Facile Synthesis of Methyl 2-amino-3-(2-methyl-3-quinolyl)propanoate†

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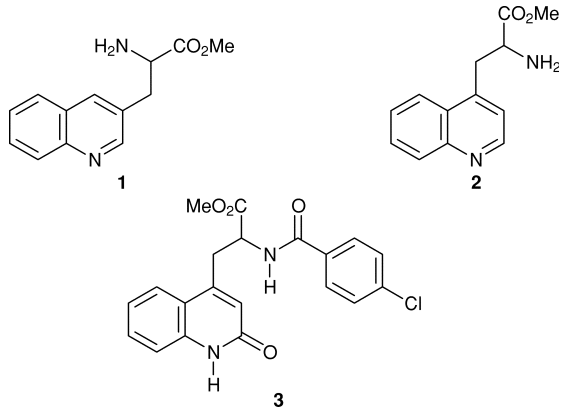
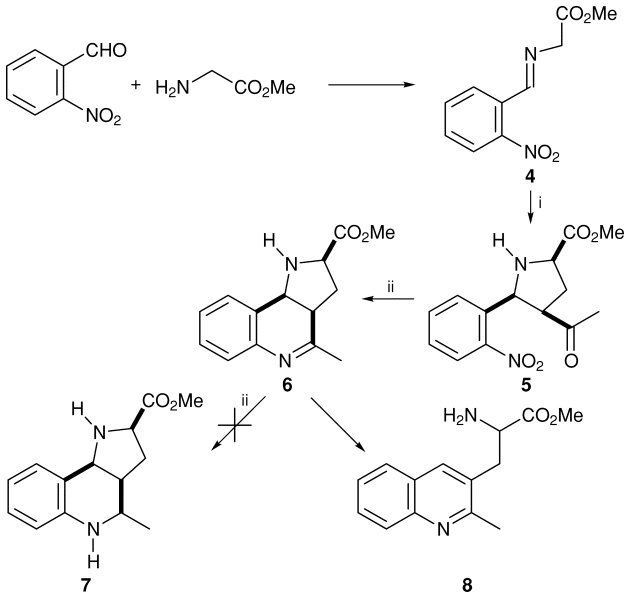
Methyl 4-acetyl-5-(2-nitrophenyl)pyrrolidine-2-carboxylate **5**, readily available in one step by a 1,3-dipolar cycloaddition, undergoes reduction, cyclisation and fragmentation to the corresponding quinoline when treated with hydrogen and palladium.

Quinolines are common in nature and form the core unit of a number of bioactive substances.[1] 3-Quinolylalanine **1** is a useful unusual amino acid and has been used in the synthesis of bioactive peptides,[2] and 4-quinolylalanine **2** is an intermediate in the synthesis of the antiulcer drug (*S*)-(−)rebamipide **3**[3] (Scheme 1). Methods for preparing quinolines have been reviewed[4] with a popular method being the Friedlander quinoline synthesis. We now report a mild facile approach to the synthesis of 2-methylquinolinylalanine methyl ester based on a three component coupling, namely *o*-nitrobenzaldehyde, glycine methyl ester and methyl vinyl ketone.



Scheme 1

In model studies directed towards the synthesis of the substituted pyrroloquinoline skeleton **7**, present in martinelline,[5] the 1,3-dipolar cycloaddition of imine **4**, derived from glycine methyl ester and *o*-nitrobenzaldehyde, with methyl vinyl ketone was investigated (Scheme 2). Using the modified literature conditions,[6] silver acetate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetonitrile the reaction was complete within 1 h at room temperature and gave the all-*cis* trisubstituted pyrrolidine **5** in 34% isolated yield. As expected the reaction was completely regio- and stereo-selective giving only the racemic diastereoisomer **5**. The low yield of **5** is largely due to the instability of the imine **4** in the presence of base (DBU). Reduction of pyrrolidine **5** with hydrogen and palladium gave none of the expected pyrroloquinoline **7** but instead gave predominantly the quinoline derivative **8**. Presumably the intermediate *β*-amino imine **6** is unstable, even under the reducing reaction conditions, and simply aromatises by loss of amine, giving amino acid ester **8**. When the hydrochloride salt of the amine **5** was employed a much cleaner reaction results and quinoline **8** was isolated in 72% yield after a basic work-up.



Scheme 2 (i) Methyl vinyl ketone, DBU, silver acetate in MeCN; (ii) hydrogen, Pd/C

In conclusion we have demonstrated that 1,3-dipolar cycloaddition is an effective method for coupling the components glycine methyl ester, *o*-nitrobenzaldehyde and methyl vinyl ketone for a quinoline synthesis. Since good asymmetric induction is achieved when chiral *α*,*β*-unsaturated ketones are employed in 1,3-dipolar cycloaddition reactions,[7] this methodology should be amenable to chiral quinoline amino acids.

Experimental

IR spectra were recorded on a Perkin-Elmer Model 983G instrument coupled to a Perkin-Elmer 3700 Data Station as potassium bromide (KBr) disks or films (liquids), ^{1}H NMR spectra at 300 and 500 MHz using General Electric QE 300, Bruker DPX 300 and DRX 500 spectrometers. Chemical shifts are given in ppm (δ) downfield from tetramethylsilane as internal standard. Mass spectra were recorded using a Double Focusing Triple Sector VG Auto Spec and accurate molecular masses were determined by the peak matching method using perfluorokerosene as standard reference and were accurate to within ±0.006 mass unit. In both cases chemical ionisation was employed giving rise to M + 1 peaks. Analytical TLC was carried out on Merck Kielselgel 60_{254} plates and the spots visualised using a Hanovia Chromatolite UV lamp. Flash chromatography was effected using Merck Kielselgel 60 (230–400 mesh).

Methyl 4-Acetyl-5-(2-nitrophenyl)pyrrolidine-2-carboxylate **5**.—A solution of glycine methyl ester hydrochloride (1.82 g, 14.5 mmol), ethyldiisopropylamine (1.88 g, 14.5 mmol) and *o*-nitrobenzaldehyde (2.00 g, 13.2 mmol) in methylene chloride (10 ml) was stirred for 20 min. The solvent was then removed at room temperature and dry acetonitrile (40 ml) added to the residue. This slurry was added to a mixture of silver acetate (4.41 g, 26.4 mmol), DBU (4.02 g, 26.4 mmol) and methyl vinyl ketone (4.02 g, 26.4 mmol) in dry acetonitrile (60 ml) at 0 °C with magnetic stirring. After 20 min saturated ammonium chloride solution (50 ml) was added followed

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by diethyl ether (30 ml) and methylene chloride (80 ml) and stirred for 10 min. The insoluble material was filtered off, and the organic layer separated and dried over magnesium sulfate. Concentration gave a brown oil which was purified by flash chromatography to give compound **5** (1.31 g, 34%) as a clear oil, R_f 0.55 (ether) [$C_{14}H_{16}N_2O_5$ requires 293.1137 (M + 1). Found 293.1137]; $\tilde{\nu}_{max}$ (KBr, film) 3339, 2954, 1741, 1710, 1525 cm^{-1}. δ_H ($CDCl_3$, 500 MHz). Coupling constants (J) are given in Hz. 1.67 (3 H, s, CH_3CO), 2.36 (1 H, dt, $J = 13.1$, 8.3, NCHC*H*H), 2.45 (1 H, ddd, $J = 13.1$, 7.7, 5.1, NCHCH*H*), 3.82 (3 H, s, OCH_3), 3.82 (1 H, td, $J = 8.0$, 5.3, CH_3COCH), 3.94 (1 H, t, $J = 7.7$, NC*H*CO_2Me), 4.91 (1 H, d, $J = 8.0$, ArC*H*N), 7.41 (1 H, td, $J = 7.4$, 1.4, ArH-4), 7.61 (1 H, td, $J = 7.7$, 1.2, ArH-5), 7.87 (1 H, dd, $J = 7.9$, 1.3, ArH-6), 7.91 (1 H, dd, $J = 8.1$, 1.3, ArH-3). δ_C ($CDCl_3$, 75.438 MHz) 31.4, 33.0, 52.7, 54.9, 59.6, 60.9, 124.7, 128.9, 130.1, 133.8, 135.2, 149.3, 173.9, 209.0. m/z 293 (M + 1, 12), 244(15), 231(62), 214(28), 171(33), 143(85), 83(100), 49(100%).

Methyl 2-Amino-3-(2-methyl-3-quinolyl)propanoate **8**.—Ether (10 ml) was saturated with hydrogen chloride. This was then added to a solution of compound **5** (90 mg, 0.31 mmol) in methanol (5 ml) and the resulting solution stirred for 10 min. The solvents were removed under reduced pressure and methanol (10 ml) added followed by 10% palladium on charcoal (5 mg). The resulting mixture was placed under 1 atm of hydrogen for 15 h. The solution was filtered through Celite and saturated sodium bicarbonate (5 ml) added to the filtrate. This was extracted with methylene chloride (3 × 10 ml), dried over magnesium sulfate and concentrated. Flash chromatography gave compound **8** (54 mg, 72%) as a pale yellow oil, R_f 0.32 (ethyl acetate–methanol 19:1) [$C_{14}H_{16}N_2O_2$ requires 245.1290 (M + 1). Found 245.1290]; $\tilde{\nu}_{max}$ (KBr, film) 3367, 2951, 1737 cm^{-1}. δ_H ($CDCl_3$, 300 MHz) 1.87 (2 H, br, NH_2), 2.74 (1 H, s, CH_3), 2.95 (1 H, dd, $J = 14.2$, 8.5, ArC*H*H), 3.31 (1 H, dd, $J = 14.2$, 5.2, ArCH*H*), 3.71 (3 H, s, CH_3O), 3.76 (1 H, dd, $J = 8.5$, 5.2, CH_2CHCO_2Me), 7.56 (1 H, s, Ar H-4), 7.57 (1 H, m, ArH-6), 7.72 (1 H, t, $J = 8.5$, ArH-7), 7.78 (1 H, d, $J = 8.0$, ArH-5), 8.72 (1 H, d, $J = 8.7$, Hz ArH-8). δ_C ($CDCl_3$, 125.758 MHz) 15.0, 39.0, 52.3, 54.6, 119.7, 126.2, 127.6, 127.8, 129.9, 130.7, 139.2, 140.3, 146.2, 175.0. m/z 245 (M + 1, 10), 243(19), 183(25), 167(18), 158(64), 156(100), 114(27), 88(25%).

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