HETEROCYCLES, Vol. 55, No. 1, 2001, pp. 9 - 12, Received, 11th September, 2000

STEREOSELECTIVITY IN THE DARZENS CONDENSATION OF SUBSTITUTED CYCLOHEXANONES WITH (-)-8-PHENYLMENTHYL α-CHLOROACETATE

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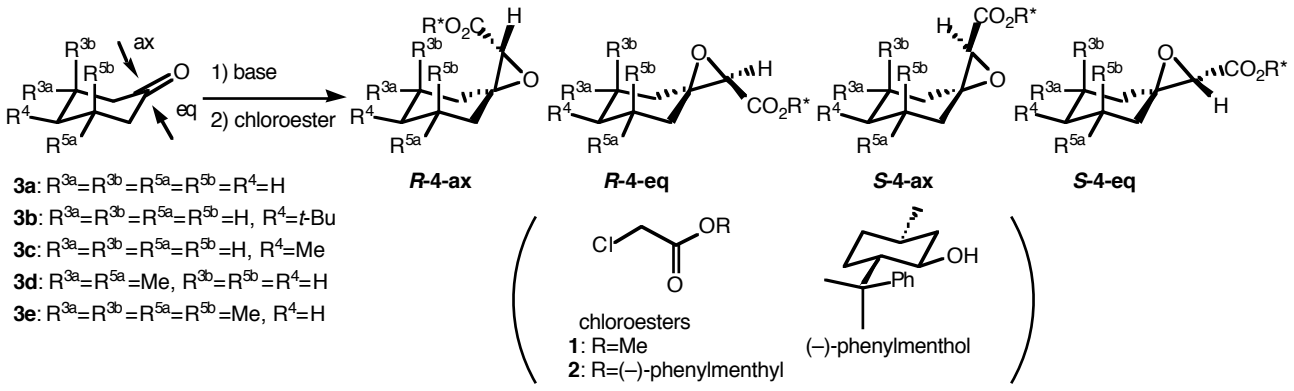
Abstract – The Darzens condensation of 4-monosubstituted and *cis*-3,5-dimethyl-cyclohexanones with (-)-8-phenylmenthyl α-chloroacetate proceeded to give mixtures of *trans*- and *cis*-glycidic esters with high enolate face selectivity (>95% de). The presence of axial methyl substituents at the 3 and 5 position lead to decrease in enolate face selectivity. The configuration of the major products was determined by NMR, derivation, and/or X-Ray crystallographic analysis.

There have been many detailed stereochemical investigations in the Darzens condensation[1] of aldehydes with α-haloacetate, and several asymmetric versions of the reaction either using chiral auxiliaries in the halogenated reagent for diastereoselective reactions[2] or mediated by chiral reagents in enantioselective reactions[3] have been reported. However, little attention has been paid to the asymmetric Darzens condensation of ketones.[4] We have recently found that the condensation of symmetric ketones with haloacetates with a (-)-8-phenylmenthyl group as the chiral auxiliary furnishes glycidic esters in 77-96% de, with especially high diastereoselectivity in the reaction of cyclohexanone (96% de).[5] Since many natural products carry chiral cyclohexane units, the high diastereoselectivity prompted us to investigate the scope of our method for cyclohexanone derivatives along with an examination of the axial-equatorial selectivity in the cyclohexanone ring. Herein we describe our results.



Scheme 1

The reactions were generally carried out by adding substituted cyclohexanones to solutions of enolates of α–haloacetates (**1**) and (**2**) generated by base at –78 °C and allowing the resulting mixture to warm to 0 °C over a few hours to afford the glycidic esters as summarized in Table 1. The reaction of achiral (**1**) with **3b** bearing a 4-*t*-butyl group gave diastereomers in the ratio of 57:43 (Run 2) favoring product from axial attack. Upon using chiral (**2**) under similar conditions, diastereomers were obtained in a 72:28 ratio. Analysis of each diastereomeric product revealed, however, that with respect to the relative stereochemistry between the chiral auxiliary and the proton adjacent to the ester group, the level of asymmetric induction was high (>95% de), yielding only ***R*-4b-ax** and ***R*-4b-eq**, respectively, both having *R* configuration at the asymmetric carbon in the epoxide. Changing the solvent and base (Run 5) resulted in essential no change upon selectivity. Maintaining the temperature at –40 °C gave similar results, thus indicating that the reaction probably requires this temperature for reaction to proceed.

Table 1. The Darzens Condensations of Cyclohexanones (**3**)[a]

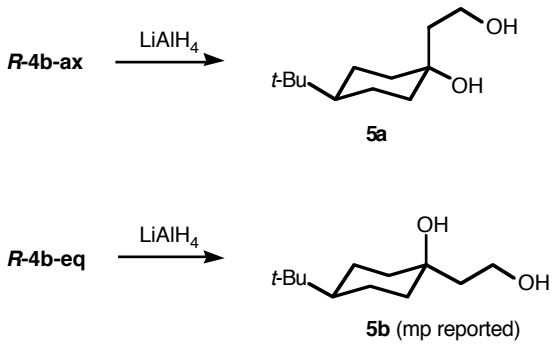
Run	Ketone	Ester	Base	Solvent	Yield[b] (%)	ax : eq[c]	% de[d] ax	% de[d] eq
1[e]	**3a**	**2**	*t*-BuOK	CH_2Cl_2	80	—	>95	
2	**3b**	**1**	*t*-BuOK	CH_2Cl_2	31	57 : 43	—	
3	**3b**	**2**	*t*-BuOK	CH_2Cl_2	63	72 : 28	>95	>95
4[f]	**3b**	**2**	*t*-BuOK	CH_2Cl_2	82	75 : 25	>95	>95
5	**3b**	**2**	KHMDS	THF	84	73 : 27	>95	>95
6	**3c**	**2**	*t*-BuOK	CH_2Cl_2	69	78 : 22	>95	>95
7[f]	**3c**	**2**	*t*-BuOK	CH_2Cl_2	81	72 : 28	>95	>95
8	**3c**	**2**	*t*-BuOK	ether	50	70 : 30	>95	>95
9	**3c**	**2**	*t*-BuOK	THF	20	77 : 23	>95	>95
10	**3d**	**2**	KHMDS	THF	82	43 : 57	>95	>95
11	**3e**	**2**	*t*-BuOK	CH_2Cl_2	31	—	78	
12	**3e**	**2**	KHMDS	THF	80	—	80	

[a] The ketones were added to the enolate at –78 °C and the solution was allowed to warm to 0 °C over 2 to 3 h unless noted otherwise. [b] The yields were not optimized. [c] Denotations ax and eq correspond respectively to products of supposed axial and equatorial attack of the enolate to the cyclohexanone ring of preferred conformation. [d] The diastereoselectivity and the geometric ratios were determined by ^{1}H NMR analysis of the crude mixture. [e] Ref. 5. [f] The reaction temperature was maintained and quenched at –40 °C.

Tentative assignments of the stereochemistry were carried out by ^{1}H NMR. In previous investigations,[5] we have found the general tendency for the epoxide ring proton to appear at lower field (δ 2.84-3.01) for the major diastereomer (2*R* configuration), in comparison with that of the minor diastereomer (2*S* configuration; δ 2.14-2.44). The difference was attributed to the magnetic anisotropy caused by the benzene ring in the (-)-8-phenylmenthyl group. The corresponding chemical shifts for products (***R*-4b-ax**) and (***R*-4b-eq**) derived from 4-*t*-butylcyclohexanone were observed at δ 3.10 and 2.91 as singlets, respectively, implying 2*R* configuration.

Since signals of axial alkyl groups tend to shift downfield compared with their equatorially substituted isomers in cyclohexane rings, the difference of Δδ=0.2 ppm suggested the former (***R*-4b-ax**) to have the 3-membered ring oxygen positioned equatorial and carbon axial.

The assigned stereochemistries of the spiro-products were confirmed by derivation and X-Ray structural analysis. Reduction of the separated diastereomeric glycidic esters (***R*-4b-ax**) and (***R*-4b-eq**) with $LiAlH_4$ (Scheme 2) yielded diastereomeric diols (**5a**) and (**5b**),[6] respectively, as single products, thus establishing the relative stereochemistry in the cyclohexane ring. The relative stereostructure of all the chiral centers in ***R*-4b-ax** were ascertained by X-Ray crystallography (Figure. 1) to be just as assumed by NMR.[7]



Scheme 2

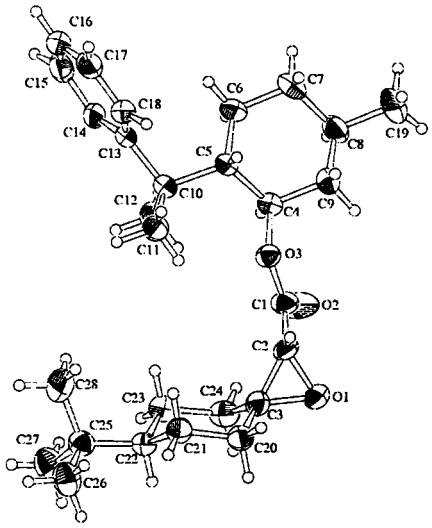
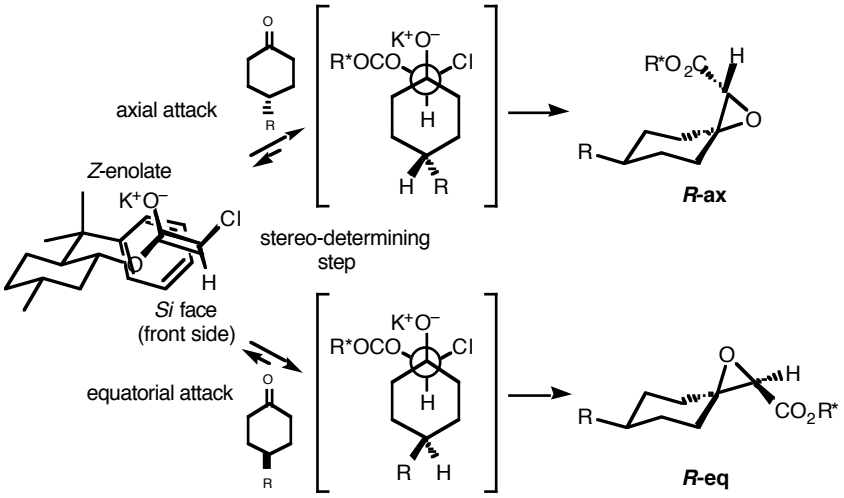


Figure 1. The ORTEP drawing of *R*-4b-ax

Not only was the reaction of **3c** (R^4=Me) virtually unaffected by change in base, but it also gave essentially the same cyclohexanone face selectivity and the same diastereoselectivity in the epoxide moiety as with **3b**. Since the difference in thermodynamical stability between equatorial and axial conformers is larger for **3b** compared with **3c** this result indicates that the reaction for both must have occurred only upon the 4-equatorial conformer, according to the Curtin-Hammett principle. Stereochemical assignments were carried out in analogy with **3b**. 3,5-Disubstituted **3d** gave the glycidic esters with cyclohexanone ring face selectivity of 43:57 in favor of equatorial attack as assumed from the chemical shift of the epoxide ring proton. Here again selectivity concerning the enolate face was exclusive. However, the substitution pattern seems to have slightly altered the reaction in favor of equatorial attack. Examined next was 3,3,5,5-tetrasubstituted **3e**, in which the presence of axial substituents are inevitable, and accordingly, attack upon the carbonyl group would be expected to occur predominantly from the equatorial direction. Here, the diastereoselectivity in regards with the epoxide ring was found to drop somewhat to about 80% de.

The generally accepted mechanism for the Darzens condensation involves the following three steps: (a) proton abstraction from the carbon which bears the α-halogen substituent in the esters; (b) addition of the resulting enolate to the aldehyde or ketone; (c) intramolecular nucleophilic displacement of the halogen ion. The second step can be considered to be the stereodetermining step. On the basis of the stereochemical outcome, it is suggested that, in our case, the aldol type reaction of the Darzens reaction occurred exclusively from the *Si*-face of the thermodynamically stable *Z*-enolate intermediate, which is not blocked by the phenyl group, as shown in Scheme 3. Of these processes, this second is subject to reverse reaction, and the presence of this process has been considered to be the cause of variations in selectivity in the case of aldehyde reactions. In our system, the reactions of aldehydes were of low diastereoselectivity in contrary with results of ketones.[5] Thus, we can assume that in the reaction of ketones, the cyclization process has become relatively faster than the retro reaction. Thus the selectivity attained at the point of the aldol process can be maintained throughout the reaction for **3b-d**, except in the case of **3e**, where the initial C–C bond formation is retarded by the buttress effect of the axial substituents while the reverse reaction is not.

Herein, we have shown that the Darzens reaction of cyclohexanone derivatives using (-)-8-phenylmenthyl as the chiral auxiliary can give spirocyclic glycidic esters effectively with high diastereoselectivity in the epoxide moiety.



Scheme 3

ACKNOWLEDGMENT

NMR and HRMS measurements were carried out on JEOL L-500 and JEOL SX-102A, respectively, at the Instrument Center for Chemical Analysis, Hiroshima University.

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7. Details of the X-Ray analysis will be reported in a full account.