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Enantioselective synthesis of (+)(*R*)- and (-)(*S*)-nicotine based on Ir-catalysed allylic amination

Carolin Welter, Rosa M. Moreno, Stephane Streiff and Günter Helmchen*

Ethyl (2*E*)-3-pyridine-3-ylacrylate

Triethyl phosphonoacetate (51.0 mL, 257 mmol) was added dropwise to a cooled (-40°C), stirred suspension of NaH (6.36 g, 265 mmol) in dry THF (200 mL). The solution was allowed to warm to room temperature. After 15 min, it was cooled again to –40°C and 3-pyridine-carboxaldehyde (24.88 g, 233 mmol) was added slowly. The resultant dark red solution was stirred at room temperature until TLC monitoring showed complete reaction. Diethyl ether (250 mL) and saturated NH_4Cl solution (250 mL) were added. After separating the layers, the aqueous phase was extracted with diethyl ether and the combined organic layers were washed with brine, dried over $MgSO_4$, and the solvents were removed under reduced pressure. The residue was subjected to flash chromatography (silica, petroleum ether/ethyl acetate 1:1) to give ethyl (2*E*)-3-pyridine-3-ylacrylate (40.63 g, 99%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 250MHz): δ 1.32 (t, *J* = 7.1 Hz, 3 H), 4.25 (q, *J* = 7.1 Hz, 2 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 7.31 (dd, *J* = 7.8 Hz, *J* = 4.8 Hz, 1 H), 7.66 (d, *J* = 16.1 Hz, 1 H), 7.81 (dt, J= 8.0 Hz, *J* = 1.8 Hz, 1 H), 8.57 (dd, *J* = 4.8 Hz, *J* = 1.7 Hz, 1H), 8.72 (s, 1 H). HR-MS m/z (EI+) calcd. for $C_{10}H_{11}NO_2$ (M^+) 177.079, found 177.078.

(2*E*)-3-Pyridine-3-ylprop-2-ene-1-ol

A 1 M solution of DIBAL-H in petroleum ether (228 mL, 228 mmol) was slowly added to a cooled (–40°C), stirred solution of (2*E*)-3-pyridine-3-ylacrylate (20.20 g, 114 mmol) in diethyl ether (300 mL). The mixture was magnetically stirred at room temperature for 20 h, then cooled to 0°C. Water (15 mL), 1 M NaOH (10 mL) and then again water (20 mL) were added dropwise. After 2 h of stirring a white precipitate had formed, which could be filtered off. The filtrate was concentrated under reduced pressure, and the residue was submitted to flash chromatography (silica, ethyl acetate, 0.1% Et_3N) to give (2*E*)-3-pyridine-3-ylprop-2-ene-1-ol (9.37 g, 61%) as a yellow-brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.35 (bs, 1 H), 4.34 (dd, *J* = 5.2 Hz, *J* = 1.3 Hz, 2 H), 6.41 (dt, *J* = 16.1 Hz, *J* = 5.0 Hz, 1 H), 6.59 (d, *J* = 16.1 Hz, 1 H), 7.23 (dd, *J* = 7.7 Hz, J = 4.5 Hz, 1 H), 7.68 (dd, *J* = 8.0 Hz, *J* = 1.8 Hz, 1 H), 8.44 (dd, *J* = 4.8 Hz, *J* = 1.8 Hz, 1 H), 8.56 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$,75.47MHz): δ 63.3, 123.5, 127.0, 131.2, 132.4, 133.0, 148.3, 148.6. HR-MS: m/z (EI+) calcd. for C_8H_9NO $(M)^+$ 135.0684, found 135.0689.

Methyl (2*E*)-3-pyridine-3-ylprop-2-ene-1-yl carbonate (1a)

A solution of pyridine (3.4 mL, 40 mmol) and (2*E*)-3-pyridine-3-ylprop-2-ene-1-ol (2.70 g, 20 mmol) in dry dichloromethane was cooled to 0°C and methyl chloroformate (3.3 mL, 44 mmol) was added dropwise. The solution was stirred for 20 h at room temperature. Volatiles were removed under reduced pressure, and then dichloromethane was added. The solution was washed three times with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (silica, petroleum ether/ethyl acetate 1:1, 0.1% Et_3N) to give methyl (2*E*)-3-pyridine-3-ylprop-2-ene-1-yl carbonate (**1a**) (3.80 g, 98%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.79 (s, 3 H), 4.79 (dd, *J* = 6.2 Hz, *J* = 1.2 Hz, 2 H), 6.34 (dt, *J* = 16.1 Hz, *J* = 6.2 Hz, 1 H), 6,65 (d, *J* = 16.1 Hz, 1 H) , 7.23 (dd, *J* = 7.7 Hz, *J* = 4.5 Hz, 1 H), 7.68 (dd, *J* = 8.0 Hz, *J* = 1.8 Hz, 1 H), 8.48 (dd, *J* = 4.8 Hz, *J* = 1.6 Hz, 1 H), 8.58 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (CDCl3, 75.47 MHz): δ 54.9, 67.8, 123.4, 124.9, 130.8, 131.7, 133.0, 148.5, 149.2, 155.6. HR-MS: m/z (EI+) calcd. for $C_{10}H_{11}NO_3$ $(M)^+$ 193.074, found 193.073.

***tert*-Butyl (2*E*)-3-pyridine-3-ylprop-2-ene-1-yl carbonate (1b)**

A solution of in n-hexane *n*-BuLi (31 mL, 1.6 M) was added dropwise to a cooled (0°C), stirred solution of (2*E*)-3-pyridine-3-ylprop-2-ene-1-ol (6.08 g, 45.0 mmol) in dry THF. A solution of di-*tert*-butyl carbonate (14.0 g, 63.0 mmol) in dry THF (25 mL) was added. The mixture was stirred at room temperature until TLC monitoring (silica, petroleum ether/ethyl acetate 1:1) showed complete conversion. Water and diethyl ether were added and the aqueous layer was extracted with diethyl ether. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (silica, petroleum ether/ethyl acetate 1:1) to give *tert*-butyl (2*E*)-3-pyridine-3-ylprop-2-ene-1-yl carbonate (8.89 g, 84 %) as a orange oil. ^{1}H-NMR ($CDCl_3$, 250MHz): δ 1.47 (s, 9 H), 4.71 (dd, *J* = 6.2 Hz, *J* = 1.1 Hz, 2 H), 6.32 (dt, *J* = 16.0 Hz, *J* = 6.1 Hz, 1 H), 6.59 (d, *J* = 16.0 Hz, 1 H), 7.23 (dd, *J* = 7.7 Hz, *J* = 4.5 Hz, 1 H), 7.68 (dd, *J* = 8.0 Hz, *J* = 1.8 Hz, 1 H), 8.44 (dd, *J* = 4.8 Hz, *J* = 1.6 Hz, 1 H), 8.56 (d, *J* = 2.0 Hz, 1 H). ^{13}C-NMR ($CDCl_3$, 75.47MHz): δ 27.9, 67.1, 82.6, 123.6, 125.6, 130.6, 132.9, 133.2, 149.2, 149.3, 153.4. HR-MS m/z (FAB) calcd. for $C_{13}H_{17}NO_3$ $(M+H)^+$ 236.129, found 236.129.