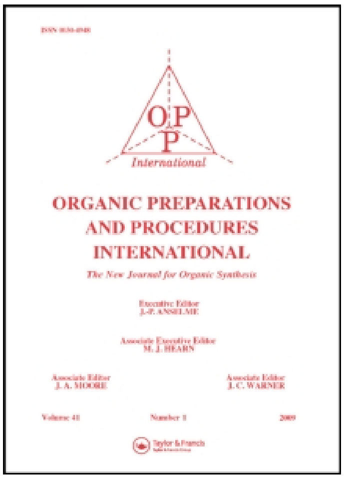

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IMPROVED PROCEDURE FOR THE SYNTHESIS OF (2*R*)-*N*-PROPENOYLBORNANE-2,10-SULTAM

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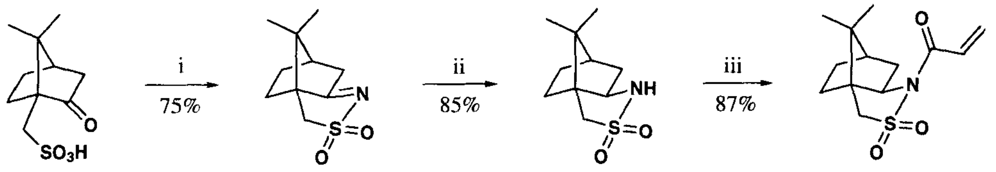
(2*R*)-*N*-Propenoylbornane-2,10-sultam (**4**), a chiral dipolarophile derived from Oppolzer's camphorsultam, has been widely used as a dienophile in Diels-Alder and 1,3-dipolar cycloaddition reactions, demonstrating excellent facial selectivity.[1] Excellent diastereoselectivity was also obtained in the asymmetric 1,3-dipolar cycloaddition of cyclic azomethine ylides and **4**.[2,3] In addition to its ability to induce chirality during cycloadditions, the chiral auxiliary is easily removed and may be recovered for re-use. Recently, we required several grams of this dipolarophile for the preparation of a library of tropane compounds.[4] While its synthesis has been reported by Oppolzer[5] and others,[6,7] access to a large quantity of **4** is restricted mainly because of the lack of a convenient procedure for the synthesis of (1*S*)-(–)-2,10-camphorsultam (**3**). This paper describes an improved procedure for the synthesis of **4** from (1*S*)-(+)-10-camphorsulfonic acid (**1**).

Some of the intermediates (**2** and **3**) for the synthesis of **4** from **1** are commercially available, but are expensive (*Scheme 1*). The two literatures for the synthesis of **3**[8,9] from the inexpensive starting material **1** are not convenient. Therefore, a number of modifications to the existing procedures have been described in this study.



1 **2** **3** **4**

i) $SOCl_2$, 0°C-rt; NH_4OH, CH_2Cl_2, rt; Amberlyst 15, toluene, reflux; ii) $LiAlH_4$, THF, reflux;
iii) TMSCl, Et_3N, C_6H_6/CH_3CN (6:1), rt; propenoyl chloride, 10 mol% anhyd. $CuCl_2$, benzene, reflux

Scheme 1

The conversion of **1** to (1*S*)-(+)-10-camphorsulfonyl chloride by PCl_5 is reported to give quantitative yield of the crude product.[8a] However, in spite of our best effort comparable yields of the crude product could not be obtained reproducibly. The crude product was very often contaminated with a significant amount of the starting acid **1**. Treatment of **1** with $SOCl_2$ in large excess of CH_2Cl_2 is also reported to give (1*S*)-(+)-10-camphorsulfonyl chloride.[9] We found that treatment of **1** with $SOCl_2$ as the solvent gave a nearly quantitative yield of the crude product.

Attempts to crystallize the crude (1*S*)-(+)-10-camphorsulfonyl chloride from different solvents (hexanes/ethyl acetate, hexanes/CH_2Cl_2 mixture, etc.) were not successful. Treatment of the crude product with ammonium hydroxide resulted in the complete conversion of (1*S*)-(+)-10-camphorsulfonyl chloride to (1*S*)-(+)-10-camphorsulfonamide, which was then converted to (1*S*)-(-)-10-camphorsulfonylimine (**2**) by refluxing a mixture of the crude product and Amberlyst 15 resin in toluene for 4 h. The resulting crude product was crystallized from ethanol to afford white crystals of camphorsulfonylimine **2** in 75% overall yield from **1**. The overall yield for this conversion is comparable to that of literature.[8,9] To avoid the risk during handling Raney nickel for the hydrogenation of **2**,[9] compound **2** was cleanly reduced to **3** with $LiAlH_4$ according to the literature procedure.[8c] However, the reported work-up procedure entails quenching the unreacted $LiAlH_4$ with 3N HCl, followed by a tedious extraction of the turbid aqueous layer with an organic solvent. It was difficult to extract the product from the aqueous layer efficiently, leading to a poor yield of **3**. Our modified work-up procedure does not involve any aqueous work-up or extraction (see *Experimental Section*). *N*-Acylation of **3** with propenoyl chloride in the presence of 10 mol% anhydrous $CuCl_2$ gave **4** in poor yield. Therefore, the *N*-trimethylsilyl derivative of **3** was prepared by stirring a mixture of **3** and TMSCl in benzene/acetonitrile mixture (6:1) in the presence of triethylamine.[7] *N*-Acylation of the crude *N*-trimethylsilyl derivative of **3** was carried out by refluxing a mixture of the crude product, propenoyl chloride, and 10 mol% of anhydrous $CuCl_2$ in benzene for 16 h. The crude product was crystallized from toluene to afford **4** in 77% yield. Concentration of the mother liquor followed by column chromatography [silica, hexanes/ethyl acetate = 7:3] of the mixture afforded additional amounts of **4** leading to an overall yield of 87% (from **3**).

An improved procedure for the synthesis of (2*R*)-*N*-propenoylbornane-2,10-sultam from the inexpensive commercially available (1*S*)-(+)-10-camphorsulfonic acid (**1**) has been described. The modified procedure is amenable to scale-up for the synthesis of **4**.

EXPERIMENTAL SECTION

All reagents were used as received unless noted otherwise. (1*S*)-(+)-10-camphorsulfonic acid (**1**) (99%) was obtained from Aldrich. All mps were determined on a Thermonik melting point apparatus. ^1H NMR (300 MHz) for compounds **2**, **3**, and **4** were recorded in $CDCl_3$ on a Bruker MSL 300 spectrometer using TMS as internal standard.

(1*S*)-(–)-5,10-Camphorsulfonylimine (2).- A 500 mL three-neck round-bottom flask equipped with a mechanical stirrer, an addition tube containing (1*S*)-(+)-10-camphorsulfonic acid (**1**) (21.0 g, 90.5 mmol), and a gas bubbler was charged with freshly distilled $SOCl_2$ (27.0 mL, 370 mmol). The addition of **1** was initiated in portions at 0°C with vigorous stirring (***Hood***). Immediate reaction was indicated by gas evolution. Addition was continued at the same temperature for 2 h. After completion of the addition, the cooling bath was removed, and the reaction mixture was stirred at room temperature for 2 h and was allowed to stand for 3-4 h. The black reaction mixture was then poured into a 500 mL beaker containing ~500 g of crushed-ice. The resulting mixture was immediately poured into another beaker containing a similar quantity of crushed-ice. The mixture was poured back and forth between the two beakers until all the evidence of reaction had disappeared. The solid product was collected and washed several times with ice-cold water. The moist product was dried under vacuum to afford crude (1*S*)-(+)-10-camphorsulfonyl chloride (19.8 g, 87%), mp. 65-67°C, *lit.*[8a] 67-69°C. The crude white solid was immediately used in the next step.

A 1L three-neck round-bottom flask equipped with a mechanical stirrer, addition funnel, and a gas outlet was charged with reagent grade NH_4OH (250 mL, excess) and cooled to 0°C. A solution of the crude camphorsulfonyl chloride in CH_2Cl_2 (250 mL) was added dropwise over 30 min and the reaction mixture was stirred at 0°C for 2 h. The reaction mixture was transferred to a 1L separatory funnel, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL), and the combined organic extracts were dried over Na_2SO_4. Filtration and removal of the solvent using a rotary evaporator gave 15.7 g, (86%) of the crude camphorsulfonamide, mp. 123-125°C, *lit.*[8b] 125-128°C. Very often the crude sulfonamide is contaminated with 5-10% of the camphorsulfonylimine **2**; its yield increases if the reaction mixture is allowed to stand at room temperature.

A mixture of the crude sulfonamide and pre-activated (dried in oven over 72 h) Amberlyst 15 resin (2 g) in toluene (250 mL) was refluxed for 4 h using a Dean-Stark apparatus, then CH_2Cl_2 (100 mL) was added to the warm reaction mixture to dissolve any crystallized camphorsulfonylimine. The solution was filtered through a sintered glass funnel, and the funnel was washed with CH_2Cl_2 (100 mL). The combined filtrate was concentrated under reduced pressure to afford a white solid. The resulting solid was crystallized from ethanol (200 mL) to give white crystals of **2** (14.6 g, 75% overall yield from **1**), mp. 221-223°C, *lit.*[8b] 225-228°C. The ^1H NMR spectra was identical with reported data.[8b]

Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.57; S, 15.03
Found: C, 56.20; H, 7.07; N, 6.65; S, 15.13

(1*S*)-(-)-2,10-Camphorsultam (3).- A 250 mL round bottom flask, equipped with a Soxhlet extractor connected to a gas bubbler, was charged with anhydrous THF (120 mL) and $LiAlH_4$ (1.27 g, 0.0320 mol). A solid sample of **2** (7.20 g, 0.0337 mol) was placed in the Soxhlet thimble, and the mixture was heated at reflux. After the entire solid had been siphoned into the reaction flask (3-4 h), the mixture was allowed to cool to room temperature and stand at room temperature for 3-4 h. The solution was filtered and an equal volume of ethyl acetate was added to the filtrate at 0°C. The unreacted $LiAlH_4$ was quenched by the careful dropwise addition of water to the solution at 0°C with constant shaking. The solution became a little turbid after the $LiAlH_4$ was fully quenched. Anhydrous Na_2SO_4 was then added to the turbid solution with constant shaking until a clear solution developed (Na_2SO_4 forms a silver-colored lump). Filtration of the solution followed by evaporation of the solvent gave a crude product, which upon crystallization from ethanol, afforded white crystals of **3** (6.17 g, 85% yield), mp. 181-183°C, *lit.*[8c] 183-184°C. $[\alpha_D]^{25}$ = -29.7°, *lit.*[8c] $[\alpha_D]^{25}$ = -30.7° (c = 2.3, $CHCl_3$). The ^1H NMR data were identical with the reported values.[8c]

Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.51; S, 14.89
Found: C, 55.88; H, 7.87; N, 6.49; S, 14.83

(2*R*)-*N*-Propenoylbornane-2,10-sultam (4).- A solution of **3** (5.00 g, 23.0 mmol) in anhydrous C_6H_6/CH_3CN (60 mL, 6:1) mixture was treated dropwise with TMSCl (14 mL, 0.11 mol) at room temperature. The mixture was then cooled to 0°C in an ice-bath. Triethylamine (3.8 mL, 26 mmol) in anhydrous C_6H_6 (20 mL) was added slowly to the cold solution resulting in the immediate formation of a white precipitate. The heterogeneous mixture was stirred at room temperature for 15 h and then concentrated to dryness under reduced pressure. The white residue thus obtained was washed with toluene (3 x 25 mL) to dissolve the product. Filtration of the combined washings followed by concentration of the filtrate gave a crystalline product which used directly in the next step.

A mixture of the crude *N*-trimethylsilyl derivative of **3**, propenoyl chloride (5.70 mL, 70.2 mmol), and freshly prepared anhydrous $CuCl_2$ (0.234 g, 1.74 mmol) in anhydrous benzene (25 mL) was heated at reflux for 16 h under N_2.[7] The warm mixture was filtered through a sintered glass funnel, and the residue on the funnel was washed several times with ethyl acetate. The combined filtrates were concentrated to afford a white solid which was crystallized from toluene to give white needles of **4** (4.80 g, 77% yield). The mother liquor was concentrated to dryness and the residue was purified by column chromatography [silica, hexanes/ethyl acetate (7:3)] to give additional 0.60 g of **4** (a total of 5.40 g, 87% yield), mp. 102-105°C, *lit.*[5] 105-107°C, $[\alpha_D]^{25}$ -45°, *lit.*[5] $[\alpha_D]^{25}$ -48° (c = 5.5, $CHCl_3$). The ^1H NMR data was identical with reported values.[5]

Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20; S, 11.90
Found: C, 57.89; H, 7.17; N, 5.29; S, 11.80

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