Synthesis of a new chiral auxiliary: non-cross-linked polystyrene bound (4*S*)-oxazolidine-2-thione

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A new chiral auxiliary, non-cross-linked polystyrene bound (4*S*)-oxazolidine-2-thione, was synthesised from L-tyrosine in 24.2% by a seven step method.

Keywords: non-cross-linked polystyrene, bound, oxazolidine-2-thione, chiral auxiliary

Oxazolidinethione is often used in asymmetric synthesis.[1] However, in most cases, chiral auxiliary can not be recovered after each asymmetric reaction. To recycle and reuse expensive chiral auxiliaries is a challenge in organic synthesis.[2,3] Insoluble polymer supports, such as Merrifield resin, Wang resin were applied previously to simplify the procedure of separation and purification. But several shortcomings were shown because of non-linear kinetic behaviour, unequal distribution or access to the chemical reaction, and synthetic difficulties in transferring standard organic reactions to the solid phase. Then chemists started to search soluble polymers as supports. This methodology is regarded as a very successful process which combines the superiorities of insoluble polymer support with the advantages of classic liquid synthesis. Our group[4-6] has undertaken a research program to develop liquid-phase methods for the syntheses of small molecule libraries using poly(ethylene glycol) (PEG) and non-cross-linked polystyrene (NCPS) as supports. The article reported a new chiral auxiliary **8** based on NCPS which could be synthesised through seven steps from the material of natural L-tyrosine (Scheme 1).

Experimental

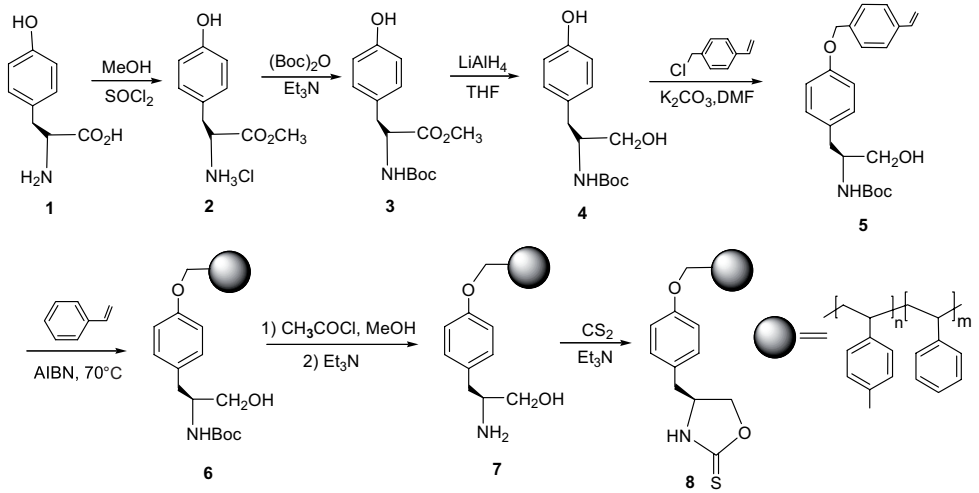
Melting points were measured on a WRS-1A digital melting point apparatus and uncorrected; polarimetric analysis were recorded on a WZZ-2B polarimeter; IR spectra were recorded on a IR- spectrum one (PE) spectrometer; ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Varian Unity INOVA 600 spectrometer in $CDCl_3$ using TMS as internal standard; elemental analyses were done on a VarioEL III (Germany) analyser; MS spectra were recorded on a Finnigan LCQ (America) mass spectrum.

Synthesis of L-tyrosine methyl ester hydrochloride **2**: Compound **2** can be synthesised according to ref.7. Yield 95%; m.p. 188–189 °C; lit.[7]190–191°C; $[\alpha]_D^{20}$ = + 69.8 (c 1.0, pyridine), lit.[7] $[\alpha]_D^{20}$ = + 70.9 (c 1.1, pyridine).

Synthesis of N-Boc L-tyrosine methyl ester **3**: Compound **3** can be synthesised according to ref.8. Yield 85%. m.p.104–105°C; $[\alpha]_D^{20}$ = + 20.4 (c 0.72, THF); ^{1}H NMR($CDCl_3$, 600 MHz): δ1.42 (s, 9H, Boc), 2.96 (dd, J_1 = 6.0 Hz, J_2 = 13.8 Hz, 2H, $ArCH_2$), 3.71 (s, 3H, CO_2CH_3), 4.53 (q, J = 6.0 Hz, 1H, ArCH), 6.73 (d, J = 7.8 Hz, 2H, Ar–H), 6.95 (d, J = 8.4 Hz, 2H, Ar–H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 173, 155.8, 155.6, 131, 128 (2C), 116(2C), 81, 55, 53, 38, 29(3C); IR(NaCl): υ = 3368, 1740, 1690 cm^{-1}; MS: *m/z* = 319.9 ($M + Na^+$).

Synthesis of N-Boc L-tyrosinol **4**: **3** (7.98 g, 27 mmol) in a solution of dry THF (40 ml) was cooled –20°C and $LiAlH_4$ (0.82 g, 21.6 mmol) in THF (40 ml) was added dropwise, then stirred at 5–10°C for 4 days before acidification to pH 6–7 with 1N HCl, filtered, extracted with ethyl acetate (3 × 70 ml). The organic layers were washed with brine, dried with $MgSO_4$, and the solvent removed in vacuum to afford organic solid. The product was further purified by column chromatograph to give **4** (5.06 g, 70%), m.p. 118–119°C; $[\alpha]_D^{20}$ = –23 (C1.2, $CHCl_3$), lit.[9] = –25(c10, MeOH); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.42 (s, 9H, Boc), 2.70(d, J = 5.4 Hz, 2H, $ArCH_2$), 3.01 (s, 1H, ArCH), 3.49(d, J = 4.8 Hz, 1H, CH_2O), 3.89 (d, J = 4.8 Hz, 1H, CH_2O), 4.06 (q, J = 4.8 Hz, 1H, ArCH), 6.72 (d, J = 7.8 Hz, 2H, Ph–H), 6.97 (t, J = 9 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$,150 MHz): δ158, 157, 130, 128(2C), 115 (2C), 70, 66, 55, 38, 29(3C); IR(NaCl): υ = 3344, 2931, 1685 cm^{-1}; MS: *m/z* = 290.1 ($M + Na^+$).

Synthesis of N-Boc O-(p-vinylbenzyl) L-tyrosinol **5**: K_2CO_3 (3.70 g, 27 mmol) was added to a solution of **4** (3.58 g, 13.5 mmol) in dry DMF (30 ml), and then catalytic amount of 18-crown-6 was added. The reaction mixture was stirred for 30 min in Ar before *p*-vinyl benzyl chloride (2.29 g, 15 mmol) in DMF (15 ml) was dropwise added. The mixture was stirred at 60–65°C for 2 days before extracting with ethyl acetate (3 × 50 ml). The organic layers were washed with



Scheme 1 Synthesis of NCPS bound (4*S*)-oxazolidine-2-thione.

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brine, dried with $MgSO_4$, and the solvent removed in vacuum. The crude product was further purified by column chromatograph to give milk white solid **5** (4.37 g, 85%). m.p. 86.7–88.7°C; $[\alpha]_D^{20}$ = –20.3 (C0.32,EtOH), ^{1}H NMR ($CDCl_3$,600 MHz): δ1.42(s, 9H, Boc), 2.78 (d, J = 6.6 Hz, 2H, $ArCH_2$), 3.47 (t, J_1 = J_2 = 7.2 Hz, 1H, CH_2 OH), 3.5 (d, J = 6.6 Hz, 1H, CH_2 OH), 3.82 (d, J = 6.6 Hz, 2H, $ArCH_2$), 4.78 (q, J = 4.8 Hz, 1H, CHN), 5.02 (d, J = 12.6 Hz, 2H, $ArCH_2O$), 5.26 (d, J = 13.2 Hz, 1H, CH_2 =CH), 5.76 (d, J = 18 Hz, 1H, CH_2 = CH), 6.73 (dd, J_1 = 10.8 Hz, J_2 = 18 Hz, 1H, CH_2=CH), 6.91 (d, J = 8.4 Hz, 2H, Ar–H), 7.12 (d, J = 7.8 Hz, 2H, Ar–H), 7.26–7.43 (m, 2H, Ar–H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ158, 157, 138, 136.9, 136.8, 130.7(C), 130(2C), 128(2C), 127(2C), 115(2C), 114, 70, 66, 65, 54, 37, 29 (3C); IR(NaCl): υ = 3356, 2979, 1686 cm^{-1}; MS: m/z = 405.8 ($M + Na^+$).

Synthesis of NCPS bound N-Boc L-tyrosinol **6**: Styrene (2.01 ml, 17.5 mmol) was dropwise added to **5** (1.34 g, 34.9 mmol) in THF (20 ml). AIBN (16 mg) was added to the monomers in Ar. The mixture copolymerised at 70°C for 4 days. Then most of the solvent was removed under reduced pressure. The residue was poured dropwise into a beaker of cold and stirring ethanol (50 ml) to precipitate white polymer. The product was washed in ethanol (3 × 8 ml) to remove any micromolecules (TLC detecting) and dried in a vacuum oven at 50°C to give polymer **6** (2.52 g, 80%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ1.26–1.42 (bm, polymer–CH_2), 1.43 (s, 9H, Boc), 1.50–2.10 (bm, polymer–CH_2), 2.72 (d, J = 7.2 Hz, 1H, $ArCH_2$), 3.47 (s, 1H, CHN), 3.63 (s, 1H, CH_2OH), 3.82 (d, J = 7.8 Hz, 2H, $ArCH_2$), 4.92 (s, 2H, $ArCH_2OH$), 6.30–7.20 (bm, polymer–ArH); ^{13}C NMR $CDCl_3$,150 MHz: δ158, 156, 145–147(polymer–C), 131, 128.1–128.9 (polymer–ArCH), 126, 115, 81, 71, 65, 55, 40.1–40.9 (polymer–CH_2), 37, 28; IR (NaCl): υ = 3428, 1697 cm^{-1}; elementary analysis for polymer **6**: C, 83.81%; H, 7.69%; N, 1.50%; capacity of NH was 1.07 mmol/(g polymer).

Synthesis of NCPS bound L-tyrosinol **7**: Acetyl chloride (0.37 ml, 5.2 mmol) in CH_2Cl_2 (5 ml) was added to dried **6** (1.55 g) in mixed solvents of CH_2Cl_2 (30 ml) and methanol (2 ml) at 0°C. After 30 min, the reaction mixture was stirred at r.t. for 8 h. Et_3N (2.38 ml, 17.2 mmol) was added to counteract produced acids. Then most of the solvent was removed under reduced pressure. The residue was poured dropwise into a beaker of cold stirred ethanol (30 ml) to precipitate white polymer. The precipitation was washed in ethanol (3 × 10 ml) and dried to give polymer **7** (1.25 g, 90%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ1.20–2.0(bm, polymer–CH_2), 2.72 (d, J = 4.8 Hz, 2H, $ArCH_2$), 3.07 (s, 1H, CHN), 3.63 (d, J = 6.6 Hz, 1H, CH_2OH), 3.85 (d, J = 7.2 Hz, 1H, CH_2OH), 4.92 (s, 2H, $ArCH_2O$), 6.25–7.20(bm, polymer–ArH); ^{13}C NMR ($CDCl_3$, 150 MHz): δ158, 145–147 (polymer–C), 131, 128.1–128.5 (polymer–ArCH), 126, 115, 71, 67, 54, 40–41 (polymer–CH_2), 30; IR(NaCl): υ = 3359 cm^{-1}; elementary analysis for polymer **7**: C, 86.85%; H, 7.68%; N,1.53%; Capacity of NH was 1.09 mmol/(g polymer).

Synthesis of NCPS bound (4S)-oxazolidine-2-thione **8**: Et_3N (0.53 ml, 3.8 mmol) was dropwise added to **7** (0.77 g) in CH_2Cl_2 (20 ml). After 30 min, CS_2 (0.23 ml, 3.8 mmol) was poured into round-bottomed flask and the reaction mixture was stirred at 50°C for 48 h. Then most of the solvent was removed under reduced pressure. The residue was poured dropwise into a beaker of cold stirred ethanol (30 ml) to precipitate white polymer. The product was washed in ethanol (3 × 5 ml) to remove micromolecules (TLC detecting) and dried to give polymer **8** (0.57 g, 70%). ^{1}H NMR ($CDCl_3$, 600 MHz): δ1.20–2.10 (bm, polymer–CH_2), 2.88(d, J = 6.0 Hz, 2H, $ArCH_2$), 2.96 (s, 1H, CHN), 3.65 (d, J = 4.8 Hz, 1H, CH_2O), 3.76 (d, J = 8.4 Hz, 1H, CH_2O), 5.03 (s, 2H, $ArCH_2O$), 6.25–7.25 (bm, polymer–ArH); ^{13}C NMR ($CDCl_3$,150 MHz): δ172, 161, 142–143 (polymer–C), 131, 128.1–128.9 (polymer–ArCH), 127, 113, 71, 66, 61, 32; IR (NaCl): υ = 3319, 1240 cm^{-1}; elementary analysis for polymer **8**: C,84.32%; H, 7.22%; S,2.95%; N,1.48%; capacity of NH was 1.05 mmol/(g polymer).

The following work: Application of chiral auxiliary into asymmetric reaction is in process.

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