

ASYMMETRIC SYNTHESIS USING α,β -UNSATURATED SULFOXIDES.

A HIGHLY SELECTIVE MICHAEL REACTION

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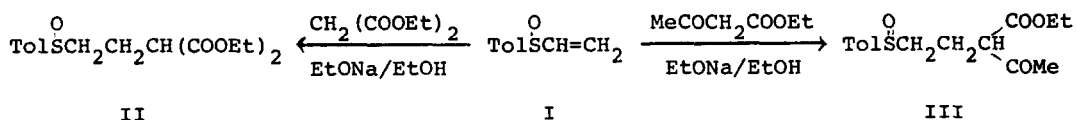
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In contrast with an α,β -unsaturated sulfone, few reports have been presented on the reaction of the corresponding sulfoxide which is regarded as an electron deficient olefin having an asymmetric center due to the tricoordinate sulfur atom¹⁾ adjacent to the carbon-carbon double bond. We have investigated the hitherto unknown Michael addition to α,β -unsaturated sulfoxides²⁾ in terms of the asymmetric synthesis involving the formation of a new carbon-carbon bond.

In the presence of an equimolar amount of sodium ethoxide in ethanol, p-tolyl vinyl sulfoxide(I) was found to react with diethyl malonate and ethyl acetoacetate affording Michael adducts II and III³⁾ in yields of 61% and 71%, respectively (Scheme 1). Thus, the Michael addition to α,β -unsaturated sulfoxides appeared to proceed readily under the usual condition⁴⁾

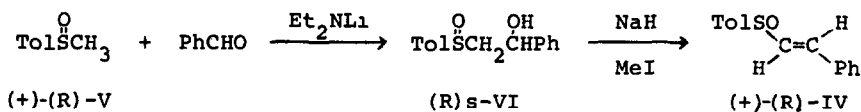
Scheme 1



In order to investigate the steric course of the reaction, trans- β -styryl p-tolyl sulfoxide(IV) was chosen as an ideal Michael acceptor by the following reasons: 1) the optically active form could be achieved easily; 2) the absolute configuration of the adduct would be determined without difficulty; 3) the conformation of IV would be fixed by bulky phenyl and p-tolyl groups in a

W-form (see Scheme 4). The preparation of (+)-(R)-trans- β -styryl p-tolyl sulfoxide(IV) was carried out by a route shown in Scheme 2. The reaction of (+)-(R)-methyl p-tolyl sulfoxide(V), $[\alpha]_D^{28.5} +145.9^\circ$ (c 1.040, acetone), $lit.^{5)} [\alpha]_D +145.5^\circ$ (acetone), with benzaldehyde in the presence of lithium diethylamide gave β -hydroxysulfoxide(VI)⁶⁾. The treatment of VI with excess amounts of sodium hydride and methyl iodide afforded (+)-(R)-IV in a 75% yield; mp 81.5-82 $^\circ$, $[\alpha]_D^{28} +164.3^\circ$ (c 1.233, CHCl₃), ν_{max}^{KBr} : 1045 cm⁻¹, δ^{CCl_4} : 2.38 (s, 3H), 6.76 (d, 1H, J=15Hz), 7.0-7.6 (m, 10H).

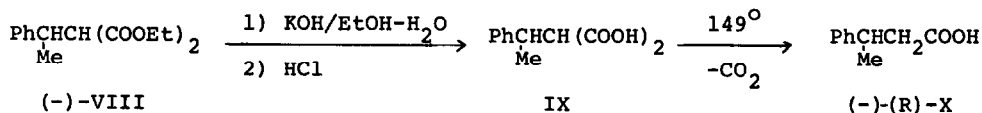
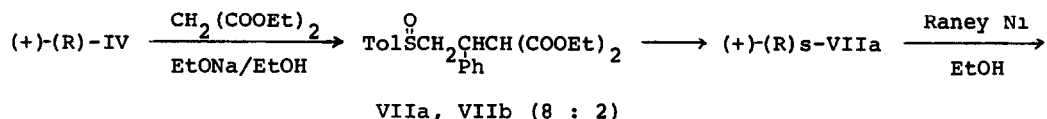
Scheme 2



An ethanol solution of (+)-(R)-IV and diethyl malonate with an equimolar amount of sodium ethoxide was heated at 80 $^\circ$ under an argon atmosphere for 18 hr. A usual work-up gave diethyl 2-(p-tolylsulfinyl)-1-phenylethylmalonate(VII), in an 82% yield, which appeared by nmr analysis to be a mixture of diastereomers VIIa and VIIb (8 : 2). Fractional recrystallization from ethanol-n-hexane afforded the major isomer VIIa in a pure form (an overall yield from IV: 51%); mp 161.5-162.5 $^\circ$, $[\alpha]_D^{27} +93.1^\circ$ (c 1.472, CHCl₃), ν_{max}^{KBr} : 1732, 1030 cm⁻¹, δ^{CDCl_3} : 1.01 (t, 3H, J=7Hz), 1.20 (t, 3H, J=7Hz), 2.34 (s, 3H), 3.07 (d of d, 1H, J=10.5, 13Hz), 3.22 (d of d, 1H, J=4.5, 13Hz), 3.72 (d, 1H, J=10.5Hz), 3.93 (q, 2H, J=7Hz), 4.15 (q, 2H, J=7Hz), 3.9-4.3 (m, 1H), 7.1-7.6 (m, 9H).

The absolute configuration of VIIa was unequivocally determined by the following way (Scheme 3). Desulfurization of VIIa with W-2 Raney nickel in ethanol gave (-)-diethyl 1-phenylethylmalonate(VIII), $[\alpha]_D^{27} -24.5^\circ$ (c 1.000, CHCl₃), in a 92% yield. Hydrolysis of VIII at 80 $^\circ$ for 3 hr with potassium hydroxide in ethanol-water followed by acidification yielded the corresponding malonic acid IX. The successive decarboxylation was effected by heating IX at 149 $^\circ$ for 22 min to afford (-)-3-phenylbutyric acid(X), $[\alpha]_D^{29} -53.9^\circ$ (c 1.396, benzene), in an 88% yield based on VIII. The specific rotation of optically pure (-)-X was reported⁷⁾ to be $[\alpha]_D^{20} -57.2^\circ$ (c 9.8, benzene) and its configuration

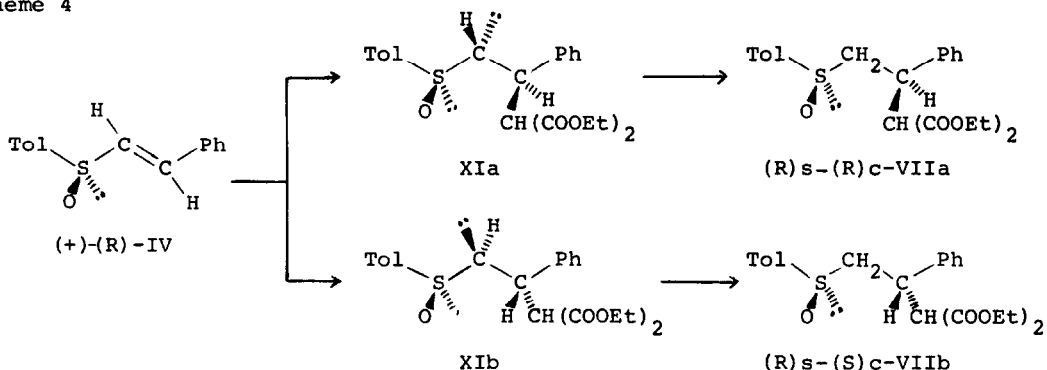
Scheme 3



was established by Prelog as (R)⁸⁾. Therefore the major isomer VIIa obtained from the Michael addition should have at least 95% optical purity and (R)s-(R)c configuration.

The facts that the adduct VIIa endures under the reaction condition and that the thermodynamic equilibrium ratio of VIIa to VIIb, determined by the Mislow's method⁹⁾, is 1 : 1 indicate that the addition of malonic ester to IV should be a kinetically-controlled irreversible process¹⁰⁾. Therefore the rate-determining step is the formation of carbanions XIa and XIb (Scheme 4).

Scheme 4



According to the Hammond's postulation¹¹⁾, the structures of the transition states should be similar to those of XIa and XIb. It is generally accepted that the most stable conformation of the α -sulfinyl carbanion is one with the carbon lone-pair orbital trans to the sulfinyl oxygen in a polar solvent¹²⁾. Therefore the anion XIa is considered to be more stable than XIb. The remarkable

selectivity in this Michael addition may be ascribed to the difference in the stability between the carbanions XIa and XIb¹³).

The highly selective Michael addition provides a new method for an asymmetric synthesis of 1-phenylethylmalonic ester VIII, which is a precursor for the synthesis of 2-amino-3-phenylbutyric acid, a naturally occurring new amino acid found to be one component of bottromycin¹⁴).

REMARKS AND REFERENCES

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