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ASYMMETRIC SYNTHESIS USING α,β-UNSATURATED SULFOXIDES. STEREOSELECTIVE FORMATION OF BROMOHYDRIN AND METHOXYBROMIDE

Gen-ichi Tsuchihashi, Shuichi Mitamura, and Katsuyuki Ogura
Sagami Chemical Research Center
Nishi-Ohnuma, Sagamihara, Kanagawa 229 Japan

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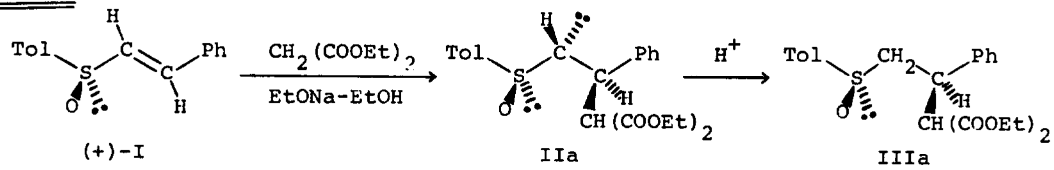
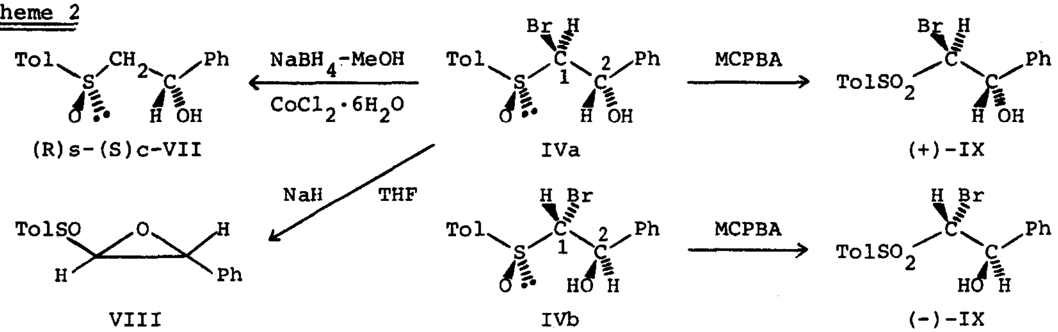
We have recently reported that the Michael addition of diethyl malonate to (+)-(R)-trans-β-styryl p-tolyl sulfoxide [(+)-I] results in a dominant formation of a diastereomer (IIIa, Scheme 1).[1,2] The high selectivity of the addition is conceived as a result of the preferential formation of carbanion IIa by the electronic demand of the adjacent chiral sulfinyl group.[3] Electronic chirality of sulfinyl group may also play an important role in electrophilic addition to α,β-unsaturated sulfoxides. Abbott and Stirling reported that addition of bromine to α,β-unsaturated sulfoxides results in the asymmetric induction of 32-43%.[4] However, the bromination may involve a free radical mechanism. In this communication, we would like to describe highly selective electrophilic addition of Br-OH or Br-OMe to I and unequivocal determination of the configurations of the adducts.

Scheme 1



To a mixture of water (10 ml) and dioxane (12 ml) were added (+)-I[1] (5.00 mmol) and N-bromosuccinimide (NBS, 8.50 mmol), and the resulting solution was stirred for 4 hr at room temperature. After addition of dichloromethane, the organic layer was separated and was subjected to column chromatography to afford 1-bromo-2-hydroxy-2-phenylethyl p-tolyl sulfoxide (IV, 62%) and 2,2-dibromo-1-phenylethanol (V, 33%).[5,6] Bromohydrin IV was a diastereomeric mixture of IVa and IVb in a ratio of 9 : 1.[7] The major isomer IVa was easily isolated in a pure form by recrystallization; mp 149-152°, $[\alpha]_D^{29}$ +220° (c 0.549, MeOH).[8] The minor isomer IVb was obtained as a colorless oil by repeated chromatography; $[\alpha]_D^{33}$ +44° (c 0.43, MeOH). The absolute configurations of IVa and IVb were determined unequivocally by the following chemical transformations (Scheme 2).

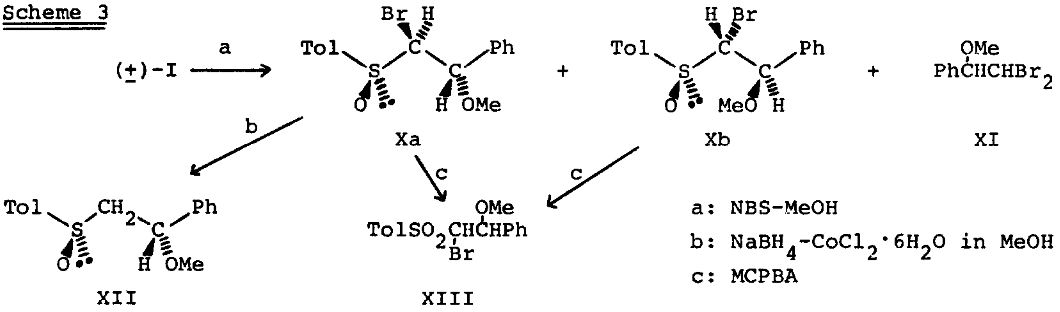
Scheme 2



Debromination of IVa with $NaBH_4$ in the presence of $CoCl_2 \cdot 6H_2O$ in methanol[9] gave (R)s-(S)c-2-hydroxy-2-phenylethyl p-tolyl sulfoxide (VII);[10] mp 95-96°, $[\alpha]_D^{26}$ +220° (c 0.344, EtOH). The optical purity was calculated to be 97% based on the maximum rotation of VII.[11] From this result, it is concluded that the configuration of IVa should be (S) at the sulfur and (S) at the carbon β to the sulfinyl group (C2). When IVa was allowed to react with NaH in THF, an epoxysulfoxide VIII was yielded quantitatively. The coupling constant (J = 2 Hz) of protons in the oxirane ring of VIII indicated trans configuration, since that of the cis isomer was reported to be 3.5 Hz.[12] The formation of trans-epoxide VIII, coupled with (S)-configuration at C2 of IVa, led to the conclusion that the configuration at C1 of IVa should be (S). Accordingly, the configuration of the major isomer IVa is (S)s-(S)c1-(S)c2 and it possesses at least 97% optical purity. The configuration of the minor isomer IVb was assigned to be (S)s-(R)c1-(R)c2 by oxidation with m-chloroperbenzoic acid to a levorotatory sulfone (-)-IX; $[\alpha]_D^{31}$ -44.7° (c 0.206, MeOH), mp 97-99°, which appeared to be an enantiomer of a dextrorotatory sulfone (+)-IX; $[\alpha]_D^{33}$ +52.2° (c 0.226, MeOH), mp 100°, derived from the major isomer IVa by a similar oxidation.

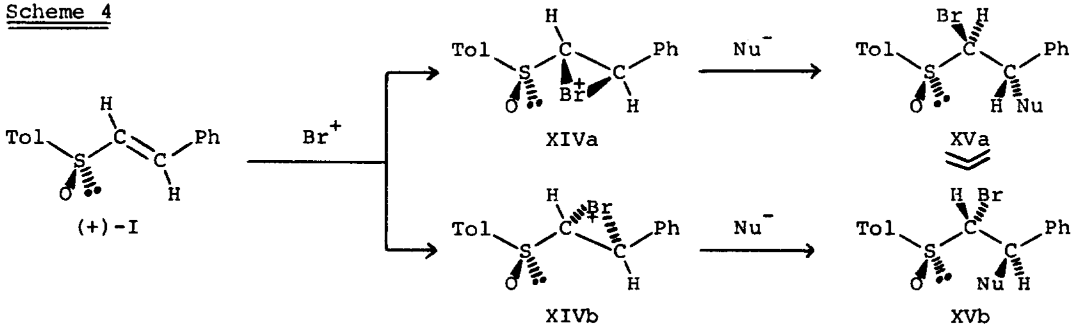
We further examined methoxybromide forming reaction of I. The reaction of racemic I with NBS in absolute methanol afforded 1-bromo-2-methoxy-2-phenylethyl *p*-tolyl sulfoxide (X, 72%) and 2,2-dibromo-1-methoxy-1-phenylethane (XI, 26%).[6,13] Methoxybromide X was a diastereomeric mixture of Xa and Xb in a ratio of 95 : 5,[7] Xa; mp 95-97°, Xb; 90-91°. Debromination of Xa by the aforementioned method gave the known diastereomer of 2-methoxy-2-phenylethyl *p*-tolyl sulfoxide[2] (XII, one of the enantiomers is shown in Scheme 3). Oxidation of either Xa or Xb with *m*-chloroperbenzoic acid gave the same sulfone XIII; mp 91-92°. Therefore, considering trans addition of MeO and Br, the configurations of Xa and Xb were respectively assigned to be those shown in Scheme 3.

Scheme 3



It is generally accepted that the reaction of NBS-H_2O or NBS-MeOH involves an electrophilic attack on the olefin to form an intermediary bridged brominium ion and subsequent reaction of the brominium ion with nucleophiles takes place at the carbon better able to stabilize a positive charge.[14] If this mechanism is adopted to the present reactions, the formation of IVa,b and Xa,b is understood as a result of nucleophilic attack of OH^- or MeO^- at the benzylic position of brominium ions (XIVa, XIVb) derived from I (see Scheme 4). It should be noted that both bromohydrin and methoxybromide forming reactions predominantly gave the same type of isomers, *i.e.*, IVa and Xa, and showed nearly the same

Scheme 4



selectivity (isomer ratios, 9-9.5 : 1-0.5), regardless of whether nucleophile was OH^- or MeO^-. Hence, the remarkable selectivity observed here should be ascribed to the preferential formation of XIVa with respect to XIVb. Presumably, the formation of XIVa is favored by the electronic demand of the adjacent chiral sulfinyl group.

A similar result is obtained for ionic bromination of (+)-I.[15] Again, (S)s-(S)c1-(S)c2-1,2-dibromo-2-phenylethyl *p*-tolyl sulfoxide (XVa, Nu = Br) is formed as a dominant isomer.[16] Details of this bromination and applications of these reactions to asymmetric syntheses will be reported shortly.

REMARKS AND REFERENCES

1. G. Tsuchihashi, S. Mitamura, S. Inoue, and K. Ogura, *Tetrahedron Lett.*, 323 (1973).
2. G. Tsuchihashi, S. Mitamura, and K. Ogura, *ibid.*, 2469 (1973).
3. The maximum stability of α-sulfinyl carbanion is attained when the carbanion electron lobe is trans to the sulfinyl oxygen; R. R. Fraser, F. J. Schuber, and Y. Y. Wigfield, *J. Amer. Chem. Soc.*, *94*, 8795 (1972).
4. D. J. Abbott and C. J. M. Stirling, *Chem. Commun.*, 472 (1971).
5. From the aqueous layer, *p*-toluenesulfinic acid was obtained in 33% yield as a salt of succinimide.
6. The formation of V and XI can be accounted for by addition of Br-OR to β-bromostyrene. This was suggested by the facts that V was yielded in a racemic form and that β-bromostyrene readily gave V or XI in respective reaction condition in good yield.
7. By repeated chromatography (silica gel, CH_2Cl_2) and NMR analysis, the ratio was established.
8. Satisfactory elemental analyses and acceptable physical data were obtained for all new compounds reported herein.
9. New debromination reaction by using this system will be published elsewhere.
10. G. Tsuchihashi, S. Iriuchijima, and M. Ishibashi, *Tetrahedron Lett.*, 4605 (1972).
11. The optical pure (R)s-(S)c-VII, $[\alpha]_D^{27}$ +226° (c 0.514, EtOH), was given by repeated recrystallization from diastereomeric VII which was synthesized by the reaction of *p*-tolylsulfinyl carbanion with benzaldehyde; see reference 10.
12. D. F. Tavares, R. E. Estep, and M. Blezard, *Tetrahedron Lett.*, 2373 (1970).
13. Methyl *p*-toluenesulfonate was also obtained in 9% yield. This compound may be formed by oxidation of the corresponding sulfinate.
14. H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Inc., Menlo Park, California, 1972, pp 422-446.
15. In order to avoid contamination of radicalic addition, hydroquinone was added to the reaction system of Br_2-CCl_4.
16. The absolute configuration was determined by X-ray diffraction method by Dr. F. Iwasaki (The University of Electro-Communications). We are grateful for her kind information prior to publication.