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# Asymmetric Aziridination by Reaction of Chiral Sulfinimine Derived From (+)-Camphor with Dimethyloxosulfonium Methylide

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# ASYMMETRIC AZIRIDINATION BY REACTION OF CHIRAL SULFINIMINE DERIVED FROM (+)-CAMPHOR WITH DIMETHYLOXOSULFONIUM METHYLIDE

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**ABSTRACT:** Addition of dimethyloxosulfonium methylide to chiral nonracemic pure (+)-camphor-derived sulfinimine 1 affords N-sulfinyl aziridine, which are easily separated. The N-(+)-camphor-based-sulfinyl auxiliary was removed without ring opening by treatment with MeLi.



Chiral nonracemic aziridines are versatile synthetic intermediates for asymmetric synthesis because of their high reactivity.[1] Tanner has demonstrated their utility as chiral substrates, chiral auxiliaries and chiral ligands in efficient asymmetric synthesis.[2] While racemic aziridines are readily available, procedures for their synthesis in enantiomerically form are limited. [1] Because their enantiomerically form are usually synthesized from optically active epoxides (obtained by asymmetric hydroxylation of alkenes or epoxidation of allylic alcohols) or β-aminoalcohols (derived from amino acids) their most usual compounds which are not available easily.[3] In recent years, Garcia Ruano with his coworkers and F. A. Davis et. al. independently reported a diastereoselective

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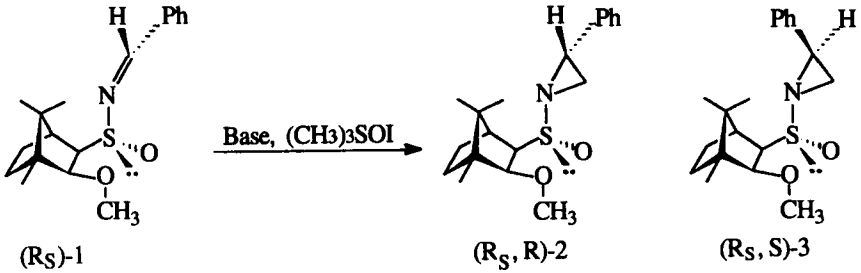
synthesis of aziridines via reaction of sulfur ylides with chiral (S)-(+)-N-benzylidene-*p*-toluenesulfinamide. [4] Here we describe preliminary results of asymmetric synthesis of N-substituted aziridine via addition of dimethyloxosulfonium methylide to chiral sulfinimine which was derived from (+)-camphor (Scheme 1).

Preparation of the sulfinimine 1 ($R_S$) from (+)-camphor has been reported by us previously. [5] To a THF (or other solvents) solution of trimethyloxosulfonium iodide (3 equiv.) was added the appropriate base (3 equiv.) and controlled the temperature after stirred 2h. Then the sulfinimine 1 (1 equiv.) was added and the reaction mixture was stirred for 3~24h (until the starting material was consumed). And ice water was poured to the mixture to quench the reaction.

In all case the reaction gave a mixture of the diastereoisomers of N-(+)-camphor-derived-sulfinyl-2-phenylaziridine (2) and (3) in good to modest yield.[6] The ratios of two diastereoisomers were determined on the reaction mixture by $^1$H NMR. The results are summarized in the Table.

From the Table the fact can be deduced that the diastereoselectivity of the reaction depends on the reaction conditions (such as base, solvent and temperature). The solvent polarity has a significant effect on the stereochemical outcome of this aziridination. When using sodium hydride as base, a decrease of the solvent polarity resulted in an increase of the diastereoselectivity and a decrease of yield (entry 1~6). In the polar solvent such as DMSO and DMF, because of their excellent solubility and coordinative activity with metal ion, there gave good yield and low diastereoselectivity, and the major product is aziridine 3 but in other solvents is aziridine 2 (entry 1 and 2). The highest 2:3 ratio was observed in *o*-xylene at room temperature but with low yield (84:16, entry 6). Changing the starting temperature of the reaction there is a small change of the ratio of the diastereoisomers (entry 4, 7~9). Under -78°C, there gave ratio 86:14




Scheme 1

**Table: Addition of Dimethyloxosulfonium Methylides to Enantiomerically Pure Sulfinimine 1**

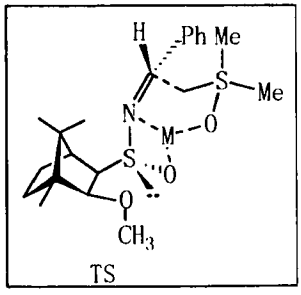
| Entry | Base | T (°C) | Solvent | Yield [a] (%) | Ratio [b] 2 : 3 |
|---|---|---|---|---|---|
| 1 | NaH | rt. | DMSO | 89 | 42 : 58 |
| 2 | NaH | rt. | DMF | 91 | 47 : 53 |
| 3 | NaH | rt. | $CH_2Cl_2$ | 82 | 57 : 43 |
| 4 | NaH | rt. | THF | 83 | 74 : 26 |
| 5 | NaH | rt. | Toluene | 45 | 78 : 22 |
| 6 | NaH | rt. | *o*-Xylene | 38 | 84 : 16 |
| 7 | NaH | 0~rt. | THF | 81 | 80 : 20 |
| 8 | NaH | -20~rt. | THF | 78 | 84 : 16 |
| 9 | NaH | -78~rt. | THF | 85 | 86 : 14 |
| 10 | *n*-BuLi | rt. | THF | 56 | 64 : 36 |
| 11 | *n*-BuLi | -78~rt. | THF | 56 | 69 : 31 |
| 12 | NaHMDS | rt. | THF | 71 | 74 : 26 |

a) Isolated yields. b) The ratio determined on the crude mixture by $^1H$ NMR

of 2:3 (entry 6). Finally, the diastereoselectivity of the reaction seems to be dependent on the nature of the metal ion. When using *n*-BuLi as base the ratio of 2:3 is lower than the ratio when using NaH as base under the same condition (entry 4, 9~11). While substituting sodium hydride by sodium bis(trimethylsilyl)-amine (NaHMDS) there gave the same outcome (74:26, entry 4, 12).

The diastrereoisomers were readily separated in excellent yields by a simple flash chromatography on silica gel. For the assignment of the absolute stereochemistry the major product 2 was treated with 1.5 equiv. methyllithium at −78°C followed by quenching with sat. $NH_4Cl$. The known R-(-)-phenylaziridine (4) was isolated in 48% yield (Scheme 2) [7] The absolute configuration at C-2 of the major product, determined to be (R), is consistent with chair-like transition state **TS** followed by intramolecular ring closure.[4]

In summary, the study reported herein had led to an efficient entry to the 2-phenylaziridine in their both possible configuration.

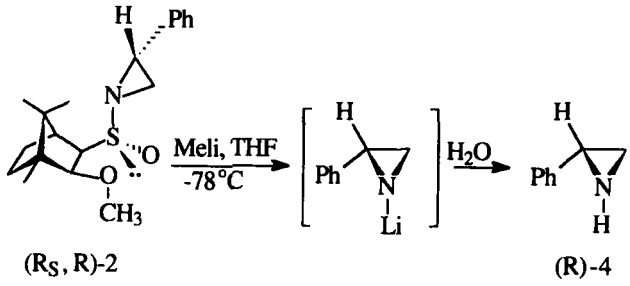


TS



**Experimental section:**

**General aspects:** Optical rotations were recorded on a P-E341 polarimeter. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on VARIAN UNITY INOVA-400 spectrometers with chemical shifts (δ) given in ppm from internal TMS. Mass spectra were recorded on a VG-7070E GC/MS/DS instrument. Microanalyses were carried out on CARLO ERBA 1106 Elemental Analyzer.




($R_S$, R)-2 (R)-4

Scheme 2

**General procedure for the aziridation of 'sulfinimine (1) with dimethyloxosulfonium methylide:** 0.45 mmol (3equiv.) of prewashed NaH (or another base) was added to a solution of 0.45 mmol (3equiv.) of trimethyloxosulfonium iodide in THF (or another solvent) (5 ml). After stirring at room temperature for two hours, 0.15 mmol (1 equiv.) of sulfinimine (1) in 5 ml solvent was added, and the reaction temperature was controlled. The reaction mixture was stirred until all the material was consumed, and then poured onto crushed ice and extracted with ethyl acetate (3×30 ml). The organic layer was washed with brine (30 ml), dried over $MgSO_4$ and evaporated under *vacuo*. The resulting mixture of diastereoisomers was analyzed by $^1H$ NMR to determine the ratio on the crude mixture and then separated by silica gel column chromatography.

**($R_S$, $R_{C2}$)-N-(+)-camphor-based-sulfinyl-2-phenylaziridine 2**: $[\alpha]_D^{20}$ = -173.7°(c, 3.5 $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400MHz) δ 7.33(s, 5H, PhH), 3.49(s, 3H, $OCH_3$), 3.42(d, J=7.6, 1H, OCH), 3.21(dd, J=7.2, 3.6, 1H, PhCH), 2.88(d, J=7.2, 1H, CH), 2.82(d, J=7.6, 1H, SOCH), 2.45(d, J=3.6, 1H, CH), 1.93(d, J=3.6, 1H, CH), 0.91~1.80(m, 4H, $CH_2CH_2$), 1.15(s, 3H, $CH_3$), 0.98(s, 3H, $CH_3$), 0.84(s, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$, 100MHz) δ 137.69, 128.36, 127.60, 126.47, 90.33, 78.58,

61.74, 50.49, 48.99, 46.77, 35.10, 32.95, 28.40, 26.58, 21.35, 20.64, 11.17; MS 333.0($M^+$); Anal. Calcd for $C_{19}H_{27}O_2N_1S_1$: C, 68.43; H, 8.16; N, 4.20; S, 9.61. Found: C, 68.37; H, 8.28; N, 4.23; S, 9.54.

**($R_S$, $S_{C2}$)-N-(+)-camphor-based-sulfinyl-2-phenylaziridine 3:** $[\alpha]_D^{20}$ = +113.6°(c,1.2 $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400MHz) δ 7.27(s, 5H, PhH), 3.58(dd, J=6.4, 4.0, 1H, PhCH), 3.46(s, 3H, $OCH_3$), 3.34(d, J=7.6, 1H, OCH), 2.81(d, J=7.6, 1H, SOCH), 2.35(d, J=6.4, 1H, CH), 2.22(d, J=4.0, 1H, CH), 2.20(s, 1H, CH), 0.66~1.53(m, 4H, $CH_2CH_2$), 1.15(s, 3H, $CH_3$), 0.93(s, 3H, $CH_3$), 0.82(s, 3H, $CH_3$); $^{13}C$ NMR ($CDCl_3$, 100MHz) δ 137.16, 128.41, 127.50, 126.53, 90.23, 78.92, 61.74, 50.48, 49.19, 46.61, 32.73, 31.34, 30.30, 27.76, 21.34, 20.57, 11.13; MS 333.0($M^+$); Anal. Calcd for $C_{19}H_{27}O_2N_1S_1$: C, 68.43; H, 8.16; N, 4.20; S, 9.61. Found: C, 68.46; H, 8.23; N, 4.22; S, 9.55.

**Preparation of (R)-(-)-2-phenylaziridine from ($R_S$, $R_{C2}$)-N-(+)-camphor-based-sulfinyl-2-phenylaziridine (2):** To a solution of ($R_S$, $R_{C2}$)-N-(+)-camphor-based-sulfinyl-2-phenylaziridine (2) (0.44 mmol) in tetrahydrofuran (10 ml) was slowly added a solution of methyllithium (0.66mmol, 1.5equiv.) in ether at –78°C. After stirring at –78°C for 10 minutes the reaction was quenched with sat. $NH_4Cl$ (10 ml) and extracted with ethyl acetate (6×20 ml). The organic layer was dried over $MgSO_4$ and evaporated under *vacuo*.. Then the crude product was purified by silica gel column chromatography.

**(R)-(-)-2-phenylaziridine (4)**: C.Y.: 48%. $[\alpha]_D^{20}$ = -42.8°(c, 0.96 ethanol); [lit.[4a] : (R)-(-)-5: $[\alpha]_D^{20}$ = -43.4°(c, 1.0 ethanol)].

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**References and Notes:**

1 See Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599 and references cited therein.

2. Tanner, D. *Pure & Appl. Chem.* **1993**, *65*, 1319.

3. Berry, M. B. and Craig, D. *Synlett.* **1992**, 41.

4. (a) Davis, F. A.; Zhou, P.; Chang, H.-L. and Reddy, R. E. *Tetrahedron: Asymmetry*, **1995**, *6*, 1511.

(b) Garcia Ruano, J. L.; Fernandez, I. and Hamdouchi, C. *Tetrahedron Letters*, **1995**, *36*, 1511.

(c) Garcia Ruano, J. L.; Fernandez, I.; Catalina, M. P. and Cruz, A. A. *Tetrahedron: Asymmetry*, **1996**, 7, 3407

5. (a) Yang, G -S.; Li, Y.; Fang, Z.-Q.; Xiao, X. and Jiang, Y.-Z. *Chinese Journal of Synthetic Chemistry*, **1994**, *2*, 154.

(b) Yang, T.-K.; Chen, R.-Y.; Lee, D.-S.; Peng, W.-S.; Jiang, Y.-Z.; Mi, A.-Q. and Jong, T.-T. *J. Org. Chem.* **1994**, *59*, 914.

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