Tetrahedron Letters,Vol.31,No.2,pp 239-242,1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

STEREOSELECTIVE SYNTHESIS AND STEREOSPECIFIC ASYMMETRIC 1,2-REARRANGEMENTS OF CHIRAL SULFINYLCYCLOPROPANE DERIVATIVES

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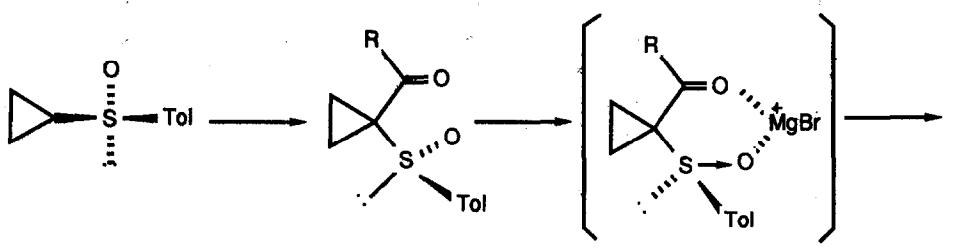
Abstract: Stereoselective synthesis of chiral sulfinylcyclopropane derivatives and stereochemistry of the asymmetric 1,2-rearrangements are described. Heating of each stereoisomeric mesylate of (Ss)-1-(1-hydroxy-1-phenylethyl)-1-p-toluenesulfinylcyclopropane, followed by reduction of the sulfinyl group with acetyl chloride, provided (R)-(-)-4-methyl-4-phenyl-1-p-toluenesulfenylcyclobutene. In contrast, the same sequences of the stereoisomeric tosylates gave the corresponding enantiomeric sulfides stereospecifically with inversion of configuration.

Thermal rearrangements in cyclopropane derivatives[1] have received much attention in recent years for the synthesis of synthetically valuable frameworks such as cyclobutane, cyclopentane, and cycloheptane ring systems. No report has appeared on synthesis of such frameworks by asymmetric rearrangements of chiral cyclopropane systems.[2] We have reported successful stereoselective acid-catalyzed transformation of chiral 1-(1-hydroxyalkyl)-1-sulfinylcyclopropanes into cyclobutane derivatives,[3] using chirality of optically active sulfinyl groups.[4]

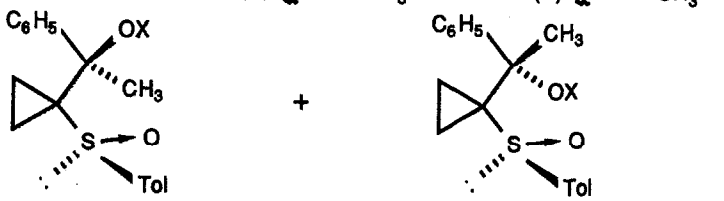
We wish to communicate herein stereoselective construction of chiral stereoisomeric 1-(1-hydroxyalkyl)-1-p-toluenesulfinylcyclopropanes and stereochemistry of asymmetric 1,2-rearrangements of the cyclopropanes via the mesylates or tosylates.

Acylation of α-carbanion of (R)-p-toluenesulfinylcyclopropane (1),[5] generated by treating 1 with n-butyllithium at 0 °C for 1.5 h in tetrahydrofuran (THF), with methyl benzoate or ethyl acetate was carried out in THF at -78°C for 4-5 h to give (S)-1-benzoyl- or acetyl-1-p-toluenesulfinylcyclopropane (2a) or (2b) in 62 or 74% yield. Addition of methyl- or phenylmagnesium bromide to the ketones 2a or 2b at 0 °C for 16 h in THF produced 4a and 4b with extremely high stereoselectivity (4a:4b=90:10 or 9:91) in 60 or 87% yield, respectively. This high stereoselectivity can be rationalized by preferential attack of the Grignard reagents from the direction of the smallest group (lone pair of the sulfinyl group) of steric bulkiness in a six-membered transition state 3 formed by chelation of the magnesium cation with oxygen atoms of the carbonyl and the sulfinyl groups.

Mesylation of 4a or 4b with methanesulfonyl chloride in pyridine at 0 °C gave mesylates 5a or 5b in quantitative yield. Heating of 5a or 5b in refluxing benzene for 8 h, followed by reduction of the produced sulfoxide



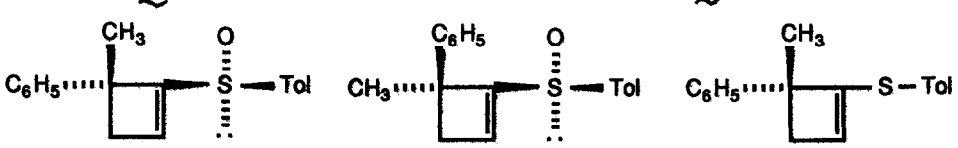
(R)-1 (S)-2a R=C_6H_5 (S)-3a R=C_6H_5
(S)-2b =CH_3 (S)-3b =CH_3



(R, Ss)-4a X = H (S, Ss)-4b X = H
5a = SO_2CH_3 5b = SO_2CH_3
6a = $SO_2C_6H_4CH_3$-p 6b = $SO_2C_6H_4CH_3$-p

7a with acetyl chloride (at room temperature for 2 h), provided (R)-(-)-8 with complete stereospecificity. On the other hand, tosylates 6a,b of 4a,b underwent smooth stereospecific 1,2-rearrangements in the cyclopropane systems to afford the corresponding enantiomers of 8 with high enantiomeric excess. Upon treatment of 4a with p-toluenesulfonyl chloride in pyridine at 0 °C for 9 h, 4a underwent a stereospecific 1,2-rearrangement via the tosylate 6a to give sulfinylcyclobutene 7b. Reduction of this sulfoxide 7b with acetyl chloride at room temperature for 2 h resulted in the formation of (S)-(+)-8 with 78% enantiomeric excess. However, the same procedures of 4b under the same conditions produced (R)-(-)-8 with 99% enantiomeric excess. Hydrolysis of the enol thioether in (S)- or (R)-8 with titanium(IV) chloride provided (S)- or (R)-2-methyl-2-phenylcyclobutanone of known absolute configuration,[3] respectively. Direct heating of 4a and 4b without derivation in the presence of a catalytic amount of p-toluenesulfonic acid (TsOH), followed by reduction with acetyl chloride, produced (R)-(-)-8 with extremely high stereoselectivity. The results are summarized in Table I.

These stereochemical results are reasonably elucidated in the following way. On heating of the hydroxy compounds 4a,b (with TsOH) or the mesylates 5a,b, a common cationic intermediate 9 would be generated



(4R, Ss)-7a (4S, Ss)-7b (R)-8

Table I. Stereochemistry of 1,2-Rearrangements of 4a,b via the Mesylates 5a,b and the Tosylates 6a,b[a)]

4-6	Solvent	Reaction temp.(°C)	Reaction time (h)	Yield[b)] of 7 (%)	[α]D(EtOH) of 8 (Abs.Config.)	Stereospecificity (%)[d)]
4a	C_6H_6	80	4	88[c)]	-13.3° (R)	91
4b	C_6H_6	80	4	88[c)]	-14.1° (R)	96
5a	C_6H_6	80	8	62	-14.7° (R)	100
5b	C_6H_6	80	8	62	-14.7° (R)	100
6a	Pyridine	0	9	65	+11.4° (S)	78
6b	Pyridine	0	9	65	-14.6° (R)	99

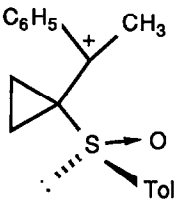
a) Reduction of 7a,b with acetyl chloride (5 equiv.) was carried out in CH_2Cl_2 at room temperature for 2 h, giving 8 in good yields (85-90%).

b) Yields based on the recovered starting material.

c) Heated in refluxing benzene in the presence of a catalytic amount of p-toluenesulfonic acid.

d) The stereospecificity in 4-6 → 8 was calculated based on the optical rotation of the optically pure sulfide 8: [α]D-14.7°(EtOH).

from both isomers. The stereochemistry of this rearrangement would be created by the effect of thermodynamic stability of intermediates 10a,b, due to difference of the steric hindrance between the methyl or phenyl groups and an oxgen atom or a lone pair of the sulfinyl group. Therefore the mesylates 5a and 5b would undergo a 1,2-rearrangement through the thermodynamically more stable intermediate 10a via a cationic intermediate 9, preferable to 10b because of steric interference between the phenyl substituent and an oxygen atom of the sulfinyl group in 10b, to yield (R)-



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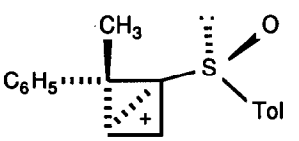
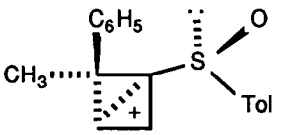
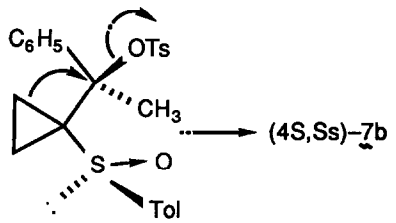


10a



10b



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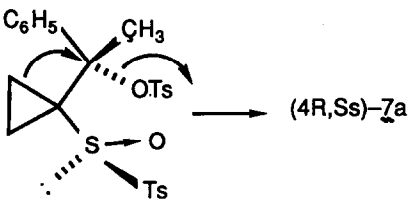

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(-)-8. On the other hand, the rearrangement of the cyclopropane rings in the tosylate 6a or 6b would proceed, as shown in 11 or 12, from the back side of the tosyl groups stereospecifically to provide (S)-(+)- or (R)-(-)-8 with high enantiomeric excess, respectively. The striking difference of stereochemical results obtained from the mesylates 5 and the tosylates 6 would stem from that of the reactivity between 5 and 6. Heating is required for the 1,2-rearrangement of 5a,b, because of the poor reactivity of the mesyl group. A small amount of methanesulfonic acid would presumably be generated at the initial stage of the heating and it accelerated the reaction as an acidic catalyst, giving almost the same result as that of 4a,b. However the more reactive tosyl group is stereospecifically substituted by the rearrangement of a carbon-carbon bond of the cyclopropane with inversion of configuration under milder conditions, yielding 1,2-rearranged products, cyclobutene derivatives. A little lower stereospecificity in the rearrangement of 6a suggests the partial participation of the route via 9, besides the main path via 11.

Thus, both of the enantiomeric cyclobutane derivatives were readily available from chiral sources with sulfinyl groups of the same absolute configuration, depending on the reaction sequences employed.

Acknowledgements

The present work was partially supported by a Grant-in-Aid for Scientific Research No. 62570950 from the Ministry of Education, Science, and Culture.

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(Received in Japan 27 October 1989)