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A Convenient, Improved Synthesis of (Camphoryl)sulfonyl Oxaziridines.

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Abstract:: A convenient, efficient procedure for the large scale synthesis of chiral oxidizing reagents (+), and (-)-((8,8-dichlorocamphoryl)sulfonyl)oxaziridine, **5**, as well as of 8,8 unsubstituted (+), and (-) (camphoryl)sulfonyl oxaziridine, **4**, from (+), or (-) (camphorylsulfonyl)imine, **2**, in step yields of 83% to 95%, is reported.

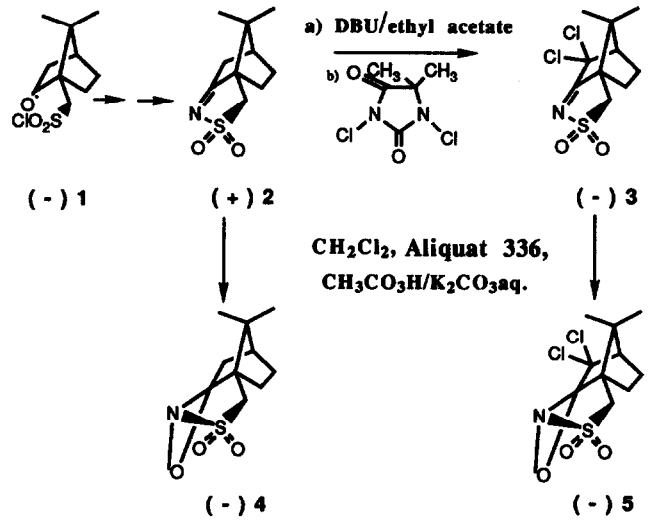
The use of camphorylsulfonyl oxaziridines for the syntheses of chiral compounds is of current interest.[1-3] Recently the use of (+), and (-) (camphoryl)sulfonyl oxaziridine, **4**, as well as of (+), and (-)-8,8-((dichlorocamphoryl)sulfonyl)oxaziridine, **5**, as efficient hydroxylating reagents for the synthesis of chiral α-hydroxyketones has been reported.[1,4] In order to investigate whether the above hydroxylation procedure is suitable for a large scale (kilo quantities) synthesis of chiral intermediates of pharmaceutical interest, we needed multikilo quantities of **4**, and **5**. The preparation of **5** involves the oxidation of dichloro camphor sulfonylimine **3**, which in turn can be prepared either from camphorsulfonyl chloride **1**[5] or from camphor.[6] The preparation of **4** and **5** is achieved via the intermediate **2**. Since a detailed high yielding preparation of **2** from **1**, suitable for the large scale synthesis of **2**, is available,[5,7] the work described in this paper focusses on improving the conversion of **2** to **4**, and **5**.

In the published procedures for the conversion of **2** to **4**, or **5**, the following conditions are undesirable for a large scale preparation of the oxaziridines: (i) The formation of the anion of **2** with bis(trimethylsilyl)amide (i.e. sodium hexamethyldisilazane (NaHMDS)) at a low temperature (-78°) followed by its slow cannulation into a solution of *N*-chlorosuccinimide (NCS) in anhydrous THF also maintained at (-78°). At this low temperature a large volume of anhydrous THF is needed to maintain a homogeneous solution of the anion of **2** so that it can be cannulated. This in turn adds to the cost of cooling, and lengthens the addition time. (ii) Both, NaHMDS, and NCS are expensive, and the handling of the former is difficult. (iii) The formation of trichlorinated byproducts resulting from this procedure[8] lowers the yield of the desired product, necessitating chromatographic purification of **3**, resulting in only 64% yield of pure **3**. (iv) The use of excess (and in some cases, purified, >95%) *m*-chloro perbenzoic acid (*m*CPBA) is cost prohibitive as well as hazardous. In our hands, after the oxidation, the purification of **4**, or **5** from *m*CPBA/*m*CBA was difficult requiring repeated filtrations or crystallizations of the oxaziridines and resulting in the loss of product.

The following improved procedure overcame the impracticality, cost, and safety issues. It was postulated that the use of moderately reactive reagents may allow higher reaction temperature, which in turn would allow more concentrated reactions. Since it is known in the literature that the reaction of **2** with bases can lead to rearranged products,[9] we first focussed our attention on the chlorinating reagent. We report here that at -78° NCS can be substituted with inexpensive dichlorodimethylhydantoin (DCDMH),[17] and that it can be directly added to the anion of **2** thus eliminating the inverse cannulation. Furthermore, the use of this reagent

significantly minimized the formation of multichlorinated byproducts, thus eliminating the chromatographic purification of **3**. Our subsequent work revealed that the less reactive bases, Na-O-*t*Bu, K-O-*t*Bu, DBN, DBU, etc. can replace NaHMDS, with a varying degree of success, for the conversion of **2** to **3**. Since DBU is readily available in large quantities, and can be recycled,[10] efforts were concentrated on optimizing conditions associated with the use of DBU for the chlorination of **2**. During this optimization work, it was established that *(a)* inexpensive ethyl acetate can replace anhydrous THF as a solvent, and that *(b)* the reaction can be run at room temperature allowing a 20% reaction concentration (vs. ≈1% at -78°). The optimized conditions, detailed in the experimental section, gave 95% yield of excellent quality **3**. Thus the undesirable conditions [(i) to (iii) mentioned above] associated with the synthesis of 8,8 dichloro (camphorylsulfonyl)imine were eliminated.

Scheme I



(-) **1** (+) **2** (-) **3**

(-) **4** (-) **5**

As for the oxidizing reagent, commercially available[11] 50-60 % *m*CPBA proved a reasonable alternative to purified *m*CPBA for the oxidation of **3** (which is more hindered than **2**, and hence more difficult to oxidize). However, in order to avoid the formation of less polar byproducts (observable by tlc), it was necessary that the oxidation of the imines **2**, and **3** be completed in a short period of time. This necessitated a large excess of *m*CPBA, which in turn made the work up/isolation of the oxaziridines **4**, and **5**, respectively, difficult. The sensitivity of oxaziridines to acid or strong aqueous bases limited the choice of alternative work ups. Work in our laboratories demonstrated that the oxidation of **2** could be carried out with Oxone®, peracetic acid, or magnesium monoperoxyphthalate. Of these reagents, based on cost, reproducibility of the reaction, and operational ease, peracetic acid became the reagent of choice for further optimization. Thus the search to replace *m*CPBA culminated in the development of phase transfer catalyzed [12] peracetic acid oxidation of **3**. This procedure, reported in the experimental section, gave highly pure **4**, and **5** in 86%, and 95% yield, respectively. For those locations where the use of CH_2Cl_2 is undesirable,we have established that EtOAc can be used as a solvent for the above reaction with a 90% isolated, unoptimized step yield for the synthesis of more hindered **5**.

Camphorylsulfonyl oxaziridines have been previously reported to be thermally stable compounds,[5] however no data on their thermal stability is available. In order to use these reagents safely on a large scale, they were subjected to hazard evaluation.[13,14] Based on these studies, it was concluded that these oxaziridines can be handled, and stored safely at a temperature of 50°C or lower.

In summary, a practical, efficient procedure for the large scale synthesis of (-), and (+) -((8,8-dichlorocamphoryl)sulfonyl)oxaziridines, **5**, as well as of (-), and (+) (camphorylsulfonyl)oxaziridines, **4**, from (camphorylsulfonyl)imine **2**, has been developed. Several kilos of (camphoryl)sulfonyl oxaziridines were made using this procedure.[16] A systematic hazard evaluation of oxaziridines **4**, and **5** was conducted, and guidelines are issued for their safe, large scale, synthetic use. It is hoped that this convenient synthesis and the guidelines for the safe use of oxaziridines will promote interest in this class of compounds. This, in turn, should encourage scientists to explore the applications of oxaziridines in the synthesis of chiral compounds.

EXPERIMENTAL SECTION

(-)-((8,8-Dichlorocamphoryl)sulfonyl)imine (3): To a suspension of 200 g (0.938 moles) of (+)-(camphorsulfonyl)imine **2** [15] in 1.0 l ethyl acetate 284 g (1.865 moles) 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) was added. After stirring for 30 minutes at room temperature 206 g (1.046 moles) of 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) was added in portions over ca. 90 minutes maintaining the temperature between 20° to 25°C by cooling with an ice/water bath. At the end of the reaction 1.6 l water was added slowly, keeping the temperature between 20° to 25°C (pH of water phase: ca. 13). The pH was adjusted to 7 - 7.5 by the addition of ca. 100 ml conc. HCl at 25° to 30°C. Ethyl acetate was then removed *in vacuo* at max. 60°C (bath temperature). The suspension was stirred for ca. 1 hour at 20° to 25°C and filtered. The product was washed with 2.0 l water and dried in a draft oven at 50°C to obtain 252g (95%) of the title compound, identical to the product obtained via the literature procedure,[4] m.p.170° to 175°C, $[\alpha]^{20}_D$ -97.8° (c = 1; CH_3CN).This product is suitable for further reactions without purifications.

For identification purpose,the product (9 g) was purified by recrystallization from isopropanol (155 ml) to give white crystals, 7.2 g (80%) (m.p. : 177° to 179°C); lit.[4] m.p. 174°C, $[a]^{20}_D$ -8.6° (c=1.3; $CHCl_3$).

(+)-((8,8-Dichlorocamphoryl)sulfonyl)imine (3): In a typical experiment, starting from 350g, of (-)-(camphorsulfonyl)imine **2** [15] ,(+)3, identical to one obtained via the literature procedure,[4] was obtained in 90% yield.

(-)-((8,8-Dichlorocamphoryl)sulfonyl)oxaziridine (5): To a stirred solution of 191.8 g (0.68 moles) of (-)-8,8-((dichlorocamphoryl)sulfonyl)imine[11], (-)3, in 1.2 l methylene chloride, 14 g Aliquat 336 was added. Next a solution of 476 g (3.44 moles) of potassium carbonate in 1.0 l water was added slowly to the reaction mixture maintaining the temperature between 0° and 10°C. To this vigorously stirred reaction mixture 136 g (0.751 moles) of peracetic acid (42% in acetic acid) was added at such a rate (over ca. 30 minutes) that the temperature remained between 0° to 3°C.

At the conclusion of the reaction 5 g (39.7 mmol) sodium sulfite was added and the cold reaction mixture stirred for 30 min. Next 30 ml of 30% aq. NaOH was added and the reaction mixture was warmed to 20°C. The phases were separated and the aqueous phase was extracted with 2x100 ml methylene chloride. The combined organic phase was washed with 200 ml sat. aq. $NaHCO_3$ followed by 2X 200 ml H_2O. From this *ca.* 850 ml methylene chloride was removed *in vacuo* maintaining the internal temperature below 40°[13,14]. During distillation crystallization occured. The resultant slurry was treated with 700 ml *n*-hexane, cooled (0° to 5°C) and stirred for 1 hour. The product was filtered, washed with 2x100 ml *n*-hexane and dried at max. 40°C in an air draft oven. Yield 194.0 g (95.7%),identical to the product obtained via the literature procedure,[4] m.p. 184° to 186°C, $[\alpha]_D^{20}$ -92° (c = 0.5; $CHCl_3$); lit.[4] m.p. 178-80°C, $[a]^{20}_D$ -88.3° (c=1.3; $CHCl_3$).

The product (100 g) can be recrystallized, if necessary, from ethanol/ethyl acetate (1.5 l/300 ml) to give white crystals (72 g + 16 g from mother liquor) in 88% yield.

(+)-((8,8-Dichlorocamphoryl)sulfonyl)oxaziridine(5): In a typical experiment, starting from 270g of (+)-8,8-((dichlorocamphoryl)sulfonyl)imine 3, (+) 5, identical to the one one obtained via the literature procedure,[4] was prepared in 83% yield using the above procedure.

(-)-(camphoryl)sulfonyl oxaziridine (4): In a typical experiment, starting from 100g of (+)-(camphorsulfonyl)imine 2 [15], (-)4, identical to material obtained via the literature procedure[5] was obtained in 86% yield using the above procedure.

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8. The tetrachlorinated byproduct, which is eventually detrimental to the enantiomeric excesses during the hydroxylation of ketones, was isolated as the major byproduct in our laboratories. These are unpublished results.
9. Davis, F. A.; Weismiller, M.C., Lal G. S.; Chen, B. C.; Przeslawski, R. M.; *Tetrahedron Lett.*, **1989**, *30*, 1613.
10. This recovery is important from a cost point of view, as well as from an ecological point of view. Towards this end, our limited work suggests that a partial recovery and the recycle of DBU is possible with ion exchange resins.
11. This is available, e. g., from Aldrich Chemical Co., Milwaukee, Wisconsin, USA.
12. A PTC catalyzed oxidation (of benzophenone hydrazones) at alkaline pH was the basis of this work. Adamson, J. R.; Bywood, R.; Eastlick, D. P.; Gallagher, G.; Walker, D.; Wilson, E. M*J.C.S. Perkin I*, **1975**, 2030.
13. Buckley, J. T.; Marino, J. P.; Emery, R. L. in "Process Hazard Identification in the Pharmaceutical Industry" Am. Inst. of Chem. Engineers, Spring National Meeting, April, 9, 1991, Houston, Texas.
14. We thank Dr. W. Hoffmann at Goedecke, Freiburg, Germany for conducting ARC safety studies on the oxaziridines.
15. (+)-(Camphorsulfonyl)imine was synthesized from (1R)-(-)-10-camphorsulfonic acid purchased from Calaire Chimie S.N.C. using the procedure described in references 5, and 7.
16. Compounds (+)5, and (-)5 have recently beccame commercially available from Fluka Chemie AG.
17. Although the use of this inexpensive reagent in place of NCS as a source of chlorine via free radical mechanism is known since early 1950s (e.g. *C. A. 47*:3244*a*; *C.A. 49*:11006*h*), its use as a source of electrophilic chlorine reported in this article is new. It is hoped that this report would encourage others to evaluate DMDCH in place of NCS for similar reactions.

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