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Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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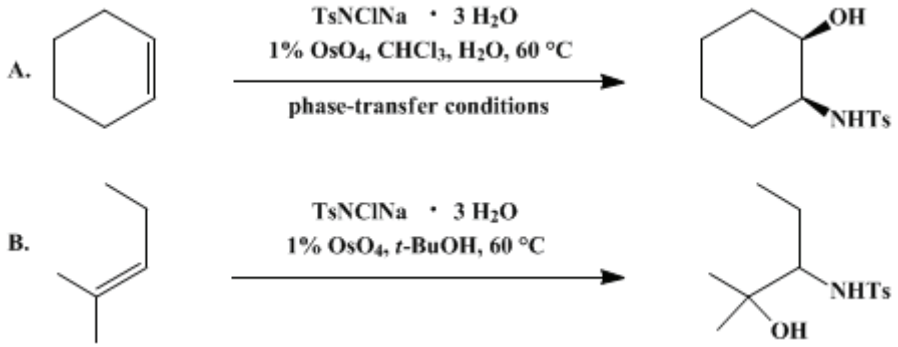
OSMIUM-CATALYZED VICINAL OXYAMINATION OF OLEFINS BY CHLORAMINE-T: *cis*-2-(*p*-TOLUENESULFONAMIDO) CYCLOHEXANOL AND 2-METHYL-3-(*p*-TOLUENESULFONAMIDO)-2-PENTANOL

[Benzenesulfonamide, *N*-(2-hydroxycyclohexyl)-4-methyl-, *cis* and Benzenesulfonamide, *N*-(1-ethyl-2-hydroxy-2-methylpropyl)-4-methyl-]



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Checked by Rita Locher, Thomas Weller, and Dieter Seebach.

1. Procedure

Caution! Because of the volatility and toxic nature of OsO_4, these reactions should be carried out in a well-ventilated hood.

A. *cis-2-p(Toluenesulfonamido)cyclohexanol*. A 1-L, three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, thermometer, and reflux condenser. The flask is charged with 8.2 g (0.1 mol) of cyclohexene (Note 1), 250 mL of reagent grade chloroform (Note 2), and 10 mL (1 mmol) of osmium tetroxide catalyst solution (Note 3). To the resulting black solution is added a solution of 35.2 g (0.125 mol) of chloramine-T trihydrate (Note 4) and 1.1 g (5 mmol) of benzyltriethylammonium chloride (Note 5) in 250 mL of distilled water. Vigorous stirring is begun, and the reaction mixture is brought to 55–60°C by means of a heating mantle.

After 10 hr at 55–60°C, 14.2 g (0.1 mol) of sodium sulfite (Note 6) is added and the mixture is refluxed for 3 hr. The hot reaction mixture (Note 7) is transferred to a 1-L separatory funnel and allowed to stand for 10 min. The organic layer is collected in a 500-mL, round-bottomed flask. The aqueous layer is extracted once with 25 mL of $CHCl_3$ that is then combined with the original organic layer. Removal of solvent with a rotary evaporator provides a residue (Note 8) that is transferred to a 350-mL fritted-glass funnel and triturated successively with 200 mL and 100 mL of saturated sodium chloride solution containing 1% sodium hydroxide (Note 9) and finally with two 50-mL portions of distilled water.

The resulting solid is placed in a 500-mL Erlenmeyer flask and dissolved in a mixture of 250 mL of $CHCl_3$ and 25 mL of CH_3OH. Anhydrous magnesium sulfate (ca. 8–10 g) is added and the resulting suspension is stirred magnetically for 5 min. Filtration of this suspension through a Celite mat on a sintered-glass funnel (Note 10), followed by evaporation of the solvent, affords (after drying under reduced pressure) 20.3–22 g (75–81.2%) of almost pure *cis*-2-(*p*-toluenesulfonamido)cyclohexanol, mp 155–157°C (Note 11). The oxyaminated product may be purified further by washing with toluene to give 20–21.8 g (74.3–80.9%); mp 157–158°C (Note 12).

B. *2-Methyl-3-(p-toluenesulfonamido)-2-pentanol*. A 500-mL, three-necked, round-bottomed flask is equipped with an efficient mechanical stirrer, thermometer, and reflux condenser. The flask is

charged with 8.4 g (0.1 mol) of 2-methyl-2-pentene (Note 1), 100 mL of reagent-grade *tert*-butyl alcohol (Note 2), 10 mL (1 mmol) of osmium tetroxide catalyst solution (Note 3), and 35.2 g (0.125 mol) of chloramine-T trihydrate (Note 4). Vigorous stirring is begun, and the reaction mixture is brought to 55–60°C by means of a heating mantle.

After ca. 20 hr at 55–60°C, the mixture is cooled to room temperature using a water bath, and then 1.1 g (0.03 mol) of sodium borohydride is added (Note 6). Stirring is continued at room temperature for about 1 hr. Removal of the solvent on a rotary evaporator gives an oil that is taken up in 100 mL of ethyl acetate and washed once with a solution that is prepared by mixing 100 mL of saturated sodium chloride solution containing 1% sodium hydroxide (Note 13) with 25 mL of distilled water. The organic layer is washed twice more with 200 mL of saturated sodium chloride solution containing 1% sodium hydroxide and finally with 100 mL of saturated sodium chloride solution (Note 9) and (Note 14). Addition of anhydrous magnesium sulfate, filtration through a column of 75 g of silica gel (Note 15), elution with ethyl acetate (Note 16), and evaporation of the solvent on a rotary evaporator provides 21.5 g of the crude oxyaminated product (Note 17). The solid is then washed twice with ether (Note 18) to give 13.8–14.9 g (51–55%) of white, crystalline 2-methyl-3-(*p*-toluenesulfonamido)-2-pentanol, mp 96–97°C. Concentration of the ether yields an additional 4.0–5.0 g (15–18%) of oxyaminated product, mp 95–97°C (Note 19).

2. Notes

1. Cyclohexene and 2-methyl-2-pentene were used as commercially available.
2. The amount of solvent used is not critical. Several experiments have been performed at higher and lower concentrations and in all cases the yields were very much alike.
3. Osmium tetroxide was supplied commercially in 1-g amounts in sealed glass ampuls. The procedure we describe below should be followed to prepare the osmium tetroxide catalyst solution. Work in a well-ventilated hood. One ampul is scored in the middle, broken open, and the two halves are dropped into a clean brown bottle containing 39.8 mL of reagent grade *tert*-butyl alcohol and 0.20 mL of 70 or 90% *tert*-butyl hydroperoxide. The bottle is capped (use caps with Teflon liners) and then swirled to ensure dissolution of the OsO_4. Each milliliter of this stock solution contains 25 mg (ca. 0.1 mmol) of OsO_4. These solutions are stored in the hood at room temperature and seem to be very stable. We have also prepared five times more dilute solutions of OsO_4 in *tert*-butyl alcohol, which we use for small-scale experiments.[2]
4. Chloramine-T trihydrate (CT) was obtained commercially. Excess chloramine-T is used because we have observed traces of the α-ketosulfonamide in those cases where the oxyaminated product contains a secondary hydroxyl group. We have also observed that these α-ketosulfonamides are further oxidized under the reaction conditions in a process that consumes several moles of chloramine-T.
5. Benzyltriethylammonium chloride was used as purchased.
6. The rates of reduction of the osmate esters vary considerably. We found that, although the sulfite method (in the past we have also used sodium bisulfite) would reduce osmate esters from monosubstituted and 1,2-disubstituted olefins, osmate esters derived from trisubstituted and 1,1-disubstituted olefins were more inert to this treatment. Sodium borohydride reduces even these more hindered osmate esters rapidly at room temperature.
7. The oxyaminated product derived from cyclohexene is highly crystalline and begins to crystallize if the chloroform phase is allowed to cool.
8. The residue is dried under reduced pressure to remove the last traces of chloroform and *tert*-butyl alcohol, and then pulverized with a mortar and pestle.
9. In this way the *p*-toluenesulfonamide by-product along with some other impurities are removed from the oxyaminated product.
10. This treatment removes the suspended osmium particles from the solution.
11. GLC analysis revealed a purity of 99%.
12. The product obtained by this procedure is pure enough for most purposes. Its melt, however, is faintly cloudy. A product of higher purity, giving a clear melt, mp 158–159°C, can be obtained by recrystallization from about 10 mL of $CHCl_3$ per gram of oxyaminated product. The structural characterization of *cis*-2-(*p*-toluenesulfonamido)cyclohexanol, mp 158–159°C, is as follows. Anal. calcd. for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20. Found: C, 57.81; H, 6.98; N, 5.19. ^{1}H NMR ($CDCl_3$) δ: 1.2–1.9 (m, 8 H, C*H*), 2.26 (d, 1 H, J = 4, O*H*), 2.44 (s, 3 H, Ar CH_3), 3.30 (m, 1 H, NC*H*), 3.80 (m, 1

H, OC*H*), 5.30 (d 1 H, *J* = 7, N*H*), 7.55 (AA'BB' pattern, 4 H, *J* = 8, Ar*H*); IR (KBr pellet) cm^{-1}: 3420, 3150, 1305, 1285, 1145, 1085, 550 all (s); 2920, 2850, 1440, 970, 930, 890, 815, 660 all (m): 1590, 1370, 1250, 1195, 1185, 1060, 1000 all (w). GC analysis was carried out using the following conditions: 6-ft × 2-mm glass column, packed with 5% OV-17 on 80/100 GasChrom Q, at 70 ρ 250°C (32°C/min), retention time 9.50–9.60 min.

13. First a 1% solution of NaOH is prepared and then sodium chloride is added until saturation is reached. For the first washing, 25 mL of distilled water is added to 100 mL of the above solution in order to dissolve the inorganic salts present in the reaction mixture.

14. When ethyl acetate is used as the extracting solvent, rapid separation of the two phases was achieved. If a slight emulsion forms at the interphase during the last wash, the addition of celite and subsequent filtration improves the separation.

15. Silica Gel 60 (70–230 mesh ASTM) was used as obtained commercially. A column 50 cm long by 3.5 cm in diameter was used.

16. Approximately 700 mL of EtOAc was necessary to elute all the oxyaminated product from the silica gel column (monitoring by TLC elution with EtOAc is continued until a UV active spot does not appear on TLC). To speed up filtration, a slight pressure of 4 psi is applied.

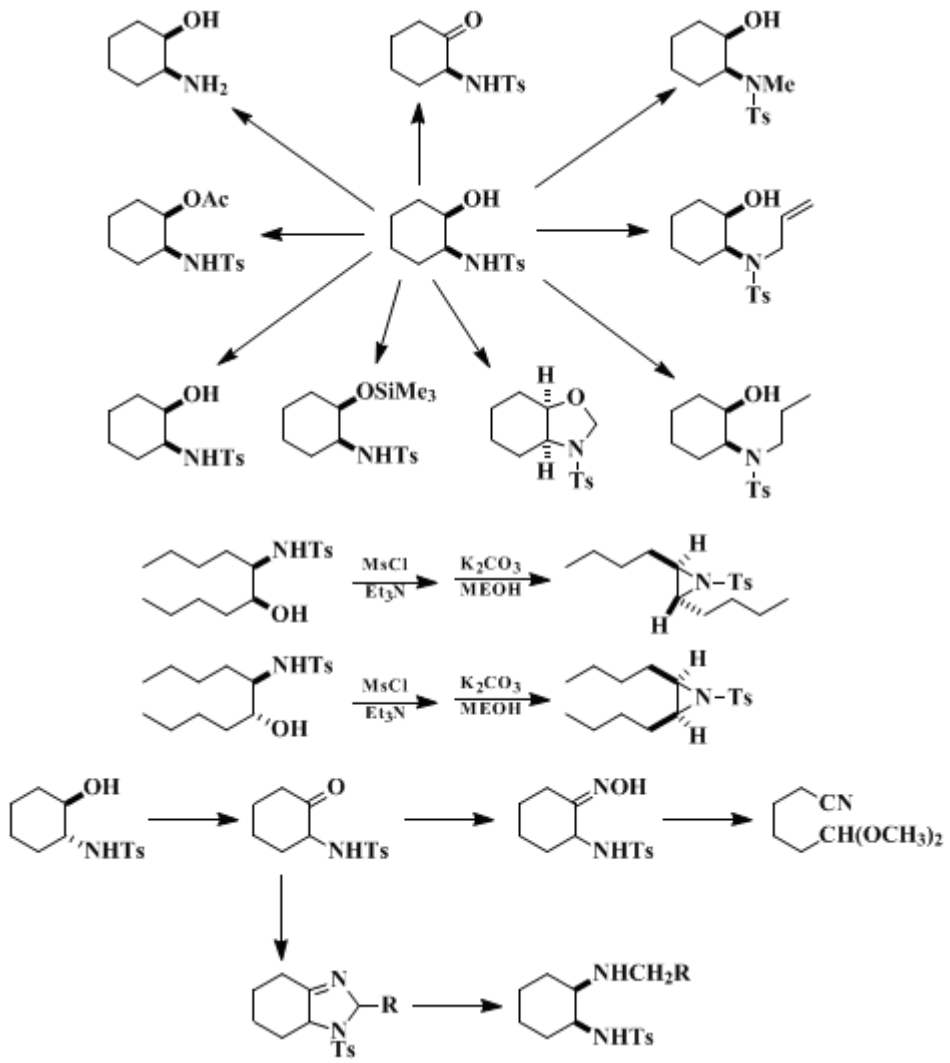
17. The product is a yellowish-brown solid that usually crystallizes when the last traces of EtOAc are removed on the rotary evaporator. If problems are encountered in inducing crystallization, either high vacuum or addition of ether followed by concentration should yield the desired solid.

18. The solid was washed in a 60-mL, sintered-glass funnel, the first time with 30 mL of ether and the second time with 25 mL.

19. The product obtained by this procedure is relatively pure. However, a product of higher purity, giving a clear melt, mp 99–100°C, can be obtained by recrystallization from about 1 mL of toluene per gram of oxyaminated product.

3. Discussion

This osmium-catalyzed procedure provides the first practical and direct means for the cis addition of a hydroxyl group and an arylsulfonamido moiety ($ArSO_2NH$) to an olefinic bond. The resulting vicinal hydroxy arylsulfonamides may in some cases be useful in their own right, but they are easily transformed in a variety of selective and potentially useful ways. Some of the interesting transformations that we[3] have observed are shown below:



Procedure (Step) A is very effective for most monosubstituted and 1,2-disubstituted olefins. This method,[2] using phase-transfer conditions (PTC), has been developed recently in our laboratory and represents a substantial improvement over our former procedures.[4] [5] [6] Cyclooctene, (*Z*)-5-decene, stilbene, ethyl crotonate, and 1-decene are among the olefins that are readily oxyaminated under the conditions described in Procedure A.

It is important to point out that the work-up we have used in the case of cyclohexene is a peculiar one because of the exceptional crystallinity of the oxyamination product. Generally, removal of the *p*-toluenesulfonamide is accomplished by shaking the chloroform layer with a saturated sodium chloride solution containing 1% sodium hydroxide.

The chloramine derivatives ($ArSO_2NClNa$) of a variety of other arylsulfonamides (Ar = phenyl, *o*-tolyl, *p*-chlorophenyl, *p*-nitrophenyl, and *o*-carboalkoxyphenyl) have been used successfully in these catalytic oxyaminations. Since only chloramine-T (Ar = *p*-tolyl) and chloramine-B (Ar = phenyl) are commercially available, we have developed a convenient procedure for generating the chloramines in situ for use in the modification involving phase-transfer catalysis. One simply stirs a suspension of the arylsulfonamide with an equivalent of sodium hypochlorite (Clorox) until a homogeneous solution is obtained. When this solution is used in the PTC method (see 2 for experimental details), the yields of oxyaminated product are comparable with those obtained with isolated chloramine salts.

The PTC method gives poor results with trisubstituted and 1,1-disubstituted olefins. The oxyamination product may still form, but it is accompanied by a number of by-products. Fortunately, this class of olefins is successfully oxyaminated by the alternative procedure (B). Methylcyclohexene,

α-methylstyrene, 2-methyl-2-hepten-6-one, and its ketal are examples of olefins that give oxyamination products in good yield following Procedure B.

Addition of a phase-transfer catalyst such as dicyclohexyl-18-*crown*-6 to the reaction mixture (in Procedure B) results in a faster reaction rate. However, there are no significant changes in the final yield of oxyamination product.

We have carried out experiments on a 1-mol scale in the case of cyclohexene and α-methylstyrene (in the cyclohexene 1-mol experiment, the reaction mixture was 2.5 times more concentrated than described here), and have realized 70–80% and 65–75% yields, respectively, of the oxyaminated products.

Procedure A does not succeed with diethyl fumarate and 2-cyclohexen-1-one. Both chloramine-T and part of the olefin are consumed, but the oxyamination product has not been detected in the reaction mixtures. It seems likely that it forms, but is unstable to the reaction conditions. Both of these olefins do form isolable oxyamination products under the milder conditions (room temperature) of a more recent oxyamination procedure.[7,8]

Procedure B does not succeed with tetramethylethylene and cholesterol, and it seems reasonable to anticipate negative results with most hindered tri- and tetrasubstituted olefins. No reaction occurs, and chloramine-T is not consumed.

The sulfonamide protecting group on the nitrogen may be undesirable in some cases. For this reason we have developed an analogous osmium-catalyzed procedure that effects cis addition of hydroxyl and carbamate (ROCONH) moieties across the olefinic linkage.[7,8] β-Amino alcohols with benzyloxycarbonyl (Z or CBZ) and *tert*-butoxycarbonyl (BOC) protecting groups on the nitrogen are accessible directly from the corresponding olefins by the new method.[7,8]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 7, 223

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

silica gel

OsO_4

cis-2-p(Toluenesulfonamido)cyclohexanol

CH_3OH

ethyl acetate,
EtOAc (141-78-6)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydroxide,
NaOH (1310-73-2)

chloroform,
$CHCl_3$ (67-66-3)

Cyclohexene (110-83-8)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

sodium bisulfite (7631-90-5)

toluene (108-88-3)

diethyl fumarate (623-91-6)

sodium hypochlorite (7681-52-9)

tetramethylethylene (563-79-1)

magnesium sulfate (7487-88-9)

Cholesterol (57-88-5)

stilbene

osmium tetroxide (20816-12-0)

ethyl crotonate (623-70-1)

Methylcyclohexene

tert-butyl alcohol (75-65-0)

α-methylstyrene (98-83-9)

sodium borohydride (16940-66-2)

cyclooctene

2-cyclohexen-1-one (930-68-7)

benzyltriethylammonium chloride (56-37-1)

tert-butyl hydroperoxide (75-91-2)

2-methyl-2-hepten-6-one (110-93-0)

1-decene (872-05-9)

2-methyl-2-pentene (625-27-4)

p-toluenesulfonamide (70-55-3)

cis-2-(p-Toluenesulfonamido)cyclohexanol (58107-40-7)

2-Methyl-3-(p-toluenesulfonamido)-2-pentanol,
Benzenesulfonamide, N-(1-ethyl-2-hydroxy-2-methylpropyl)-4-methyl- (87291-33-6)

Benzenesulfonamide, N-(2-hydroxycyclohexyl)-4-methyl-, cis

chloramine-T trihydrate

(Z)-5-decene