SHORT PAPER

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Application of aminocarbonylation in the synthesis of a lavendamycin synthon†

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An efficient route to a key intermediate in the synthesis of lavendamycin from a suitably substituted 2-chloroquinoline derivative *via* aminocarbonylation with tryptophan methyl ester as nucleophile, is reported.

Keywords: aminocarbonylation, lavendamycin, palladium catalysis, tryptophan, quinolines

Lavendamycin **(1)**[1] is an antitumour antibiotic isolated from *Streptomyces lavendulae* and is structurally related to streptonigrin**(2)**[2]. Our objective was to develop a general method which will allow access to lavendamycin as well as a range of its analogues required for the study of physiological structure–activity relationships. We recently reported[3] the successful application of palladium catalysed cross coupling strategies[4] towards the synthesis of the streptonigrin tetracyclic ring system. While application of this approach to the synthesis of lavendamycin **(1)** is still under investigation the improvement of published methods[5] is also receiving attention. These methods often involves the preparation of an intermediate amide such as **3a** from a suitably substituted quinaldic acid and a tryptophan derivative followed by a Bischler–Napieralski cyclisation to furnish a lavendamycin pentacyclic precursor. However, the synthesis of the required quinaldic acid via the corresponding nitrile is not only tedious and difficult (involving several oxidation and reduction reactions), but also suffer from low overall yields.[6] Therefore, it was envisaged in our strategy that a pivotal step to the key intermediate amide **(3b)** would involve a one pot palladium catalysed aminocarbonylation reaction[7] of an appropriately substituted 2-chloroquinoline derivative **(4a)** with tryptophan as the nucleophile.

Some initial model reactions were undertaken to gauge the viability of such an approach. Thus, 2-chloroquinoline **(4b)**, a slight excess of benzylamine, 25 mole % of $PdCl_2(PPh_3)_2$ and tri-*n*-butylamine was heated to 95°C in the presence of carbon monoxide at atmospheric pressure to furnish product **(5)** in a yield of 84%. On changing the nucleophile to tryptophan methyl ester (as the HCl salt) the addition of a solvent such as DMF was necessary. However, the aminocarbonylation to provide **3c** proceeded in a very low yield (6.5%) and could not be improved substantially by using the tryptophan methyl ester as the free base or by changing to another ligand, *e.g.* P(*o*-tol)$_3$. At a higher carbon monoxide pressure (4 bar) the yield improved to 42%. However, on substituting the tryptophan methyl ester HCl salt with the corresponding trifluoracetate salt **(6)** the aminocarbonylation proceeded smoothly. The reaction was completed within 6 hours at 80°C under 4 bar of CO to furnish the required amide **(3c)** in a yield of 70%. The aminocarbonylation was also successfully repeated with tryptamine as nucleophile to furnish amide **(3d)** (87%).

Appropriately substituted 2-chloroquinolines were subjected to the same protocol. However, aminocarbonylation of 2-chloro-8-methoxyquinoline **(4a)** failed and furnished mainly unchanged starting material, even in the presence of more catalyst. Poor results were also obtained with the more reactive tryptamine indicating that the difficulties could possibly be inherent to the substrate **(4a)**. Several other quinoline derivatives (*e.g.* **4c** and **4d**) also failed to undergo efficient aminocarbonylation under the described conditions. However, initial aminocarbonylation of 2-chloro-8-methoxyquinoline **(4a)** in the presence of **(6)** at 105°C under 4 bar of CO yielded the amide **(3b)** in a yield of 40%, although palladium precipitation was observed. By increasing the CO pressure to 5 bar and eventually to 10 bar, palladium precipitation no longer occurred and the yields of the amide **(3b)** could be increased to 60% and 89%, respectively. The reaction was also successfully repeated with the benzyl derivative **(4e)** resulting in a quantitative conversion to **3e**. While the difficulty experienced with the carbonylation of the electron rich systems **4a** and **4e** compared to that of **4b** could be due to electronic effects, the possibility that the former compounds behave as bidentate ligands, thus deactivating the catalyst, cannot be excluded. Some support for the latter proposition is provided by the fact that another electron rich derivative, 2-chloro-6-methoxyquinoline **(4f)** could be readily aminocarbonylated. The reaction with **6** proceeded smoothly under 4 bar and 105°C with no palladium precipitating and the corresponding amide **(3f)** obtained in a yield of 82%.

The next step in the synthesis of lavendamycin, the Bischler–Napieralski cyclisation, has been previously employed by the groups of Kende[8] and Rao,[5,6] reporting respective yields of 40 and 88%. However, when using the experimental conditions which Rao reported (xylene, 4 h at reflux) for amide **(3c)**, the pentacyclic product **7** was isolated in the unexpectedly low yield of 23% together with polymeric material. Similar disappointing results were recently reported by a French group.[9] The application of other reaction conditions for the Bischler Napieralski cyclisation gave no better results.[10] Variation of the reaction conditions including the addition of a Lewis acid such as $ZnCl_2$, lowering the reaction temperature (xylene, 90°C) or changing the reagent to triflic anhydride did not improve the yield. Furthermore, the attempted cyclisation of the tryptamine derived amide **(3d)** resulted only in degradation of the starting material while cyclisation of the lavendamycin precursor **(3b)** gave **8** in a yield of 18%.

It is of interest to note that no cyclisation products were obtained when the reaction was carried out in degassed solvents indicating that oxygen is required for the process of aromatisation. Clearly unoxidised indolic intermediates are polymerised rapidly under the reaction conditions. Since indoles are acid-sensitive compounds it was anticipated that better yields could be achieved by reducing exposure of cyclised products to the acidic reaction conditions. Thus, yields as high as 60% were obtained over three to four successive steps by stopping the reaction at relatively low

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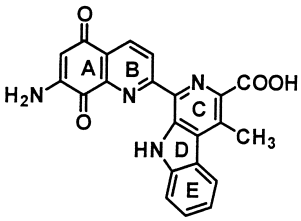
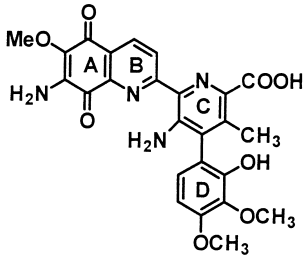
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

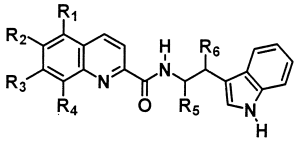


1 lavendamycin



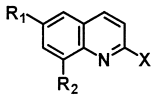
2 streptonigrin

Scheme 1

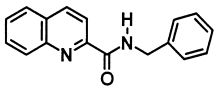


3a $R_1 = OCH_3$ or NO_2, $R_2 = H$, $R_3 = Br$,
$R_4 = OCH_3$, $R_5 = CO_2CH_3$, $R_6 = CH_3$
3b $R_1 = R_2 = R_3 = R_6 = H$, $R_4 = OCH_3$, $R_5 = CO_2CH_3$
3c $R_1 = R_2 = R_3 = R_4 = R_6 = H$, $R_5 = CO_2CH_3$
3d $R_1 = R_2 = R_3 = R_4 = R_5 = R_6 = H$
3e $R_1 = R_2 = R_3 = R_6 = H$, $R_4 = OBn$, $R_5 = CO_2CH_3$
3f $R_1 = R_3 = R_4 = R_6 = H$, $R_2 = OCH_3$, $R_5 = CO_2CH_3$

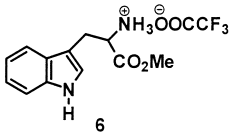
Scheme 2



4a $R_1 = H$, $R_2 = OMe$, X = Cl
4b $R_1 = R_2 = H$, X = Cl
4c $R_1 = H$, $R_2 = OMe$, X = Br
4d $R_1 = H$, $R_2 = OCH_2CH{=}CH_2$, X = Cl or Br
4e $R_1 = H$, $R_2 = OBn$, X = Cl
4f $R_1 = OMe$, $R_2 = H$, X = Cl

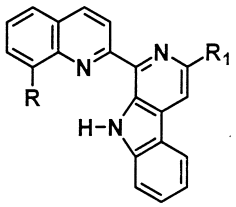


5



6

Scheme 3



7 R = H, $R_1 = CO_2Me$
8 R = OMe, $R_1 = CO_2Me$

Scheme 4

conversion (< 30%) and recycling the unchanged starting material. Our approach[11] to the completion of the synthesis involves introduction of the methyl substituent into the C-ring using DoM-methodology[12] followed by known functional group transformations.[5,6] The DoM approach readily allows preparation of lavendamycin analogues.

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 (2–10 bar) were carried out in thick-walled pressure vessels of glass or stainless steel while the necessary safety precautions were taken. All reagents were obtained from commercial suppliers and used without purification unless otherwise indicated. 2-Chloro-8-methoxyquinoline **(4a)**[13] and 8-benzyloxy-2-chloroquinoline **(4e)** were readily prepared from the commercially available 8-hydroxyquinoline involving the following sequence of reactions: protection of the hydroxyl group, *N*-oxidation with *m*-CPBA[14] and a rearrangement step utilising phosphorous oxychloride.[15] Solvents were purified and distilled prior to use, according to standard procedures.[16] Dichloro-*bis*-(triphenylphophine)palladium(II) was prepared as per literature procedures1[17] and stored under argon at –20°C. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60 F_{254}) plates precoated (0.25 mm) with fluorescent indicator. Indoles were detected using Van Urk's spray reagent (4-dimethylaminobenzaldehyde-HCl) followed by heating over an open flame. '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. NMR spectra (^{1}H (300.060 MHz) and ^{13}C (75.459 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). 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 Koffler hot-stage apparatus, and are uncorrected. Optical rotations were obtained on a Jasco DIP 370 digital polarimeter.

N-[2-(indolyl-3)-1-methoxycarbonyl-ethyl]-8-methyloxy-2-quinaldic acid amide **(3b)**: To a 50 ml stainless steel pressure vessel equipped with a magnetic stirrer bar were added sequentially: the 2-chloro-8-methoxyquinoline **(4a)** (80 mg, 0.413 mmol), DMF (4 ml), $PdCl_2(PPh_3)_2$ (36 mg, 0.0413 mmol), tryptophan methyl ester trifluoroacetate salt **(6)** (150mg, 0.455 mmol) and triethylamine (0.22 ml, 1.65 mmol). The system was sealed, cooled down with liquid nitrogen, evacuated, purged with argon and charged with CO (10 bar). The mixture was heated to 105°C for 11 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 **(3b)** (150 mg, 89%) as orange brown oil, $[\alpha]_D^{22}$: -21.51 (*c*, 1.0, MeOH). ^{1}H NMR δ: 3.43 (2H, dd $J_{2',1'}$ = 6.0 Hz, J' = 1.8 Hz, H-2′), 3.61 (3H, s, CO_2CH_3), 3.96 (3H, s, OCH_3), 5.06 (1H, dt $J_{1',2''}$ = 7.8 Hz, $J_{1',NH}$ = 6.0 Hz, H-1′), 7.96–7.09 (3H, , H-2″, H-5″ and H-7), 7.11 (1H, d J = 2.1 Hz, H-2″), 7.25 (1H, d $J_{7'',6''}$ = 8.7 Hz, H-7″), 7.31 (1H, d $J_{4',5'}$ = 8.1 Hz, H-4″), 7.45 (1H, t, $J_{6,7} = J_{6,5}$ = 7.8 Hz, H-6), 7.60 (1H, d $J_{5',6'}$ = 7.5 Hz, H-5′), 8.14 (1H, br s, N*H*), 8.15 (1H, d $J_{4,,3}$ = 8.4 Hz, H-4), 8.21 (1H, d $J_{,3,4}$ = 8.4 Hz, H-3), 8.83 (1H, d, J = 7.8 Hz, -N*H*). ^{13}C NMR δ: 27.95 (C-2′), 52.18 (CO_2CH_3), 53.14 (OCH_3), 55.92 (C-1′), 108.32 (C-7), 109.66 (*ipso*, C-3″), 111.09 (C-7″), 118.37 (C-5), 119.05, 119.09 and 119.19 (C-3, C-4″ and C-6″), 121.61 (C-5″), 123.07 (C-2″), 128.19 (C-6), 131.75 and 131.88 (C-4 and C-3″a), 136.09 (C-7″a), 137.03 (C-4), 138.29 (C-8a), 147.70 (*ipso*, C-2), 155.39 (*ipso*, C-8), 164.30 (-*C*ONHCH$_2$-), 172.15 (-*C*O$_2$CH$_3$). MS *m/z*: 404 (M^+ + 1, 12%), 201 (M^+- $(OCH_3)C_9H_6N_1CONH$, 26%), 186 (M^+- NHCH $(CO_2CH_3)CH_2C_8H_6N$, 9%), 158 (M^+- $CONHCH(CO_2CH_3)$ $CH_2C_8H_6N$, 32%). HREI-MS *m/z*: 403.1538, ($C_{23}H_{21}N_3O_4$ requires 403.1532)

*2-(3-Methoxycarbonyl-*β*-carbolin-1-yl)-8-methoxyquinoline* **(8)**: A solution of amide **(3b)** (83 mg, 0.204 mmol) and $POCl_3$ (0.5 ml) in dry xylene (5 ml) was heated under reflux with stirring for 2 hours. The flask was cooled and the contents poured over crushed ice while stirring. This solution was neutralised to pH = 8 with sodium carbonate followed by extraction with dichloromethane (3 × 30 ml portions). The combined organic fractions were dried over $MgSO_4$ and the solvent removed *in vacuo*. The residue was purified by flash chromatography using hexane:EtOAc (3:1) as eluent to afford **(8)** (18 mg, 23%) as light yellow crystals, M.p. 140°C. ^{1}H NMR δ: 4.10 (3H, s, -O*CH*$_3$), 4.26 (3H, s, COO*CH*$_3$), 7.14 (1H, dd $J_{7,6}$ = 7.8 Hz, $J_{7,5}$ = 1.5 Hz, H-7), 7.35 (1H, ddd $J_{6',7'} = J_{6',5'}$ = 8.1 Hz, $J_{6',8'}$ = 1.2 Hz, H-6′), 7.41–7.70 (4H, m, H-5, H-6, H-7′, and H-8′), 7.23 (1H, d $J_{5',6'}$ =9.0 Hz, H-5′), 8.32 (1H, d $J_{4,3}$ = 8.7 Hz, H-4), 8.95 (1H, d $J_{3,4}$ = 8.7 Hz, H-3), 8.96 (1H, s, H-4′), 12.50 (1H, br s, -N*H*). ^{13}C NMR δ: 52.69 (-COO*CH*$_3$), 56.29 (-O*CH*$_3$), 107.82 (C-7), 112.33 (C-8′), 118.57 (C-4′), 119.49 (C-3), 119.55 (C-5), 120.68 (C-6′), 121.61 (C-5′a), 121.93 (C-5′), 127.18 (C-6), 128.75 (C-7′), 128.82 (C-4a), 136.43 (C-4), 138.75 (C-3′), 130.45 133.13, 136.53, 136.84, 137.85 (5 quaternary carbon signals), 141.29 (C-8a), 155.54 (C-8), 166.72 (-*C*OOCH$_3$). MS *m/z*: 384 (M^+ + 1, 45%). HREI-MS *m/z*: 383.1266,

($C_{23}H_{17}N_3O_3$ requires 383.1269). The yield of this reaction was improved to 60% by stopping the reaction at 30% conversion and recycling of the starting material.

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