Tetrahedron Letters No. 11, pp 855 - 858, 1976. Pergamon Press. Printed in Great Britain.

ASYMMETRIC SYNTHESIS USING α,β-UNSATURATED SULFOXIDES. CREATION OF BOTH (R)- AND (S)-ASYMMETRIC CENTERS FROM A SINGLE CHIRAL ORIGIN.

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(Received in Japan 24 January 1976; received in UK for publication 3 February 1976)

We previously reported that the Michael addition of diethyl malonate to (+)-(R)-<u>trans</u>-β-styryl p-tolyl sulfoxide [(+)-I] in a usual condition (EtONa/EtOH) resulted in the dominant formation of IIIa with respect to its diastereomer IIIb.[1] By the reductive desulfurization of pure IIIa, (-)-(R)-diethyl (1-phenylethyl)malonate [(-)-IV] was obtained in over 95% optical purity. We have further investigated on the stereochemical course of the Michael addition under various reaction conditions and found that the product ratio (IIIa : IIIb) varies remarkably, depending upon the solvent used and the nature of the counter cation (M^+ in Scheme 1). In this letter, we would like to communicate our new finding that either diastereomer IIIa or IIIb can be obtained preferentially under the specified condition and the realization of the asymmetric synthesis of both enantiomers (-)- and (+)-IV, starting from a single chiral compound (+)-I.

The stereochemical course of the reaction was studied by measuring the ratio of the products IIIa and IIIb. The results were summarized in the Table. In ethanol (M^+ = K^+, Na^+), the ratio of IIIa : IIIb was 8 : 2 (runs 1 and 2). On the other hand, in THF, the ratio decreases with the decrease of the ionic radius of the counter cation ($K^+ > Na^+ > Li^+$, runs 3, 4, and 5) and THF-Li^+ system afforded IIIb predominantly, IIIa : IIIb being ca. 2 8 (runs 5 and 6).

Scheme 1

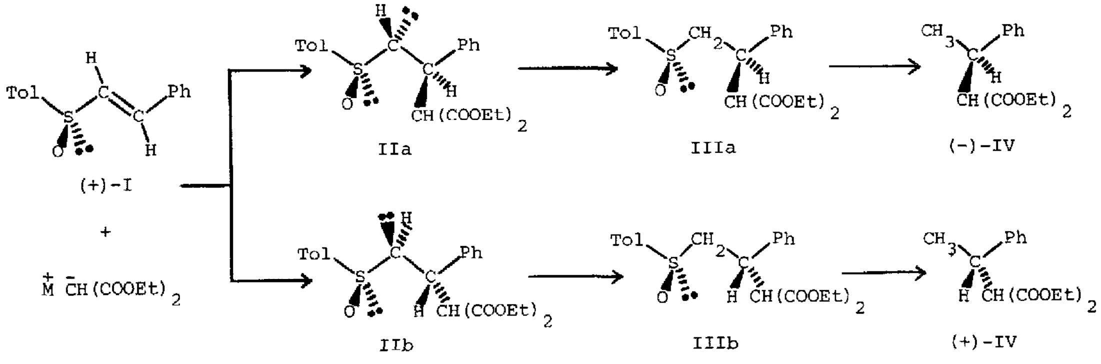


Table. The ratio (IIIa : IIIb)[a] in the addition of $\overset{+}{M}\,\overset{-}{C}H(COOEt)_2$ to I.[b,c]

run	solvent	M^+	time (hr)	% of III[d]	IIIa : IIIb
1	EtOH	Na^+	13	87	81 : 19
2		K^+	13	88	79 : 21
3	THF	K^+	115	76	55 : 45
4		Na^+	115	65	36 : 64
5		Li^+	115	60	22 : 78
6	THF - n-hexane (3:2)	Li^+	156	63	21 79

[a] The ratio was determined by the relative intensities of NMR signals for methyl protons in the p-tolyl group. The use of a shift reagent, $Eu(fod)_3$, was effective in differentiating these signals

[b] The lithiation was performed by the action of n-butyllithium The potassium and sodium salts were obtained by the use of the corresponding metal hydrides except for run 1 (EtONa)

[c] All reactions were carried out under an argon atmosphere at reflux temperature

[d] Yields based on the unrecovered I

The isomer IIIb was isolated and subjected to the reductive desulfurization to give (+)-(S)-diethyl (1-phenylethyl)malonate [(+)-IV] in the following manner. A solution of diethyl lithiomalonate was prepared by adding a solution of 3.9 mmol of n-butyllithium (1.3 M n-hexane solution) to a solution of 6.0 mmol of diethyl malonate in THF (4.5 ml) at -60°. To this, was added 2.0 mmol of (+)-I, $[\alpha]_D^{22}$ +159.5° (c 0 874, $CHCl_3$); optical purity of 97%, and the mixture was refluxed for 6.5 days under an argon atmosphere. A usual work-up gave a mixture of diastereomers IIIa and IIIb (2 : 8) in 63% yield. Then, IIIb was isolated by column chromatography (on silica gel, eluted with CH_2Cl_2) and purified by recrystallization from n-hexane-CCl_4 IIIb: mp 85-87°, $[\alpha]_D^{22}$ +54 0° (c 1.305, $CHCl_3$); δ^{CDCl_3} 0.99 (t, 3H), 1 22 (t, 3H), 2.42 (s, 3H), 3.2-3.9 (m, 4H), 3.95 (q, 2H), 4.29 (q, 2H), 7.1-7.6 (m, 9H). The reductive desulfurization of IIIb with Raney Ni in ethanol gave (+)-IV in 92% yield. (+)-IV: an oil, $[\alpha]_D^{23}$ +21.7° (c 0.845, $CHCl_3$).[2,3]

We already obtained (-)-IV from (+)-I <u>via</u> IIIa Thus, asymmetric synthesis of both enantiomers (-)- and (+)-IV from single chiral (+)-I was realized. To our best knowledges, this is the first instance for the preferential creation of either of (R)- and (S)-asymmetric centers using the same reagents and a single chirality, but with the change of the reaction conditions [4]

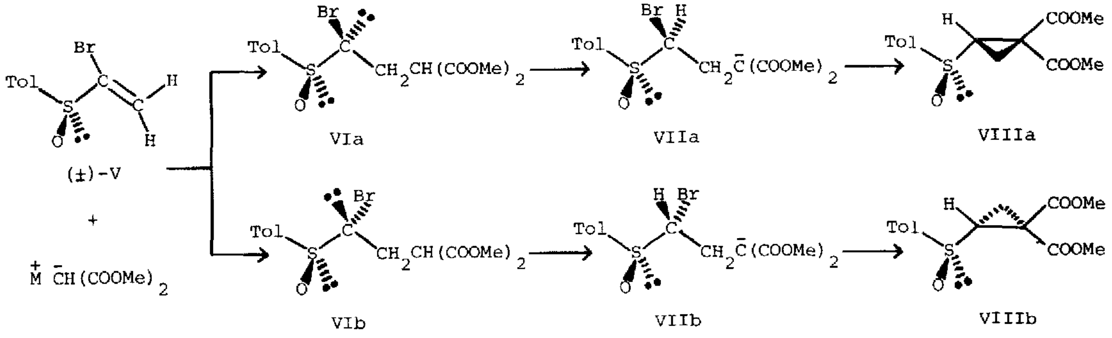
The selective formation of IIIb in THF-Li^+ system can be explained by the following proposal Since this Michael addition is kinetically controlled and the rate determining step is the formation of the anion IIa or IIb,[1,5] it is reasonable to assume that the transition state is close proximity to the anion

IIa or IIb, the stability of which determines the stereochemical course of the reaction. The conformational stability of the carbanion adjacent to the chiral sulfinyl group has been extensively studied and recent publications revealed that, in polar protic solvents, the maximum stability is attained when the electron lobe of the carbanion is trans to the sulfinyl oxygen,[6] while, in THF-Li$^+$ system, the conformer in which the electron lobe is gauche to the sulfinyl oxygen is preferred.[7] If one assumes that the W-shape conformation as shown in Scheme 1 is the most stable for IIa or IIb, the electron lobe in IIa is trans and the lobe in IIb is gauche to the sulfinyl oxygen Then, in polar protic solvents, IIa is the preferred conformation, whereas IIb is preferred in THF-Li$^+$ system. This accounts well for the reason why IIIa is predominantly formed in ethanol, and the formation of IIIb is predominant in THF-Li$^+$ system.

We have further investigated the Michael addition of dimethyl malonate to 1-bromovinyl p-tolyl sulfoxide [(±)-V], which afforded, with the concomitant dehydrobromination, dimethyl 2-(p-tolylsulfinyl)cyclopropane-1,1-dicarboxylate (VIIIa or VIIIb) as shown in Scheme 2. When the reaction was carried out in methanol in the presence of sodium methoxide (1 equiv.), a diastereomeric mixture of VIIIa and VIIIb (84 : 16) was obtained in 75% yield. VIIIa: mp 107-109°; δ^{CDCl_3}: 1.61 (d of d, 1H, J=6 and 9 Hz), 2.32 (d of d, 1H, J=6 and 7 Hz), 2.41 (s, 3H), 2.92 (d of d, 1H, J=7 and 9 Hz), 3.74 (s, 3H), 3.84 (s, 3H), 7.2-7.6 (q, 4H).[8] When the reaction was carried out in THF in the presence of sodium hydride, it resulted in the exclusive formation of VIIIb (89%): mp 69-71°; δ^{CDCl_3}: 1.63 (d of d, 1H, J=6 and 9.5 Hz), 1.92 (d of d, 1H, J=6 and 7 Hz), 2.41 (s, 3H), 3.19 (d of d, 1H, J=7 and 9.5 Hz), 3.75 (s, 3H), 3.89 (s, 3H), 7.3-7.7 (q, 4H).[8] The absolute configurations of VIIIa and VIIIb were unequivocally established by X-ray diffraction analyses:[9] (R_c, S_s), (S_c, R_s) is for VIIIa and (R_c, R_s), (S_c, S_s) for VIIIb, and Scheme 2 shows (S_c, R_s)-VIIIa and (R_c, R_s)-VIIIb.

Thus, by the use of the appropriate solvent, either VIIIa or VIIIb can be

Scheme 2



synthesized selectively. This is another example for the preferential induction of either (R)- or (S)-asymmetric center from the same reagents with different reaction conditions.

It should be noted that the present examples for the alteration of the stereochemical course by changing the solvent and/or the counter cation can hardly be explained by the simple "repulsive steric effect" and we assume that the most important in the stereochemistry for this type of the reaction is the stability and the reactivity of the carbanion adjacent to the chiral sulfinyl group.

Acknowledgment We wish to express our thanks to Dr. F. Iwasaki (The University of Electro-Communications) for her kind information of the results of X-ray crystallographic analyses.

REMARKS AND REFERENCES

1. G. Tsuchihashi, S. Mitamura, S. Inoue, and K. Ogura, Tetrahedron Lett., 323 (1973).
2. The specific rotation of (-)-IV (optical purity of over 95%) was reported to be $[\alpha]_D^{27}$ -24.5° (c 1 000, $CHCl_3$).[1] Accordingly, the optical purity of (+)-IV obtained here was estimated to be over 84%. The NMR and IR data of (+)-IV agreed in every respect with those of (-)-IV.
3. Recrystallization of the diastereomeric mixture was not effective for the complete separation of IIIb from IIIa, due to higher solubility of IIIb than IIIa. A more precise separation of IIIb by column chromatography followed by the reductive desulfurization will afford (+)-IV of higher optical purity.
4. Recently, Meyers and Knaus reported an elegant method for the selective synthesis of either of (R)- and (S)-enantiomers utilizing a single chiral oxazoline with different reagents: A I. Meyers and G. Knaus, J. Amer. Chem. Soc , **96**, 6508 (1974).
5. Controlled experiments revealed that the addition process is irreversible.
6. R. R. Fraser, F. J. Schuber, and Y. Y. Wigfield, J. Amer. Chem. Soc., **94**, 8795 (1972) and references cited therein.
7. a) T. Durst, R. R. Fraser, M. R McClory, R. B Swingle, R. Viau, and Y. Y. Wigfield, Can. J. Chem., **48**, 2148 (1970); b) J. F. Biellmann and J. J. Vicens, Tetrahedron Lett., 2915 (1974). Biellmann and Vicens proposed a chelating effect of the sulfinyl oxygen to the counter lithium cation to account for the conformational preference of the carbanion of which the lobe is in the gauche position.
8. Satisfactory elemental analyses were obtained for these compounds.
9. F. Iwasaki, S Mitamura, and G. Tsuchihashi, to be published.