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ASYMMETRIC SYNTHESIS OF (*S*)-2-*sec*-BUTYL-4,5-DIHYDROTHIAZOLE, A PHEROMONE COMPONENT OF THE *Mus musculus*

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*The asymmetric synthesis of (*S*)-2-*sec*-butyl-4,5-dihydrothiazole, one of the pheromone components of the male mouse,* Mus musculus*, has been achieved by induction of chirality through stereoselective alkylation reaction using non-cross-linked polystyrene (NCPS) supported 2-phenylimino-2-oxazolidine as a chiral auxiliary. This method is efficient, and the chiral auxiliary can be recovered by simple filtration. The final product was obtained in 91%* ee *and 23% overall yield.*

Keywords: asymmetric synthesis, pheromone, mouse, *Mus musculus*.

To the best of our knowledge, not only insects but also higher animals such as the house mouse utilize pheromones for their chemical communication. 2-*sec*-Butyl-4,5-dihydrothiazole (**1**) was identified from the urine of the male mouse, *Mus musculus*, as one of the pheromone components [1–3]. It acts synergistically in promoting internal aggression, sex attraction, and estrus synchronization in female mice [4]. The absolute configuration of **1** was determined by Cavaggioni and co-workers as *S*-configuration [5].

Most of the existing methods for the construction of a dihydrothiazole ring are not sufficiently mild to avoid racemization of **1** at the asymmetric center α to the 2-position of the heterocycle, and (±)-**1** was obtained as the product [4]. The first report on the synthesis of optically active **1** was that by Masaki et al. in 1988 [6]. They prepared both (*R*)- and (*S*)-**1** by condensation of (*R*)- and (*S*)-2-methylbutanenitrile with cysteamine. In 1999, Tashiro and Mori published another method for the synthesis of (*R*)- and (*S*)-**1** involving the addition of esters to a complex generated from triisobutylaluminum and cysteamine hydrochloride [7]. However, the optically active (*R*)- and (*S*)-**1** have only been obtained by the use of an optically active substance as chiral starting material, but no asymmetric synthesis involving induction of chirality has been reported so far.

Recently, our group has undertaken a research program on the investigation of chiral auxiliaries and their application to synthesize the insect pheromones [8–11]. In this paper we report the first asymmetric synthesis of (*S*)-**1** through the key step of a stereoselective alkylation reaction using our previously prepared non-cross-linked polystyrene (NCPS) supported 2-phenylimino-2-oxazolidine [12] as a chiral auxiliary.

Scheme 1 shows our synthesis of (*S*)-**1**, and the stereoselective alkylation reaction induced by NCPS supported 2-phenylimino-2-oxazolidine was the key step in the total synthesis of (*S*)-**1**. Firstly, NCPS supported 2-phenylimino-2-oxazolidine chiral auxiliary **2** reacted with butanoyl chloride in the presence of Et_3N and DMAP to give NCPS supported *N*-butyryl-2-phenylimino-2-oxazolidine **3**. Then **3** was treated with LDA at –78°C to generate the lithium enolate, and subsequent addition of methyl iodide yielded the alkylated product **4**. Treatment of the alkylated product **4** with sodium ethoxide to bring about nondestructive removal of the auxiliary group gave (*S*)-ethyl 2-methylbutanoate **5** in good yield as well as with high enantiomeric purity (99% *ee*), which was analyzed by HPLC, and NCPS supported chiral auxiliary **2** was recovered by simple filtration.

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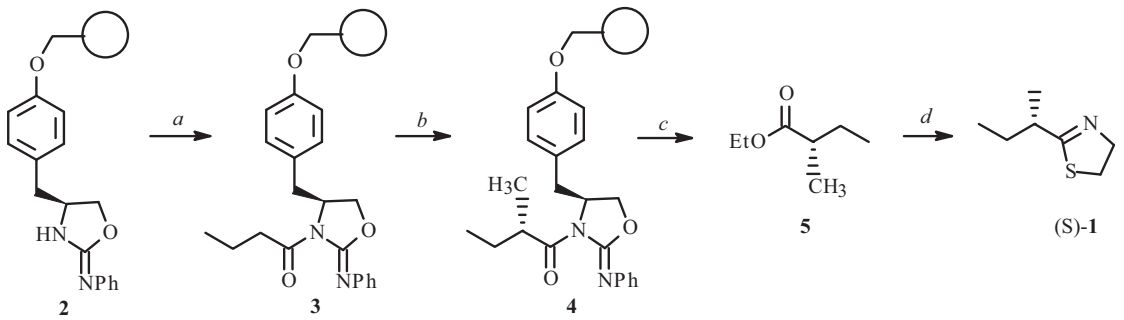

a. $CH_3C_2H_4COCl$, DMAP, Et_3N, CH_2Cl_2, 0°C–room t.; *b*. LDA, THF, CH_3I, –78°C; *c*. EtONa, CH_2Cl_2, 0°C–room t.; *d*. $(i\text{-Bu})_3Al$, toluene, $HSC_2H_4NH_2{\cdot}HCl$, reflux

Scheme 1

The resulting ester (*S*)-**5** was then treated with a complex generated by the addition of triisobutylaluminum to a suspension of cysteamine hydrochloride in toluene to give (*S*)-**1**, according to Tashiro and Mori [7]. The enantiomers of **1** were analyzed by HPLC, and the (*S*)-**1** obtained was of 91% *ee*. Tashiro′s reported enantiomeric purity of their (*S*)-**1** was 92% *ee*, and they also reported that racemization of **1** took place by an acid- or base-catalyzed process. Just like Tashiro, we also encountered racemization of **1**. Chromatographic purification of (*S*)-**1** (91% *ee*) on silica gel caused partial racemization to give (*S*)-**1** with an *ee* of as low as 60%. So we purified our (*S*)-**1** as rapidly as possible by chromatography on aluminum oxide basic, and our product was 91% enantiomerically pure.

In conclusion, the first asymmetric synthesis of (*S*)-2-*sec*-butyl-4,5-dihydrothiazole (**1**), one of the pheromone components of the male mouse, *Mus musculus*, has been achieved by induction of chirality through stereoselective alkylation reaction using NCPS supported 2-phenylimino-2-oxazolidine as a chiral auxiliary. This method is efficient and the chiral auxiliary can be recovered by simple filtration. In view of the optical instability of the enantiomers of **1**, we were unable to secure the pure enantiomer of **1**. The final product was obtained in 91% *ee* and 23% overall yield.

EXPERIMENTAL

All organic solvents were dried by standard methods. TLCs were performed on precoated plates of silica gel HF254 (0.5 mm, Yantai, China). Flash column chromatography was performed on silica gel H (Yantai, China) and aluminum oxide basic (Shanghai, China). Optical rotations were determined with a Perkin–Elmer Model 241 MC polarimeter. IR spectra were recorded with an IR-Spectrum One (Perkin-Elmer) spectrometer. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded with a Varian Unity INOVA 600 spectrometer in $CDCl_3$ using TMS as an internal standard. HPLC analyses were carried out on a Dionex chromatograph (Chiralcel OD-H; hexane–2-propanol 90:10; flow rate 1.0 mL/min; UV detector 254 nm).

NCPS Supported *N*-Butyryl-2-phenylimino-2-oxazolidine (3). To NCPS supported 2-phenylimino-2-oxazolidine **2** (4.90 g) in CH_2Cl_2 (60 mL) were added Et_3N (1.24 mL, 8.09 mmol) and DMAP (0.18 g, 1.45 mmol), and then butanoyl chloride (0.92 mL, 8.82 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture at 0°C. The resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and filtered, and most of the solvent was removed under reduced pressure. The viscous solution was dropped into cold ethanol, and the precipitated solid was filtered and dried at 65°C for 2 h under vacuum to afford polymer **3** (4.95 g, 92%). IR (NaCl, ν, cm^{-1}): 3058, 3026, 2926, 1703, 1685, 1595, 1510, 737, 699. ^{13}C NMR ($CDCl_3$, δ, ppm): 172.2, 157.1, 147.7, 138.1, 136.8, 133.5, 129.1, 128.9, 127.7, 127.3, 125.5, 124.6, 117.5, 114.9, 69.8, 65.2, 48.8, 47.5.

NCPS Supported *N*-(2′-Methyl)-butyryl-2-phenylimino-2-oxazolidine (4). Polymer **3** (4.95 g) was dissolved in THF (50 mL) under argon atmosphere. The solution was cooled down to –78°C and LDA was added dropwise (6.40 mL, 2M in THF, 12.80 mmol). The reaction mixture was stirred for 1 h at this temperature and methyl iodide (1.20 mL, 19.19 mmol) was added slowly. After stirring for 1 h at –78°C and 1 h at 0°C, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried with $MgSO_4$ and filtered. Then, most of the solvent was removed under reduced pressure, and the viscous solution was dropped into cold EtOH. The precipitated solid was filtered and dried at 65°C for 2 h under vacuum to afford polymer **4** (3.92 g, 78%). IR (NaCl, ν, cm^{-1}): 3026, 2924, 1715,

1678, 1510, 787, 699. ^{13}C NMR ($CDCl_3$, δ, ppm): 173.5, 158.7, 147.7, 139.6, 130.7, 130.0, 129.5, 127.6, 127.9, 127.3, 125.6, 122.4, 122.6, 113.4, 112.5, 74.3, 71.2, 65.7, 43.5, 31.8.

(*S*)-Ethyl 2-Methylbutanoate (5). To a solution of polymer **4** (3.92 g) in CH_2Cl_2 (50 mL) at 0°C was added EtONa (0.70 g, 10.05 mmol), and then the reaction mixture was stirred for 6 h at 0°C and 5 additional hours at room temperature. After evaporation of the solvent, the viscous solution was dropped into cold EtOH, and the precipitated solid was filtered. The filtrate was concentrated, and the crude product was purified by distillation (130–135°C) to afford (*S*)-ethyl 2-methylbutanoate (**5**) as a colorless oil (0.52 g, 80%). $[\alpha]_D^{25}$+24.5° (*c* 0.98, CH_2Cl_2). IR (NaCl, ν, cm^{-1}): 2960, 2922, 1736, 1261, 800, 702. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 4.11 (2H, q, J = 10.8), 2.15–2.07 (1H, m), 1.72–1.58 (2H, m), 1.24 (3H, t, J = 11.4), 1.16 (3H, d, J = 10.8), 0.96 (3H, t, J = 11.4). ^{13}C NMR ($CDCl_3$, δ, ppm): 170.5, 63.2, 45.6, 28.5, 22.3, 18.4, 15.5.

(*S*)-2-*sec*-Butyl-4,5-dihydrothiazole ((*S*)-1). To a suspension of 2-aminoethanethiol (cysteamine) hydrochloride (0.53 g, 4.69 mmol) in dry toluene (20 mL) under argon atmosphere, a solution of (iBu)$_3$Al (1.0 M in toluene, 4.20 mL, 11.77 mmol) was added dropwise at room temperature. The solution was refluxed for 30 min, then (*S*)-**5** (0.52 g, 4.04 mmol) was added dropwise. After stirring for 3 h under reflux, the mixture was diluted with toluene (25 mL), cooled to room temperature, and quenched with MeOH (10 mL). The mixture was stirred at room temperature for 20 min, and then a saturated aqueous $NaHCO_3$ solution (20 mL), brine (20 mL), and diethyl ether (50 mL) were successively added, and the mixture was stirred vigorously for 15 min. The organic phase was then separated and the aqueous phase was extracted with an additional amount of diethyl ether. The combined organic phases were dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on alumina (*n*-pentane–diethyl ether, 6:1) to give (*S*)-**1** as a colorless oil (0.22 g, 40%). $[\alpha]_D^{25}$+21.1° (*c* 0.78, $CHCl_3$) [7], $[\alpha]_D^{22}$ +21.6° (*c* 1.04, $CHCl_3$). IR (NaCl, ν, cm^{-1}): 2965, 2928, 1642, 1261, 795, 705. ^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 4.08 (2H, t, J = 8.4), 3.15 (2H, t, J = 8.4), 2.58–2.42 (1H, m), 1.62–1.48 (2H, m), 1.15 (3H, d, J = 7.2), 0.85 (3H, t, J = 7.8). ^{13}C NMR ($CDCl_3$, δ, ppm): 171.0, 64.5, 43.3, 33.8, 27.6, 22.4, 21.8.

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