.02 (1H, d J = 8.4 Hz), 8.24 (1H, dd J = 8.4 Hz, J, = 0.4 Hz), 10.27 (1H, d J = 0.9 Hz). ^{13}C NMR: δ 56.29, 108.46, 117.82, 119.49, 129.68, 131.19, 137.20, 139.72, 151.28, 155.86, 193.48. MS *m*/*z*: 187 (M^+, 100 %), 158 (78 %), 142 (18 %), 128 (68 %). HREI-MS *m*/*z*: 187.0625 ($C_{11}H_9NO_2$ requires 187.0633).

6-Methoxyquinoline-2-carboxaldehyde (**5d**): Colourless crystals (60 %). m.p.: 102–103 °C (lit.[9c] 105 °C). ^{1}H NMR: δ 3.96 (3H, s), 7.11 (1H, d J = 3.0 Hz), 7.45 (1H, dd J = 9.3 Hz, J = 3.0 Hz), 7.98 (1H, d J = 8.4 Hz), 8.11 (1H, dd J = 9.3 Hz, J = 0.9 Hz), 8.16 (1H, dd

J = 9.3 Hz, J = 0.9 Hz), 10.27 (1H, d J = 0.9 Hz). ^{13}C NMR: δ 56.29, 108.46, 117.82, 119.49, 129.68, 131.19, 137.20, 139.72, 151.28, 155.86, 193.48. HREI-MS *m*/*z*: 188.0712 ($C_{11}H_9NO_2$ requires 188.0712)

1-Naphthaldehyde[9d] (**7**): Oil (59 %).

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