Synthesis of non-cross-linked polystyrene supported 5,5-dimethyl oxazolidinone chiral auxiliary

Yadong Wan, Cuifen Lu, Junqi Nie, Guichun Yang, Zuxing Chen*

Ministry-of-Education Key Laboratory for the Synthesis and Application of Organic Functional Molecules and Faculty of Chemistry and Chemical Engineering, Hubei University, Wuhan, 430062, P. R China

A new chiral auxiliary, non-cross-linked polystyrene supported 5,5-dimethyl oxazolidinone was synthesised in 25.1% yield using L-tyrosine as the starting material using a six-step method.

Keywords: non-cross-linked polystyrene, support, chiral auxiliary, 5,5-dimethyloxazolidinone

Oxazolidinone, the most versatile and widely used chiral auxiliary, was devised by Evans *et al.*[1] This, so called, Evans' auxiliary has been utilised in a particularly wide variety of high diastereoselective reactions.[2] However, the application of Evans' oxazolidinone is limited due to the drawbacks of the Evans methodology which involves the cleavage of the auxiliary.[3] In order to address fully this troublesome cleavage problem, a new class of chiral auxiliary, the 5,5-dimethyloxazolidinone has been developed.[4] The improved auxiliary provides superior performance to many other chiral auxiliaries currently in common usage. It has proved to be particulary efficacious in terms of diastereoselectivity, yield and solubility.[5-7]

Recently, the attachment of Evans' oxazolidinone to polymer-support has been reported.[8-9] The use of polymer-supported chiral auxiliaries gives some benefits: (1) easy separation and recovery of the expensive chiral material; (2) simple isolation of the desired chiral adduct; and (3) possible extension to a continuous system. But to the best of our knowledge, polymer-supported 5,5-dimethyloxazolidinone chiral auxiliary has not been reported. Our group has undertaken a research program to develop a new chiral auxiliary using non-cross-linked polystyrene (NCPS) as support.[10] In our study another new chiral auxiliary based on NCPS was synthesised through six steps from the material of natural L-tyrosine (Scheme 1). It will be widely used in asymmetric synthesis, such as chiral alkylation, Aldol condensation, Diels–Alder and Michael addition.

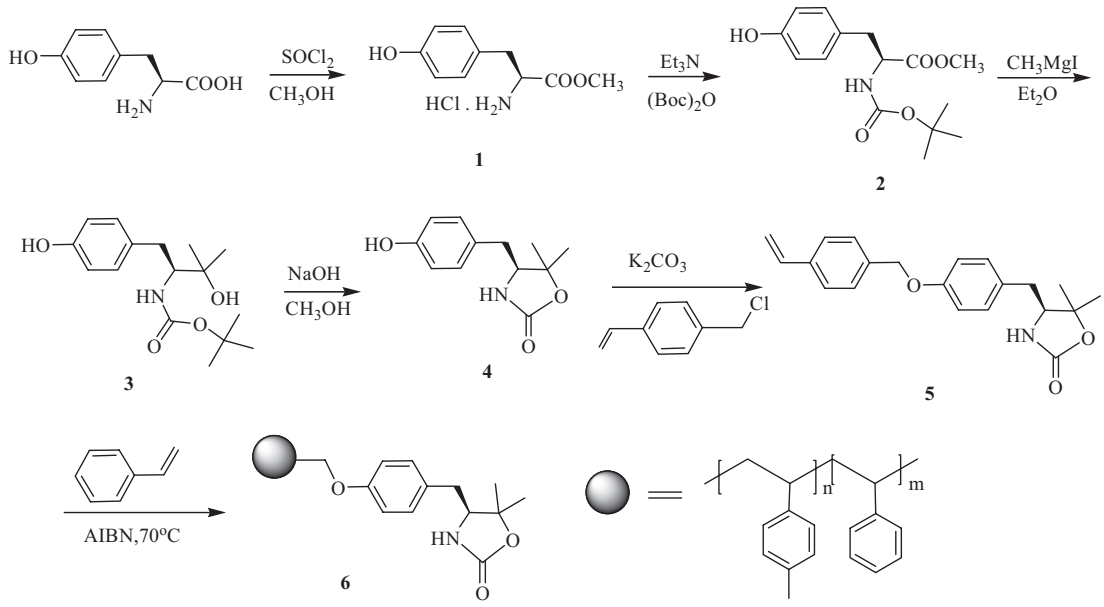
Experimental

Melting points were measured on a WRS-1A digital melting point apparatus and uncorrected; polarimetric analysis was recorded on a WZZ-2_B^A polarimeter; IR spectra were recorded on an IR-spectrum One spectrometer (PE); ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Varian Unity INOVA 600 spectrometer using TMS as internal standard; element analysis was determined by a VarioEL β(Germany) analyser; MS spectra were recorded on Finnigan LCQ DUO MS system.

Synthesis of L-tyrosine methyl ester hydrochloride **1***:* Compound **1** was obtained as white crystals in yield (97%). m.p. 189–190°C (lit.[11]190–191°C),$[\alpha]_D^{25}$=+69.8(c1.06,pyridine)[lit.[11]$[\alpha]_D^{20}$=+70.9 (c 1.1, pyridine)].

Synthesis of N-Boc L-tyrosine methyl ester **2***:* Compound **2** can be synthesised according to ref.12.Yield 86%. m.p. 104–105°C [lit.[13] 102°C], $[\alpha]_D^{20}$ = + 20.4 (c 0.72, THF) [lit.[13] $[\alpha]_D^{20}$ = -50.0 (c 1.0, $CHCl_3$)]. IR(NaCl): υ = 3365, 1740, 1689 cm^{-1}; ^{1}H NMR(600 MHz, $CDCl_3$): 6.96(2H, d, *J* = 8.4 Hz, Ar–H), 6.72(2H, d, *J* = 8.4 Hz, Ar–H), 5.03(1H, m, OH), 4.54(1H, m, CH), 3.71(3H, s, O–CH_3), 3.01(1H, m, CH_2–Ar), 2.98 (1H, m, CH_2–Ar), 1.42(9H, s, C–CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): 173.1, 155.8, 155.6, 130.8(2C), 127.9, 115.9(2C), 80.7, 55.0, 52.7, 38.0, 28.7(3C); MS: *m/z* = 319.9 (M + Na^+).

Synthesis of (3S)-3-(N-Boc-amino)-4-(4-hydroxyphenyl)-2-methyl-butan-2-ol **3***:* The compound **2** (13.3 g, 45 mmol) in ether (150 ml) was added dropwise to a solution of methylmagnesium iodide in ether (300 ml) [From methyl iodide (28 ml, 450 mmol) and magnesium (12 g, 500 mmol)]. The mixture was stirred at room temperature for 48 h. Then the mixture was hydrolysed with ice and 2M HCl until the magnesium was consumed. The ether layer was separated and the aqueous layer was extracted with ether (30 ml × 3). The combined ether layer was dried over $MgSO_4$ and evaporated to afford a pale



Scheme 1 Synthesis of NCPS supported 5,5-dimethyloxazolidinone.

* Correspondent. E-mail: chzux@hubu.edu.cn.

yellow solid. Recrystallisation from EtOH–CH_3COOEt–H_2O (2:3:2, v/v) gave **3** as colourless crystals (7.8 g, 58%). m.p. 155.6–156.3°C, $[\alpha]_D^{20}$ = −39.4 (c 0.91, THF); IR(NaCl): υ = 3355, 1686 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): 7.05(2H, d, *J* = 7.8 Hz, Ar–H), 6.70(2H, d, *J* = 7.8 Hz, Ar–H), 5.67(1H, m, OH), 3.65(1H, m, CH), 3.05(1H, m, CH_2–Ar), 2.52(1H, m, CH_2–Ar), 1.20-1.18(15H, t, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): 155.7, 155.6, 130.8, 129.2(2C), 115.8(2C), 80.4, 72.4, 68.2, 37.4, 28.8(3C), 26.7, 21.2; MS: *m/z* = 318.1 (M + Na^+). Elementary analysis calcd for compound **3**: C, 65.06%, H, 8.53%, N, 4.74%; found: C, 65.18%; H, 8.51%; N, 4.59%.

Synthesis of (S)-4-(4-hydroxybenzyl)-5,5-dimethyloxazolidinone **4***:* The *N*-Boc amino alcohol **3** (7.5 g, 25.5 mmol) was suspended in 5% NaOH (7.2 g, wt%) in MeOH (75 ml), refluxed for 12 h. The mixture was evaporated and the residue diluted with water (20 ml) and ethyl acetate (30 ml). The aqueous layer was extracted with ethyl acetate (30 ml × 3). Then the combined organic phase was dried over $MgSO_4$, concentrated under vacuum to give **4** (4.5 g, 81%) as pale yellow solid which was used in the next step without further purification. m.p. 138.2–139.3°C, $[\alpha]_D^{20}$ = −121.8 (c 0.8, THF); IR(NaCl): υ = 3290, 1729, 1515, 1235 cm^{-1}; ^1H NMR (600 MHz, CH_3OD): 7.00(2H, d, *J* = 8.4 Hz, Ar–H), 6.70(2H, d, *J* = 8.4 Hz, Ar–H), 3.75(1H, m, CH), 2.73(1H, m, CH_2–Ar), 2.62(1H, m, CH_2–Ar), 1.34(6H, d, CH_3); ^{13}C NMR(150 MHz, CH_3OD): 160.0, 156.3, 130.2(2C), 128.3, 115.6(2C), 84.1, 63.5, 36.1, 26.9, 21.1; MS: *m/z* = 244.0 (M + Na^+). Elementary analysis calcd for compound **4**: C, 65.14%, H, 6.83%, N, 6.33%; found: C, 65.19%; H, 6.82%; N, 6.27%.

Synthesis of (S)-4-[4-(4-vinylbenzyloxy)benzyl]-5,5-dimethyl-oxazolidinone **5***:* To a solution of **4** (3.3 g, 15 mmol) in dry DMF (20 ml) were added 4-vinylbenzyl chloride (CMS) (2 ml, 18 mmol), anhydrous K_2CO_3 (2 g, 15 mmol) and 18-crown-6 (catalyse amount). Then the resulting mixture was stirred for 12 h at r.t. The solvent was removed under vacuum and the residue diluted with H_2O (15 ml) and CH_2Cl_2 (30 ml). The aqueous layer was extracted with dichloromethane (25 ml × 3) and the combined organic phase were dried over $MgSO_4$ and evaporated to afford a pale yellow solid. Recrystallisation from EtOH–CH_3COOEt–H_2O (1 : 2 : 1, v/v) give **5** (3.6 g, 72%) as colourless crystals. m.p. 146.0–147.2°C, $[\alpha]_D^{20}$ = −53.65 (c 0.58,THF); IR(NaCl): υ = 3412, 1781 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): 7.44 (2H,d, *J* = 7.8 Hz, Ar–H),7.39 (2H, d, *J* = 7.8 Hz, Ar–H), 7.09(2H, d, = 7.2 Hz, Ar), 6.93(2H, d, *J* = 7.2 Hz, Ar), 6.75(1H, dd, J_1 = 10.8 Hz, J_2 = 17.4 Hz, =CH), 5.78(1H, d, *J* = 17.4 Hz, $=CH_2$), 5.27(1H, d, *J* = 10.8 Hz, $=CH_2$), 5.04(2H, s, O–CH_2), 4.93 (1H, s, NH), 3.62(1H, d, CH), 2.78(1H, d, CH_2–Ar), 2.63(1H, d, CH_2–Ar), 1.47-1.44 (6H, d, CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): 158.4, 158.2, 137.8, 136.8(2C), 130.3(2C), 129.5, 128.1(2C), 126.8(2C), 115.9(2C), 114.6, 83.6, 70.2, 63.6, 36.6, 27.9, 22.3; MS: *m/z* = 337.9(M^+). Elementary analysis calcd for compound **5**: C, 74.75%, H, 6.87%, N, 4.15%; found: C, 74.85%; H, 6.89%; N, 3.94%.

Synthesis of NCPS supported 5,5-dimethyloxazolidinone **6***:* To a solution of monomer **5** (3 g, 8.7 mmol) in THF (15 ml) were added styrene (1.85 g, 17.4 mmol) and AIBN (0.01 g, 0.06 mmol). The mixture was stirred at 70°C for 48 h under nitrogen atmosphere. Then most of the solvent was removed under reduced pressure. The viscous solution was dropped into cold ethanol (200 ml) and the precipitated solid was filtered and dried at 65°C for 2 h under vacuum to afford solid polymer 6 (4.32 g, 89%). IR(NaCl): υ = 3280, 1752 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): 7.25-6.45(m, broad signal due to the polymer resonance), 4.90 (2H, s, O–CH_2), 3.62(1H, s, CH), 2.75 (1H, s, CH_2–Ar), 2.60(1H, s, CH_2–Ar), 1.81–1.25(m broad signal due to the polymer resonance); ^{13}C NMR (150 MHz, $CDCl_3$): 158.4, 145.5, 130.4, 129.5, 128.1, 126.2, 115.8, 83.6, 70.5, 63.5, 40.8, 36.6, 28.0, 22.4. Elementary analysis calcd for polymer **6**: C, 81.43%; H, 7.20%; N, 2.57%; found: C, 81.83%; H, 7.22%; N, 2.48%.

NCPS supported 5,5-dimethyl oxazolidinone chiral auxiliary was characterised by IR, ^1H NMR, ^{13}C NMR, GPC, TGA and DSC. The result showed that the obtained polymer has high loading capacity, remarkable solubility, low molecule and good thermally stability. The overall yield reached 25.1%.

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