Nornicotine-Organocatalyzed Aqueous Reduction of α,β-Unsaturated Aldehydes

Supporting Information

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General Procedures

All reagents were purchased from Sigma-Aldrich, Fisher, Alfa Aesar, TCI, or Toronto Research Chemicals and used as received. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Varian INOVA-400 spectrometer at 400 MHz and 100 MHz respectively. Electrospray ionization (ESI) mass spectrometry experiments were performed on an Agilent ESI-TOF mass spectrometer. Preparative HPLC was performed on a Shimadzu preparative HPLC (model LC-8A) equipped with a column oven and UV detector (model SPD-10A) using preparative Vydac RP-C$_{18}$ columns. Yields less than 2 mg were determined by $^1$H NMR using 2,5-dimethylfuran as an internal standard. 1 With the exception of 2-methoxy-4-(3-oxopropyl)phenyl ethanoate, all other compounds were either commercially available or have been previously described. All analytical data was consistent with literature values.

General procedure for the nornicotine-catalyzed aqueous reduction of $\alpha$,$\beta$-unsaturated aldehydes

To a reaction vessel containing cinnamaldehyde (10 mg), 1,4-dihydropyridine-3,5-dicarboxylic acid (4) (1.2 equiv.) and NaHCO$_3$ (2.4 equiv.) was added DMSO (0–1.2 mL) and phosphate buffer (200 mM, pH 7.0, 2.8–4 mL). Nornicotine (20–200 mol%) was added and the mixture was capped and placed on an orbital shaker (160 rpm) at 32 °C for 0.5–23 h. Brine (5 mL) was added and the reaction mixture was extracted with DCM (3 × 5 mL). The organic layer was concentrated and the reduced product was isolated by preparative TLC (chloroform/acetone or hexanes/ethyl acetate).

2-Methoxy-4-(3-oxopropyl)phenyl ethanoate. $^1$H NMR (CDCl$_3$) δ 2.30 (s, 3 H), 2.79 (m, 2H), 2.94 (m , 2H), 3.81 (s, 3 H), 6.76 (dd, $J$ = 1.8, 8.0 Hz, 1 H), 6.80 (d, $J$ = 1.8 Hz, 1 H), 6.94 (d, $J$ = 8.0 Hz, 1 H), 6.94 (t, $J$ = 1.2 Hz, 1 H); $^{13}$C NMR (CDCl$_3$) δ 20.6, 27.9, 45.2, 55.8, 112.6, 120.3, 122.7, 138.1, 139.3, 150.9, 169.1, 201.2. HRMS (ESI-TOF): $m/z$ calcd for C$_{12}$H$_{14}$O$_4$Na, 245.0784 [M+Na]$^+$, found: 25.0786.

For the reaction using (E)-2-methoxy-4-(3-oxoprop-1-enyl)phenyl ethanoate, 3.4 equiv. of NaHCO$_3$ was used and the reduced product was purified by preparative RP-HPLC after diluting the reaction mixture with DMSO (2 mL) and acetic acid (1 mL). Gradient RP-HPLC conditions: 15-45% B (solvent B = acetonitrile with 0.09% TFA, solvent A = water with 0.1% TFA) over 30 min starting a 10 min with a solvent flow rate of 10 mL min$^{-1}$; UV detection at 214 and 254 nm; 3f retention time: 23.7 min.

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