

ASYMMETRIC SYNTHESIS BASED ON (Z)-(2R,3S)-6-BENZYLIDENE-3,4-DIMETHYL-5,7-DIOXO-2-PHENYLPERHYDRO-1,4-OXAZEPINE. SYNTHESIS OF OPTICALLY ACTIVE 3-SUBSTITUTED 3-PHENYLPROPIONIC ACIDS

Teruaki MUKAIYAMA, Takeshi TAKEDA, and Masaaki OSAKI

Department of Chemistry, Faculty of Science

The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

(Z)-(2R,3S)-6-Benzylidene-3,4-dimethyl-5,7-dioxo-2-phenylperhydro-1,4-oxazepine (I) was prepared in good yield from α -ethoxycarbonylcinnamic acid and *l*-ephedrine hydrochloride by the use of 2-chloro-1-methylpyridinium tosylate as a coupling reagent. The conjugate addition of *n*-butylmagnesium bromide to (I) in the presence of nickel chloride, followed by hydrolysis and decarboxylation gave highly enantiomerically pure (99%) 3-phenylheptanoic acid in high yield (92%).

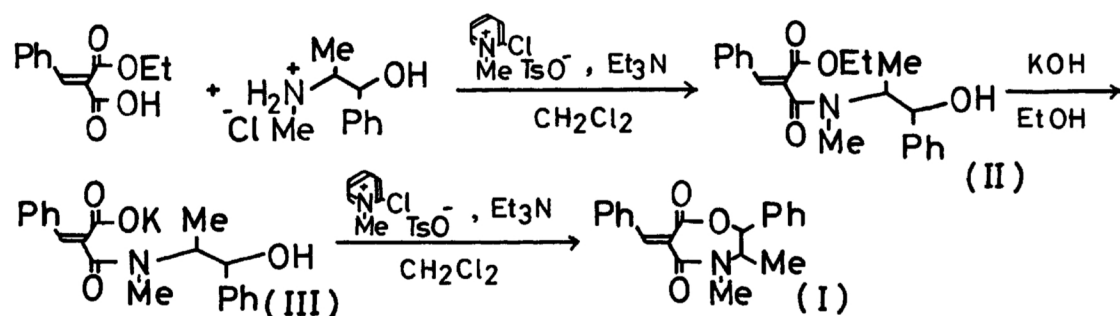
Many works have been reported on the introduction of a new asymmetric center into a carbon chain of carboxylic acid. Most of the attempts in this field consist of the conjugate addition of Grignard reagents to α,β -unsaturated carboxylic esters of optically pure alcohols, such as menthol¹⁾ or several sugar derivatives.²⁾ But only partial asymmetric inductions were achieved in these reactions. Recently, the syntheses of the highly optically pure α - and β -substituted alkanolic acids were achieved using the oxazoline derivatives.^{3,4)}

In the present communication, we wish to report the synthesis of (Z)-(2R,3S)-6-benzylidene-3,4-dimethyl-5,7-dioxo-2-phenylperhydro-1,4-oxazepine (I) and the results of the preliminary study on the asymmetric synthesis of 3-substituted 3-phenylpropionic acids by the conjugate addition of Grignard reagents to (I) in the presence of some metal salts.

The cyclic compound (I) was prepared from α -ethoxycarbonylcinnamic acid and *l*-ephedrine hydrochloride using 2-chloro-1-methylpyridinium tosylate, recently

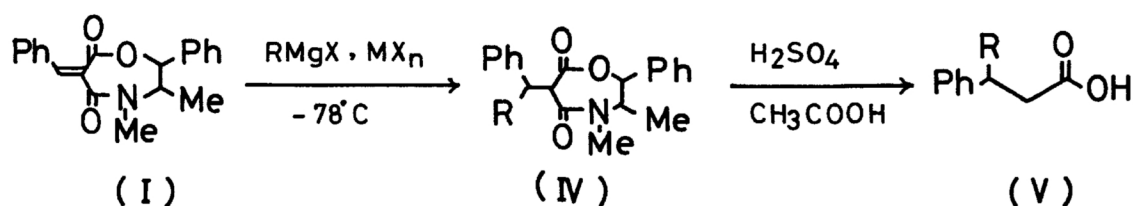
developed in our laboratory, as a coupling reagent.⁵⁾

The experimental procedure for the synthesis of (I) is as follows; to a dichloromethane (20 ml) solution of α -ethoxycarbonylcinnamic acid (10 mmol), *l*-ephedrine hydrochloride (10 mmol) and 2-chloro-1-methylpyridinium tosylate (12 mmol) was added triethylamine (34 mmol) at 0°C under an argon atmosphere. After stirring overnight at room temperature, the dichloromethane solution was washed with water and dichloromethane layer was dried over anhydrous sodium sulfate. After the extract was condensed under reduced pressure, the residue was chromatographed on silica gel and the hydroxyamide (II)⁶⁾ was obtained in 85% yield. After an ethanol (40 ml) solution of potassium hydroxide (34 mmol) was added to an ethanol (60 ml) solution of the hydroxyamide (II) (34 mmol), the reaction mixture was stirred overnight at room temperature. Then it was condensed under reduced pressure and the crude potassium salt (III)⁶⁾ was obtained. To a dichloromethane (150 ml) suspension of the crude potassium salt (III) was successively added triethylamine (41 mmol) and 2-chloro-1-methylpyridinium tosylate (41 mmol) under an argon atmosphere. After stirring overnight at room temperature, the reaction mixture was poured into a phosphate buffer solution (pH 7). An organic layer was extracted with dichloromethane and the extract was dried over anhydrous sodium sulfate. The extract was condensed under reduced pressure. The resulting oily substance was chromatographed on silica gel and the cyclic compound (I)⁶⁾ was obtained in 55% yield ($[\alpha]_D^{29} -182^\circ$ (c 7.59, CH₂Cl₂), mp 188-189°C (benzene - n-hexane)).



It was confirmed that the chiral cyclic compound (I) prepared by the above mentioned procedure contained no E-isomer by NMR spectrum and gas chromatography.

The conjugate addition of Grignard reagents to the cyclic compound (I) was carried out in the presence of some metal salts (see Table).



The typical reaction procedure is described for entry 6; to a THF (10 ml) solution of the cyclic compound (I) (1.5 mmol) and nickel chloride (0.075 mmol) was added a THF solution of n-butyrmagnesium bromide (1.8 mmol) at -78°C under an argon atmosphere. After stirring for 3 hr, the reaction mixture was poured into a phosphate buffer solution (pH 7). An organic layer was extracted with dichloromethane and the extract was dried over anhydrous sodium sulfate. After the extract was condensed under reduced pressure, the residue was chromatographed on silica gel and the adduct (IV) was isolated as a mixture of diastereomers. After 6N H_2SO_4 (20 ml) was added to an acetic acid (10 ml) solution of the adduct (IV), the reaction mixture was refluxed for 6 hr. Then the resulting oily substance was extracted with dichloromethane and the extract was condensed under reduced pressure. The residue was chromatographed on silica gel and 3-phenylheptanoic acid (V) was isolated in 92% yield. Further it was purified for the measurement of specific rotation by bulb-to-bulb distillation ($180\text{--}190^\circ\text{C}$ (bath temperature)/1.5 mmHg).

Table Asymmetric synthesis of 3-substituted 3-phenylpropionic acids

	RMgX	MXn	Solvent	Yield (%)	$[\alpha]$ (Benzene)	c	Optical Purity (%)
1	n-BuMgBr	-	THF	85	$[\alpha]_{578}^{24} -30.4^\circ$	8.25	88 ^{a)}
2		NiCl ₂	THF	92	$[\alpha]_{578}^{24} -34.0^\circ$	8.03	99 ^{a)}
3		ZnCl ₂	THF	76	$[\alpha]_{578}^{25} -29.3^\circ$	8.09	85 ^{a)}
4		FeCl ₃	THF	70	$[\alpha]_{578}^{26} -20.6^\circ$	8.00	60 ^{a)}
5	PhCH ₂ MgCl	-	THF	75	$[\alpha]_{\text{D}}^{30} +5.65^\circ$	1.93	9 ^{b)}
6		NiCl ₂	THF	78	$[\alpha]_{\text{D}}^{29} +4.17^\circ$	1.92	7 ^{b)}
7		ZnCl ₂	THF	85	$[\alpha]_{\text{D}}^{26} +8.81^\circ$	1.93	15 ^{b)}
8		FeCl ₃	THF	62	$[\alpha]_{\text{D}}^{30} +10.6^\circ$	1.93	18 ^{b)}
9		-	THF-HMPT	68	$[\alpha]_{\text{D}}^{24} -43.7^\circ$	1.92	73 ^{b)}
10		NiCl ₂	THF-HMPT	76	$[\alpha]_{\text{D}}^{26} -44.7^\circ$	1.94	75 ^{b)}

a) Based on $[\alpha]_{578}^{28} -34.4^\circ$ (c 8, benzene) for enantiomerically pure acid.⁴⁾

b) The reported $[\alpha]_{\text{D}}^{28} \text{max} -60^\circ$ (c 1.92, benzene) was determined by resolution method.²⁾

c) THF (15 ml) and HMPT (4 ml) were used as a solvent for 1.5 mmol of (I).

The result shows that the highly optically pure carboxylic acids were obtained in good yields when the reaction is carried out in the presence of nickel chloride. Though the role of metal salts in the conjugate addition reaction is not yet well known, it is assumed that the coordination of a metal salt, or an alkyl metal species, produced by the reaction of a Grignard reagent with the metal salt, to the cyclic compound (I) makes the chiral moiety of (I) more rigid and that consequently the stereoselectivity of the addition reaction is increased.

It is noted that this preliminary experiments showed the possibility of the synthesis of highly optically pure β -substituted alkanolic acids utilizing the cyclic compound (I) and related compounds.

Further study is now under investigation and will be reported soon.

References and Note

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