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A Two-Step Synthesis of Camphosultam

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A TWO-STEP SYNTHESIS OF CAMPHOSULTAM.

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ABSTRACT: Modifications of the known route to camphosultam led to an easy two-step process. The unique intermediate is simply isolated by filtration. The overall yield is 66% on a hundred gram scale.

Camphosultam is a useful asymmetry inducer used *i.a.* in 6π-cycloaddition[1], 1-4 additions and enolate trapping reactions[2]. This reagent can be prepared in several steps, but we were looking for a synthesis that would be shorter and use the reagents as safe as possible.

Preparations of camphosultam **2** normally start with camphorsulfonic acid which is converted to its chloride by means of phosphorus pentachloride[3] or thionyl chloride at various temperatures[4]. In the first syntheses of camphorsulfamide **3**, aqueous ammonia was used[5]. An improvement of this reaction was to proceed with a two-phase system by adding methylene chloride[6]. Other conversions of the acid chloride into the sulfamide are performed with gaseous ammonia in benzene[7], toluene[8] or chloroform[9].

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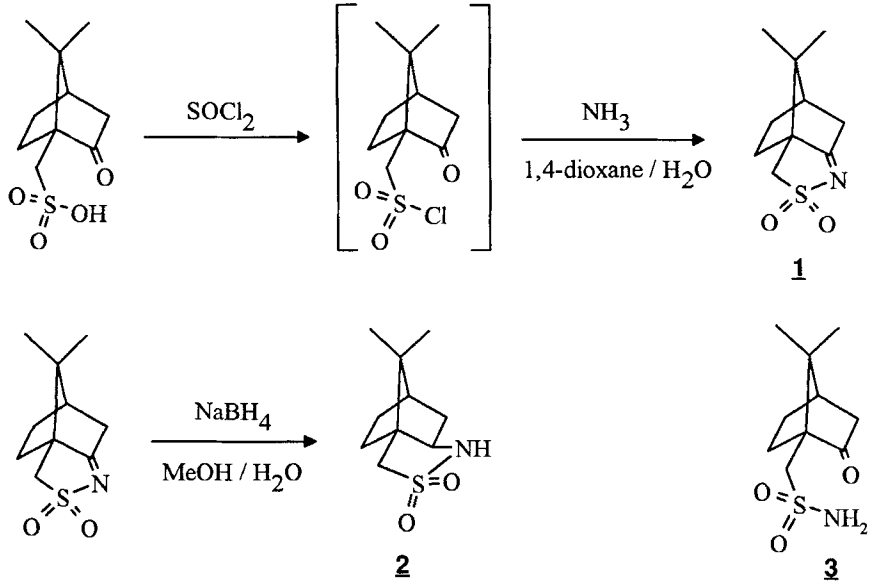
The dehydration between the sulfamide moiety and the ketone takes place in acidic[9] (Amberlyst 15 in toluene with azeotropic distillation) or basic medium[8] (sodium methylate in methanol), or even by heating at 180°C without solvent[10]. The final step is the reduction of the imine **1** with hydrogen in the presence of Raney nickel[11], lithium aluminium hydride[12], [8] or sodium borohydride in aqueous ethanol[13].



1

2

3

In the first preparation of camphorsulfamide **3**[5], an insoluble by-product was isolated, the structure of which was further established as the cyclised imine **1**[4b]. By changing the reaction conditions, we have been able to drive this side reaction to completion and obtain the sulfone-imine **1** through an easy filtration. This intermediate does not require drying before being reduced by sodium borohydride in aqueous methanol.

These latter conditions are safer than those with lithium aluminium hydride and also avoid the use of a soxhlet[12] or large amounts of tetrahydrofuran[8].

This new preparation allows a two-step preparation of the useful camphosultam **2**. It has been routinely performed on a hundred gram scale with a 66% overall yield (after recrystallization).

Experimental section.

Optical rotation was determined with a Perkin Elmer Model 241 polarimeter. NMR spectra were recorded on a Brücker WM (250 MHz) spectrometer (δ in ppm, J in Hz).

Camphorsulfone-imine **1** (3aS)-4,5,6,7-tetrahydro-8,8-dimethyl-2,2-dioxide-3H-3a,6-methano-2,1-benzisothiazole.

Thionyl chloride (60 ml, 0.88 mol) is added dropwise to camphorsulfonic acid (101.9 g, 0.44 mol). The reaction mixture is then heated at 115°C until gas evolution ceases. DMF (two drops) is then added to ensure the completion of the reaction. Excess thionyl chloride is then removed by evaporation, the remaining traces being removed by codistillation with toluene (50 ml). The resulting yellow mass is dissolved in 1,4-dioxane (200 ml) and poured into cold (7°C) concentrated ammonia (1.65 l, d = 0.866). The reaction mixture is then stirred at room temperature for two hours and heated at 90°C for four hours. After cooling to room temperature, the insoluble product is filtrated and washed with water (2x50 ml) to give the camphorsulfone-imine (83 g, 89%).M.P. = 230°C; $[\alpha]^{20}_D$ = -32.2 (c = 2; $CHCl_3$) (litt.[6] $[\alpha]^{20}_D$ = -32.7 (c = 1.9; $CHCl_3$)); ^1H NMR ($CDCl_3$) δ: 0.89 (s, 3H: CH_3), 1.10 (s, 3H: CH3), 1.49, 1.79 and 2.08 (3 m, respectively 1, 1 and 2H: CH_2CH_2), 2.26 (m, 1H: CH), 2.40 and 2.78 (respectively d and dm, J = 16 Hz, 1H each: CH_2), 2.99 and 3.18 (2d, J = 11.5 Hz, 1H each: CH_2SO_2).

Camphosultam **2** (3aS)-hexahydro-8,8-dimethyl-2,2-dioxide-3H-3a,6-methano-2,1-benzisothiazole.

Sodium borohydride (14.4 g, 0.39 mol) is added by portions to a cold (5°C) solution of camphorsulfone-imine (83 g, 0.39 mol) in methanol (390 ml) and water (130 ml). After completion of the reaction (TLC) methanol is evaporated, dichloromethane (100 ml) is added and the mixture poured into aqueous sulfuric acid (540 ml, 2N). The product is extracted with dichloromethane (2x150 ml) and the combined extracts washed with brine and dried over magnesium sulfate. Evaporation and recrystallization from ethanol (35 ml) give camphosultam (61.7 g, 74%). M.P. = 190-1°C; $[\alpha]^{20}_D$ = -31.3 (c = 5; $CHCl_3$) (litt.[13] $[\alpha]^{20}_D$ = -31 (c = 5; $CHCl_3$)); ^1H NMR (DMSO) δ: 0.88 (s, 3H : CH_3), 1.07 (s, 3H: CH_3), 1.30 (m, 2H: CH_2), 1.80 (m, 5H: CH_2 and CH), 3.07 (AB, J = 14, 2H: CH_2SO_2), 3.22 (m, 1H: CHN), 7.00 (bs, 1H: NH).

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