Supporting Information

The Asymmetric Michael Reaction Involving Chiral Imines/Secondary Enamines: Stereocontrolled Synthesis of 2,2-Disubstituted Tetrahydrothiophen-3-ones

Didier Desmaële, Sandrine Delarue-Cochin, Christian Cavé, Jean d'Angelo and Georges Morgant

a Unité de Chimie Organique associée au CNRS (UMR 8076), Centre d’Etudes Pharmaceutiques, Université Paris Sud, 5 rue J.-B. Clément, 92296 Châtenay-Malabry, France
b Laboratoire de Cristallographie Bioinorganique, Centre d’Etudes Pharmaceutiques, Université Paris Sud, 5 rue J.-B. Clément, 92296 Châtenay-Malabry, France

Experimental Procedures

Synthesis of imine 13: A mixture of 5 Å molecular sieves (7.3 g), basic alumina (1.8 g) and silica (0.9 g) was activated by heating for a few minutes at 0.05 torr with a free flame. After cooling, freshly distilled cyclohexane (25 mL) and 2-methyltetrahydrothiophen-3-one (4.15 g, 35.7 mmol, 1 equiv) were added under inert atmosphere. After degasing the solution with azote, (R)-phenylethylamine (4.72 g, 38.9 mmol, 1.1 equiv) was added. After stirring for 6 days at room temperature, the mixture was filtered, washed with anhydrous Et₂O and concentrated to yield crude imine 13 as a pale yellow oil (7.8 g, quantitative); IR (neat, cm⁻¹) 1663, 1492, 1448.

General Procedure for the Michael reaction: To a solution of imine (1 equiv) in a minimum of freshly distilled cyclohexane (0.1 mL/mmol), was added then corresponding alkene (2.5 equiv). After stirring at 45°C for 70 h ) under nitrogen, the mixture was cooled to room temperature and diluted with THF (10 mL/ mmol). 20% Aqueous acetic acid (5 mL/mmol) was then added. After further stirring for 3 h, solvents were removed and HCl 3N was added. The mixture was extracted with Et₂O, the organic layers were then washed with brine, dried over Na₂SO₄, filtered and concentrated. The residue was purified by column
chromatography over silica gel (eluting with cyclohexane/ethyl acetate: 4:1 for adducts 14, 20, 21 and with CH₂Cl₂/MeOH: 98/2 for compound 22) to yield the title adducts.

(S)-3-(2-Methyl-3-oxo-tetrahydro-thiophen-2-yl)-propionic acid methyl ester (14)

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\text{MeO}_2C-\text{S} \quad 14
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Colorless oil, bp 0.1: 80-85 °C (oil bath); \([\alpha]_D = -31\) (c 13, EtOH); IR (neat, cm\(^{-1}\)) 1733, 1713, 1436, 1349; \(^1\)H NMR (CDCl\(_3\), \(\delta\)): 3.64 (s, 3 H), 2.95-2.85 (m, 2 H), 2.71-2.64 (m, 2 H), 2.44-2.30 (m, 2 H), 2.15-1.85 (m, 2 H), 1.34 (s, 3 H); \(^13\)C NMR (CDCl\(_3\), \(\delta\)): 219.2 (C), 172.6 (C), 55.8 (C), 51.4 (CH\(_3\)), 38.1 (CH\(_2\)), 32.2 (CH\(_2\)), 29.4 (CH\(_2\)), 23.5 (CH\(_3\)), 21.1 (CH\(_2\))；MS (EI): m/z 204 (M+2, 12), 203 (M+1, 46), 202 (M, 2), 186 (6), 184 (23), 171 (15), 170 (42), 156 (8), 146 (34), 143 (30), 116 (25), 115 (37), 114 (100), 86 (76); Anal. Calcd for C\(_9\)H\(_{14}\)O\(_3\)S (202.3): C 53.44, H 6.98, found C 53.41, H 7.01.

(S)-3-(2-Methyl-3-oxo-tetrahydro-thiophen-2-yl)-propionitrile (20)

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\text{NC} \quad 20
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Colorless oil; \([\alpha]_D = -44\) (c 2.0, CH\(_2\)Cl\(_2\)); IR (neat, cm\(^{-1}\)) 2247, 1725, 1449, 1401, 1376, 1277, 1107; \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\): 3.05-2.90 (m, 2 H), 2.80-2.60 (m, 2 H), 2.60-2.30 (m, 2 H), 2.25-1.80 (m, 2 H), 1.39 (s, 3 H); \(^13\)C NMR (50 MHz, CDCl\(_3\)) \(\delta\): 213.1 (CO), 118.7 (CN), 55.1 (C), 37.6 (CH\(_2\)), 32.2 (CH\(_2\)), 23.5 (CH\(_3\)), 20.8 (CH\(_2\)), 12.5 (CH\(_2\)); Anal. Calcd for C\(_8\)H\(_{11}\)NOS (169.2): C 56.77, H 6.55, N 8.28; found: C 56.58, H 6.70, N 8.18.

(S)-2-(2′-Benzenesulfonyl-ethyl)-2-methyl-dihydro-thiophen-3-one (21)
White solid; mp 93-95°C (diethyl ether); [α]_D = -44 (c 2.0, CH₂Cl₂); IR (neat, cm⁻¹): 1727, 1447, 1307, 1289, 1243; ¹H NMR (200 MHz, CDCl₃) δ: 7.90-7.80 (m, 2H), 7.70-7.45 (m, 3H), 3.35-3.00 (m, 2H), 2.90-2.75 (m, 2H), 2.70-2.50 (m, 2H), 2.15-1.85 (m, 2H), 1.28 (s, 3H); ¹³C NMR (50 MHz, CDCl₃) δ: 213.4 (CO), 138.5 (C), 133.5 (2 CH), 129.0 (CH), 127.6 (2 CH), 55.1 (C), 51.9 (CH₂), 37.9 (CH₂), 29.8 (CH₂), 23.8 (CH₃), 21.1 (CH₂); Anal. Calcd for C₁₃H₁₆O₃S₂ (284.4): C 54.90, H 5.67, found: C 55.02, H 5.82.

(3, 2'R) 2-Acetylamino-3-(2-methyl-3-oxo-tetrahydro-thiophen-2-yl)-propionic Acid Methyl Ester (22)

White solid; mp = 99-100 °C (diethyl ether); [α]_D = -38 (c 2.0, CH₂Cl₂); IR (neat, cm⁻¹): 3294, 2955, 1728, 1658, 1535, 1435, 1372, 1277, 1206; ¹H NMR (200 MHz, CDCl₃) δ: 5.77 (broad d, J = 9.6 Hz, NH); 4.95 (td, J = 3.7 Hz, J = 9.9 Hz, 1H), 3.70 (s, 3H), 3.00-2.00 (m, 6H), 1.96 (s, 3H), 1.39 (s, 3H); ¹³C NMR (50 MHz, CDCl₃) δ: 215.8 (CO), 172.2 (CO), 170.1 (CO), 54.8 (C), 52.2 (CH₃), 49.5 (CH), 40.3 (CH₂), 38.5 (CH₂), 26.2 (CH₃), 22.7 (CH₃), 21.7 (CH₂); Anal. Calcd for C₁₁H₁₇NO₃S (259.3) : C 50.95, H 6.61, N 5.40; found: C 50.92, H 6.59, N 5.37.

(S)-7a-Methyl-2,3,7,7a-tetrahydro-6H-benzo[b]thiophen-5-one (18)

To a solution of dimethyl methylphosphonate (291 mg, 2.35 mmol) in dried THF (8 mL) was added dropwise at -78 °C, n-butyllithium (2.5 M, 0.95 mL, 2.35 mmol). After being stirred 30
min. at -78 °C, a solution of enol lactone 19 (200 mg, 1.17 mmol) in THF (1 mL) was added and the reaction mixture was stirred at -78 for 30 min. then 1 h at -20 °C. Saturated aqueous ammonium chloride was added and the mixture was warmed up to room temperature. The reaction mixture was extracted with diethyl ether (3 × 15 mL), the combined organic phases were dried and concentrated under reduced pressure. The residue was chromatographed on silica gel (cyclohexane/AcOEt, 4:1) to yield enone 18 (70 mg, 35%). Colorless oil; [α]D = +148 (c 1.5, EtOH); IR (neat, cm⁻¹) 1667, 1445, 1417, 1337, 1316, 1222, 1180; ¹H NMR (200 MHz, CDCl₃) δ: 5.65 (s, 1H), 3.05-2.72 (m, 4H), 2.50-2.10 (m, 4H), 1.51 (s, 3H); ¹³C NMR (50 MHz, CDCl₃) δ: 197.6 (CO), 170.8 (C), 120.4 (CH), 51.6 (C), 36.8 (CH₂), 35.1 (CH₃), 33.6 (CH₂), 27.0 (CH₂), 26.6 (CH₃); Anal. Calcd for C₉H₁₂O₃S (168.2): C 64.24, H 7.19; found: C 64.01, H 7.34.

(±)-3-(2-Methyl-3-oxo-2,3-dihydro-thiophen-2-yl)-propionic acid methyl ester (16)

To a solution of keto ester 14 (90 mg, 0.44 mmol) in CCl₄ (1.5 mL) at 20 °C was added portionwise N-chlorosuccinimide (70 mg, 0.52 mmol). After being stirred for 30 min. the mixture was filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (cyclohexane/AcOEt, 4:1) to yield enone 16 (74 mg, 83%). Colorless oil; [α]D = -58 (c 3.6, CCl₄); IR (neat, cm⁻¹) 1734, 1673, 1519, 1438, 1377; ¹H NMR (200 MHz, CDCl₃) δ: 8.31 (d, J = 6.0 Hz, 1H), 6.10 (d, J = 6.0 Hz, 1H), 3.60 (s, 3H), 2.30-2.00 (m, 4H), 1.51 (s, 3H); ¹³C NMR (50 MHz, CDCl₃) δ: 206.7 (CO), 172.7 (CO), 162.1 (CH), 121.7 (CH), 60.3 (C), 51.6 (C), 33.3 (CH₂), 29.4 (CH₂), 24.8 (CH₃); Anal. Calcd for C₉H₁₂O₃S (168.2): C 53.98, H 6.04; found: C 53.76, H 6.16.