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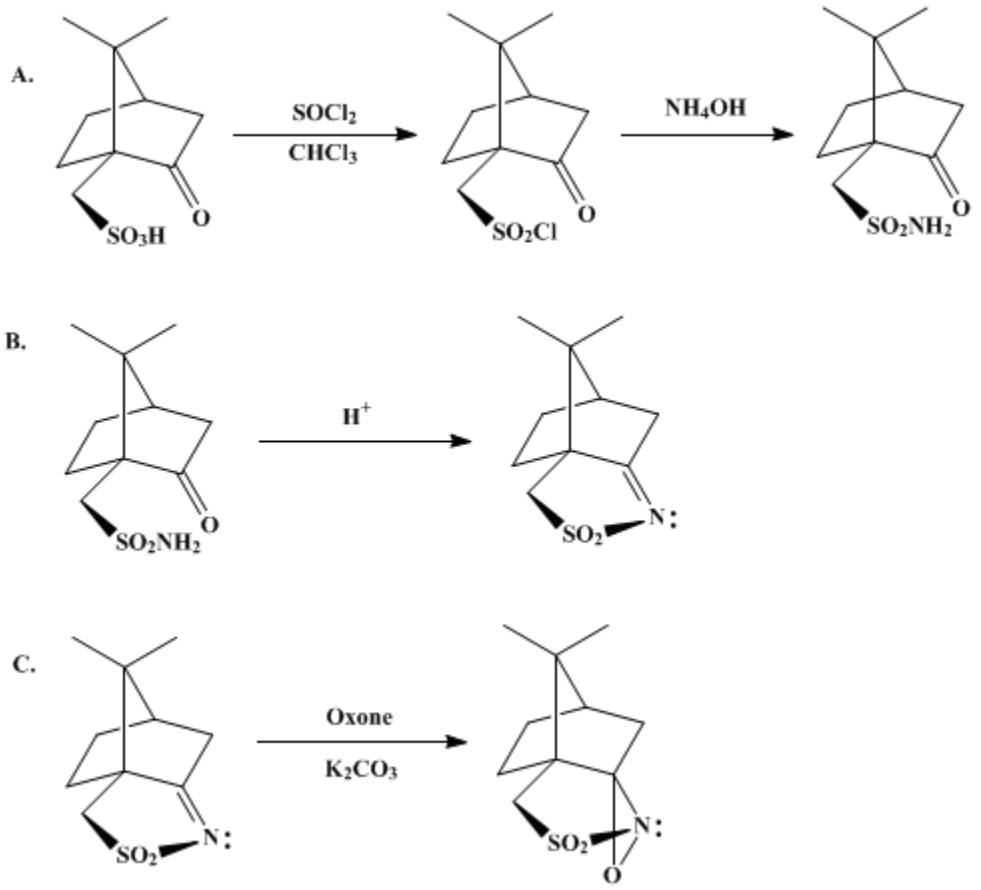
(+)-(2*R*,8a*S*)-10-(CAMPHORYLSULFONYL)OXAZIRIDINE

[4H-4A,7-Methanooxazirino[3,2-*i*][2,1]benzisothiazole, tetrahydro-9,9-dimethyl-, 3,3-dioxide, [4a*S*-(4aα,7α,8a*R**)]]



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Checked by David I. Magee and Robert K. Boeckman, Jr..

1. Procedure

A. *(+)-(1S)-10-Camphorsulfonamide*. Into a 2-L, two-necked, round-bottomed flask, equipped with a 250-mL dropping funnel, a magnetic stirring bar, and a reflux condenser fitted with an outlet connected to a disposable pipette dipped in 2 mL of chloroform in a test tube for monitoring gas evolution, were placed 116 g (0.5 mol) of camphorsulfonic acid (Note 1) and 750 mL of reagent-grade chloroform. The suspension of camphorsulfonic acid was heated to reflux and 71.4 g (43.77 mL, 0.6 mol, 1.2 equiv) of freshly distilled thionyl chloride was added dropwise over a 1-hr period. Heating was continued until gas evolution (sulfur dioxide and hydrogen chloride) had ceased (approximately 9–10 hr). The resultant solution of camphorsulfonyl chloride in chloroform was converted to camphorsulfonamide without further purification.

In a 5-L, two-necked, round-bottomed flask fitted with a 250-mL dropping funnel and a mechanical stirrer was placed a solution of 1.6 L of reagent-grade ammonium hydroxide solution and the flask was cooled to 0°C in an ice bath. The solution of the crude camphorsulfonyl chloride, prepared in the preceding section, was added dropwise to the ammonium hydroxide solution at 0–10°C over a period of 1 hr. The reaction mixture was warmed to room temperature, stirred for 4 hr, the organic layer

separated, and the aqueous layer was extracted with methylene chloride (3 × 250 mL). The combined organic layers were washed with brine (250 mL) and dried over anhydrous magnesium sulfate. Removal of the solvent on the rotary evaporator gave 104.0 g (90%) of the crude camphorsulfonamide (Note 2) and (Note 3).

B. *(−)-(Camphorsulfonyl)imine.* A 1-L, round-bottomed flask is equipped with a 2-in. egg-shaped magnetic stirring bar, a Dean–Stark water separator, and a double-walled condenser containing a mineral oil bubbler connected to an inert gas source. Into the flask are placed 5 g of Amberlyst 15 ion-exchange resin (Note 4) and 41.5 g of the crude (+)-(1*S*)-camphorsulfonamide in 500 mL of toluene. The reaction mixture is heated at reflux for 4 hr. After the reaction flask is cooled, but while it is still warm (40–50°C), 200 mL of methylene chloride is slowly added to dissolve any (camphorsulfonyl) imine that crystallizes. The solution is filtered through a 150-mL sintered glass funnel of coarse porosity an the reaction flask and filter funnel are washed with an additional 75 mL of methylene chloride.

Isolation of the (−)-(camphorsulfonyl)imine is accomplished by removal of the toluene on the rotary evaporator. The resulting solid is recrystallized from absolute ethanol (750 mL) to give white crystals, 34.5–36.4 g (90–95%), mp 225–228°C; $[\alpha]_D$ −32.7° ($CHCl_3$, c 1.9) (Note 5).

C. *(+)-(2R, 8aS)-10-Camphorylsulfonyloxaziridine*. A 5-L, three-necked, round-bottomed Morton flask is equipped with an efficient mechanical stirrer, a 125-mm Teflon stirring blade, a Safe Lab stirring bearing (Note 6), and a 500-mL addition funnel. Into the flask are placed the toluene solution of (−)-(camphorsulfonyl)imine (39.9 g, 0.187 mol) prepared in Step B and a room-temperature solution of 543 g (3.93 mol, 7 equiv based on oxone) of anhydrous potassium carbonate dissolved in 750 mL of water. The reaction mixture is stirred vigorously and a solution of 345 g (0.56 mol, 6 equiv of $KHSO_5$) of oxone dissolved in 1250 mL of water is added dropwise in three portions over 45 min (Note 7) and (Note 8). Completion of the oxidation is determined by TLC (Note 9) and the reaction mixture is filtered through a 150-mL sintered-glass funnel of coarse porosity to remove solids. The filtrate is transferred to a 3-L separatory funnel, the toluene phase is separated and the aqueous phase is washed with methylene chloride (3 × 100 mL). The filtered solids and any solids remaining in the Morton flask are washed with an additional 200 mL of methylene chloride. The organic extracts are combined and washed with 100 mL of saturated sodium sulfite, dried over anhydrous magnesium sulfate for 15–20 min, filtered, and concentrated on the rotary evaporator. The resulting white solid is crystallized from approximately 500 mL of hot 2-propanol to afford, after drying under vacuum in a desiccator, 35.9 g (84%) of white needles, mp 165–167°C, $[\alpha]_D$ +44.6° ($CHCl_3$, c 2.2) (Note 10) and (Note 11).

(−)-(2*S*,8a*R*)-10-(camphorylsulfonyl)oxaziridine is prepared in a similar manner starting from (−)-10-camphorsulfonic acid; mp 166–167°C, $[\alpha]_D$ +43.6° ($CHCl_3$, c 2.2).

2. Notes

1. (1*S*)-(+)-10-Camphorsulfonic acid was purchased from Aldrich Chemical Company, Inc.
2. The crude sulfonamide is contaminated with 5–10% of the (camphorsulfonyl)imine, the yield of which increases on standing.
3. The ^1H NMR spectrum of (+)-(1*S*)-10-camphorsulfonamide is as follows: ($CDCl_3$) δ: 0.93 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.40–2.50 (m, 7 H), 3.14 and 3.53 (AB quartet, 2 H, CH_2-SO_2, J = 15.1), 5.54 (br s, 2 H, NH_2).
4. Amberlyst 15 ion-exchange resin is a strongly acidic, macroreticular resin purchased from Aldrich Chemical Company, Inc.
5. The spectral properties of (−)-(camphorsulfonyl)imine are as follows: ^1H NMR ($CDCl_3$) δ: 1.03 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.45–2.18 (m, 6 H), 2.65 (m, 1 H), 3.10 and 3.28 (AB quartet, 2 H, CH_2-SO_2, J = 14.0); ^{13}C NMR ($CDCl_3$) δ: 19.01 (q, CH_3), 19.45 (q, CH_3), 26.64 (t), 28.44 (t), 35.92 (t), 44.64 (d), 48.00 (s), 49.46 (t), 64.52 (s), 195.52 (s); IR ($CHCl_3$) cm^{-1}: 3030, 2967, 1366. Checkers obtained material having identical melting point and $[\alpha]_D$ −32.3° ($CHCl_3$, c 1.8).
6. The SafeLab Teflon bearing can be purchased from Aldrich Chemical Company, Inc. A glass stirring bearing lubricated with silicone grease is unsatisfactory because the dissolved salts solidify in the shaft, causing freezing.
7. Efficient stirring is important and indicated by a milky white appearance of the solution.
8. Occasionally batches of oxone purchased from Aldrich Chemical Company, Inc., have exhibited

reduced reactivity in this oxidation. Oxone exposed to moisture prior to use also gives reduced reactivity in this oxidation. If this occurs, oxone is added until oxidation is complete as determined by TLC (Note 9). Potassium carbonate is added as needed to maintain the pH at approximately 9.0. Oxone stored in the refrigerator under an inert atmosphere has shown no loss in reactivity for up to 6 months.

9. Oxidation is generally complete after addition of the oxone solution. The oxidation is monitored by TLC as follows. Remove approximately 0.5 mL of the toluene solution from the nonstirring solution, spot a 250-μm TLC silica gel plate, elute with methylene chloride, and develop with 10% molybdophosphoric acid in ethanol and heating (camphorsulfonyl)imine R_f = 0.28 and (camphorylsulfonyl)oxaziridine R_f = 0.62. If (camphorsulfonyl)imine is detected, stirring is continued at room temperature until the reaction is complete (see (Note 8)). If the reaction mixture takes on a brownish color after addition of oxone and has not gone to completion after 30 min, the reaction mixture is filtered through a 150-mL sintered-glass funnel of coarse porosity, and the solids are washed with 50 mL of methylene chloride. The aqueous/organic extracts are returned to the 5-L Morton flask and stirred vigorously and 52 g (0.08 mol, 1 equiv $KHSO_5$) of oxone is added over 5 min and stirring continued until oxidation is complete (approximately 10–15 min).

10. The submitters employed a toluene solution of crude imine prepared in Part B and obtained somewhat higher yields (90–95%). However, the checkers obtained yields in this range on one half the scale using isolated sulfonylimine.

11. The spectral properties of (+)-(camphorsulfonyl)oxaziridine are as follows: ^{1}H NMR ($CDCl_3$) δ: 1.03 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.45–2.18 (m, 6 H), 2.65 (d, 1 H), 3.10 and 3.28 (AB quartet, 2 H, CH_2-SO_2, J = 14.0); ^{13}C NMR ($CDCl_3$) δ: 19.45 (q, CH_3), 20.42 (q, CH_3), 26.55 (t), 28.39 (t), 33.64 (t), 45.78 (d), 48.16 (s), 48.32 (t), 54.07 (s), 98.76 (s). The checkers obtained material (mp 165–167°C) having $[\alpha]_D$ +44.7° ($CHCl_3$, c 2.2).

3. Discussion

Camphorsulfonamide, required for the preparation of the (camphorsulfonyl)imine, was previously prepared in two steps. The first step involved conversion of camphorsulfonic acid to the sulfonyl chloride with PCl_5 or $SOCl_2$. The isolated sulfonyl chloride was converted in a second step to the sulfonamide by reaction with ammonium hydroxide. This modified procedure is more efficient because it transforms camphorsulfonic acid directly to camphorsulfonamide, avoiding isolation of the camphorsulfonyl chloride.

(Camphorsulfonyl)imine has been reported as a by-product of reactions involving the camphorsulfonamide.[2,3,4,5] Reychler in 1898 isolated two isomeric camphorsulfonamides,[2] one of which was shown to be the (camphorsulfonyl)imine by Armstrong and Lowry in 1902.[3] Vandewalle, Van der Eycken, Oppolzer, and Vullioud described the preparation of (camphorsulfonyl)imine in 74% overall yield from 0.42 mol of the camphorsulfonyl chloride.[6] The advantage of the procedure described here is that, by using ammonium hydroxide, the camphorsulfonyl chloride is converted to the sulfonamide in >95% yield.[7] The sulfonamide is of sufficient purity that it can be used directly in the cyclization step, which, under acidic conditions, is quantitative in less than 4 hr. These modifications result in production of the (camphorsulfonyl)imine in 86% overall yield from the sulfonyl chloride.

In addition to the synthesis of enantiomerically pure (camphorylsulfonyl)oxaziridine[7] and its derivatives,[8] the (camphorsulfonyl)imine has been used in the preparation of (−)-2,10-camphorsultam (Oppolzers' auxiliary),[6,9] (+)-(3-oxocamphorysulfonyl) oxaziridine,[10] and the *N*-fluoro-2,10-camphorsultam, an enantioselective fluorinating reagent.[11]

The *N*-sulfonyloxaziridines are an important class of selective, aprotic oxidizing reagents.[12] [13] [14] Enantiomerically pure *N*-sulfonyloxaziridines have been used in the asymmetric oxidation of sulfides to sulfoxides (30–91% ee),[15] selenides to selenoxides (8–9% ee).[16] disulfides to thiosulfinates (2–13% ee),[5] and in the asymmetric epoxidation of alkenes (19–65% ee).[17,18] Oxidation of optically active sulfonimines (R^*SO_2N=CHAr) affords mixtures of *N*-sulfonyloxaziridine diastereoisomers requiring separation by crystallization and/or chromatography.[3]

(+)-(Camphorylsulfonyl)oxaziridine described here is prepared in four steps from inexpensive (1*S*)-(+)- or (1*R*)-(+)-10-camphorsulfonic acid in 77% overall yield.[7] Separation of the oxaziridine diastereoisomers is not required because oxidation is sterically blocked from the exo face of the C-N

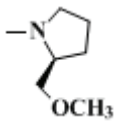
double bond in the (camphorsulfonyl)imine. In general, (camphorsulfonyl)oxaziridine exhibits reduced reactivity compared to other *N*-sulfonyloxaziridines. For example, while sulfides are asymmetrically oxidized to sulfoxides (3–77% ee), this oxaziridine does not react with amines or alkenes.[7] However, this oxaziridine is the reagent of choice for the hydroxylation of lithium and Grignard reagents to give alcohols and phenols because yields are good to excellent and side reactions are minimized.[19] This reagent has also been used for the stereoselective oxidation of vinyllithiums to enolates.[20]

The most important synthetic application of the (camphorylsulfonyl)oxaziridines is the asymmetric oxidation of enolates to optically active α-hydroxy carbonyl compounds.[14,21,22,23,24] Chiral, nonracemic α-hydroxy carbonyl compounds have been used extensively in asymmetric synthesis, for example, as chiral synthons, chiral auxiliaries, and chiral ligands. This structural array is also featured in many biologically active natural products. This oxidizing reagent gives uniformly high chemical yields regardless of the counterion, and stereoselectivities are good to excellent (50–95% ee).[9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24] Since the configuration of the oxaziridine three-membered ring controls the stereochemistry, both α-hydroxy carbonyl optical isomers are readily available. Representative examples of the asymmetric oxidation of prochiral enolates by (+)-(2*R*,8a*S*)-camphorylsulfonyl)oxaziridine are given in Tables I and II.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 110
- Org. Syn. Coll. Vol. 9, 212

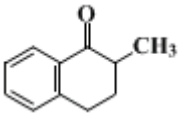
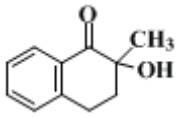
TABLE I
ASYMMETRIC OXIDATION OF LITHIUM ENOLATES OF ESTERS AND AMIDES USING (+)-(2*R*,8a*S*)-10-(CAMPHORYLSULFONYL) OXAZIRIDINE

	RC(R')=C(OLi)X						Product	
Entry	R	R'	X	Cosolvent	Temp. (°C)	Yield (%)[a]	% ee (Config.)	Ref.
1	Ph	H	$OCMe_3$	—	−90	82	71 (*R*)	21
2	$PhCH_2$	H	OMe	—	−90	73	58 (*R*)	21
				HMPA	−90	63	85 (*R*)	
3	Ph	Me	OMe	—	−78	61	45 (*R*)	21
4	Ph	H	NC_4H_8	—	−78	70	30 (*S*)	21
				HMPA	−78	74	50 (*R*)	
5	Ph	Me	NC_4H_8	—	−78	40	35 (*S*)	21
				HMPA	−78	35	20 (*R*)	
								
6	Ph	Me		—	−78	53	48 (*S*)	23
7				HMPA	−78	65	89 (*S*)	

[a]Isolated yields.

TABLE II
ASYMMETRIC OXIDATION OF KETONE-DERIVED ENOLATES USING (+)-(2*R*,8a*s*)-10-(CAMPHORYLSULFONYL)OXAZIRIDINE

					α-Hydroxy Ketone	
					Yield	% ee

Entry	Ketone	Base/Cosolvent	Temp. (°C)	(%)[a]	(Config.)	Ref.
1	$PhC(O)CH_2Ph$	LDA	0	70	68 (*S*)	22
2		LDA/HMPA	0	64	6 (*S*)	
3		NHMDS[b]	−78	84	95 (*S*)	
4	$PhC(O)CH_2Me$	LDA	0	51	43 (*S*)	22
5		NHMDS	−78	73	62 (*S*)	
6	$Me_3CC(O)CH_2Me$	LDA	0	55	32 (*R*)	25
7		NHMDS	−78	71	89 (*R*)	
8	$PhCH_2C(O)Me$	NHMDS	−78	70	40 (*S*)	25
9		NHMDS/HMPA	−78	76	76 (*R*)	25
10		LDA	0	75	30 (*R*)	25
11		NHMDS	0	80	16 (*R*)	25

[a]Isolated yields.

[b]Bis (trimethylsilyl) amide.

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

sulfonyl chloride

brine

(+)-(2R,8aS)-10-(Camphorylsulfonyl)oxaziridine

4H-4A,7-Methanooxazirino[3,2-i][2,1]benzisothiazole, tetrahydro-9,9-dimethyl-, 3,3-dioxide, [4aS-(4aα,7α,8aR*)]

(−)-(Camphorsulfonyl)imine

(camphorsulfonyl)imine

(−)-(2S,8aR)-10-(camphorylsulfonyl)oxaziridine

(−)-10-camphorsulfonic acid

sulfonamide

camphorsulfonamides

(−)-2,10-camphorsultam

(+)-(3-oxocamphorysulfonyl) oxaziridine

N-sulfonyloxaziridines

N-sulfonyloxaziridine

(1S)-(+)- or (1R)-(+)-10-camphorsulfonic acid

(camphorylsulfonyl)oxaziridines

α-hydroxy carbonyl

(+)-(2R,8aS)-camphorylsulfonyl)oxaziridine

ethanol (64-17-5)

potassium carbonate (584-08-7)

hydrogen chloride (7647-01-0)

sodium sulfite (7757-83-7)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

oxone (37222-66-5)

sulfur dioxide (7446-09-5)

toluene (108-88-3)

2-propanol (67-63-0)

ammonium hydroxide (1336-21-6)

methylene chloride (75-09-2)

lithium (7439-93-2)

magnesium sulfate (7487-88-9)

oxaziridine

camphorsulfonic acid (5872-08-2)

camphorsulfonyl chloride (6994-93-0)

Molybdophosphoric acid (51429-74-4)

camphorsulfonamide

(camphorylsulfonyl)oxaziridine,
(+)-(camphorsulfonyl)oxaziridine,
(+)-(Camphorylsulfonyl)oxaziridine,
(camphorsulfonyl)oxaziridine,
(+)-(2R, 8aS)-10-Camphorylsulfonyloxaziridine (104322-63-6)

sulfonylimine

(+)-(1S)-camphorsulfonamide,
(+)-(1S)-10-Camphorsulfonamide (60933-63-3)

(1S)-(+)-10-Camphorsulfonic acid (3144-16-9)

N-fluoro-2,10-camphorsultam