CHEMISTRY LETTERS, pp. 797-800, 1981.

THE ASYMMETRIC MICHAEL REACTION OF (2R,3S)-3,4-DIMETHYL-2-PHENYLPERHYDRO-1,4-OXAZEPINE-5,7-DIONE WITH 1-NITROCYCLOHEXENE

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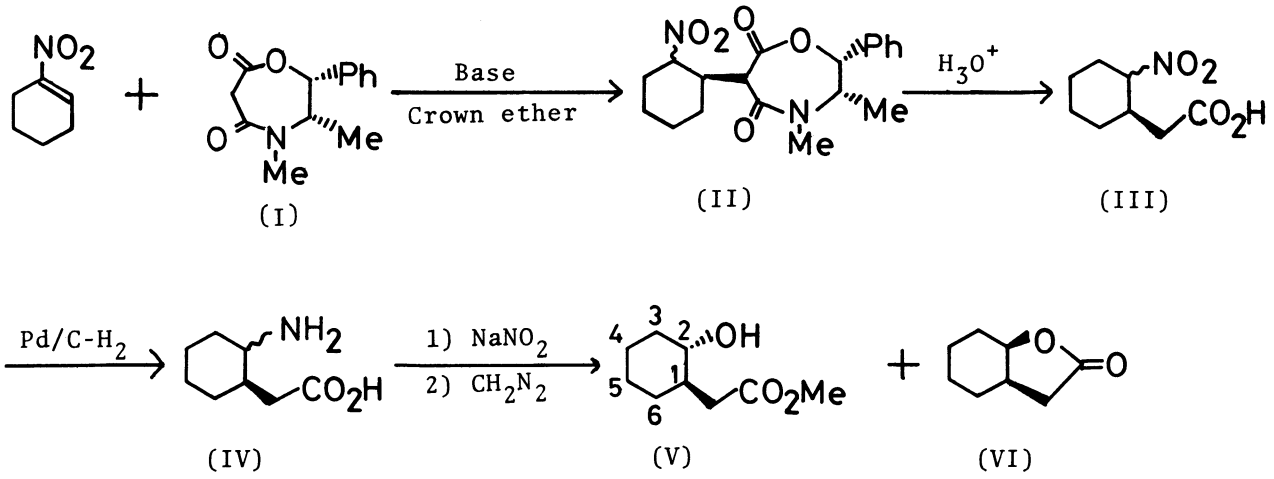
Optically active (2-nitrocyclohexyl)acetic acid(III) was obtained by the Michael reaction of (2R,3S)-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione(I) with 1-nitrocyclohexene in the presence of potassium t-butoxide (or cesium fluoride) and crown ether, followed by acid hydrolysis.

There have been developed various useful synthetic methods which enable the conversion of nitro group to the other functional groups such as carbonyl,[1] nitrile,[2] and amino[3] groups under mild conditions. Therefore, aliphatic nitro compounds frequently appeared in organic chemistry as interesting intermediates.[4]

Previously we showed that optically active δ-oxoalkanoic acids were obtained in 44-55% optical yields by the asymmetric addition of (2R,3S)-3,4-dimethyl-2-phenylperhydro-1,4-oxazepine-5,7-dione(I) to α,β-unsaturated ketones.[5] The result obtained in the above study prompted us to investigate the preparation of chiral nitro compounds by asymmetric reaction of the chiral oxazepine(I) with 1-nitro olefins. In this communication, we wish to report the results of the Michael reaction of the oxazepine(I) with 1-nitrocyclohexene as shown in the scheme. The asymmetric addition was carried out using potassium t-butoxide or cesium fluoride as a base. The adduct(II) was hydrolyzed in acidic medium to afford (2-nitrocyclohexyl)acetic acid(III) as a mixture of stereoisomers (cis/trans = 3/1-7/1)[6] in good yield. The optical purity was determined by quantitative NMR analysis using



optically active shift reagent after conversion of III to the trans-γ-hydroxy ester(V).

The typical experimental procedure was as follows; to a THF(5 ml) suspension of potassium t-butoxide(0.045 g, 0.4 mmol) were added a THF(8 ml) solution of the oxazepine(I)(1.165 g, 5 mmol) and a THF(5 ml) solution of dicyclohexyl-18-crown-6 (0.163 g, 0.44 mmol) successively at room temperature, then, cooling to 0 °C, 1-nitrocyclohexene(1.270 g, 10 mmol) in THF(7 ml) was added to the solution and stirred for 30 h. The reaction mixture was quenched with a phosphate buffer solution (pH 7). The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on silica gel and the adduct(II) was obtained as a mixture of diastereomers. The adduct(II) was dissolved in 6N H_2SO_4(7.5 ml) and AcOH (7.5 ml) and the solution was refluxed for 2 h. The acid was extracted with CH_2Cl_2 and the extract was dried and condensed under reduced pressure. The residue was chromatographed on silica gel and (2-nitrocyclohexyl)acetic acid(III)(0.807 g, 86%) was obtained. The acid(III)(0.603 g, 3.22 mmol) in MeOH(32 ml) was hydrogenated under atmospheric pressure in the presence of 10% Pd/C(0.159 g) for 2 days. The crude amino acid(IV) obtained by evaporation of solvent after filtration was washed with ether and dried. Then IV was dissolved in 50% AcOH(3.6 ml) and $NaNO_2$(1.078 g) in 50% AcOH(11 ml) was added to the solution. After stirring overnight, the reaction mixture was poured into 6N NaOH(30 ml), and then acidified with 6N HCl. The products were extracted with ether, washed with 2% HCl and brine successively. The extract was dried over Na_2SO_4 and condensed under reduced pressure. The residue was dissolved in

MeOH(10 ml) and treated with diazomethane. After evaporation of solvent, the residue was purified by silica gel chromatography and trans-hydroxy ester(V) and cis-lactone (VI) were obtained.

Table. The asymmetric Michael reaction of the oxazepine(I) with 1-nitrocyclohexene

Entry	Base	Additive	Nitrocarboxylic acid (III)	Hydroxy ester (V)		
			Yield(%)	$[\alpha]_D$ (c, $CHCl_3$)	Enantiomer excess(%)[b]	Abs. config. of C-1[c]
1	t-BuOK		90	$[\alpha]_D^{24}$-6.4°(2.3)	26	S
2	t-BuOK	dicyclohexyl-18-crown-6	86[a]	$[\alpha]_D^{25}$+19.8°(2.3)	75	R
3	CsF		98	$[\alpha]_D^{22}$-10.1°(2.4)	38	S
4	CsF	dicyclohexyl-24-crown-8	67	$[\alpha]_D^{23}$+18.5°(0.79)	71	R

a) When one equimolar amount of nitro olefin was employed, the adduct(II) was obtained in 51% yield.

b) Determined by quantitative 270 MHz NMR analysis using optically active shift reagent (tris-[3-(trifluoromethylhydroxymethylene)-d-camphorato]-europium) in CCl_4.

c) Determined by specific rotation of trans-lactone prepared from V[7] according to the method reported by House et al.[8]

In a similar manner, this asymmetric reaction was examined by changing the reaction conditions and the results are summarized in the table. The most interesting result is the effect of crown ether added. When only potassium t-butoxide or cesium fluoride was employed as a base, the products were obtained with poor optical purity. On the other hand, by the combined use of base-crown ether, optical yield was highly improved. Though the role of the crown ether is not yet clear, it is suspected that the bulky complex of the crown ether and the cation controls the stereoselective approach of the chiral oxazepine anion to nitro olefin effectively.

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(Received March 30, 1981)