Regioselective Alkylation in the Course of Aldol Condensation under Phase-Transfer Catalytic Conditions

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Synopsis. Regio- and stereoselective alkylation in the course of aldol condensation under liquid-solid phase-transfer catalytic conditions, affording conjugated dienyl ether (**5**) or α-substituted β,γ-olefinic aldehyde (**7**) depending on the starting halides, both in good yields, was disclosed. The reaction mechanism is also discussed.

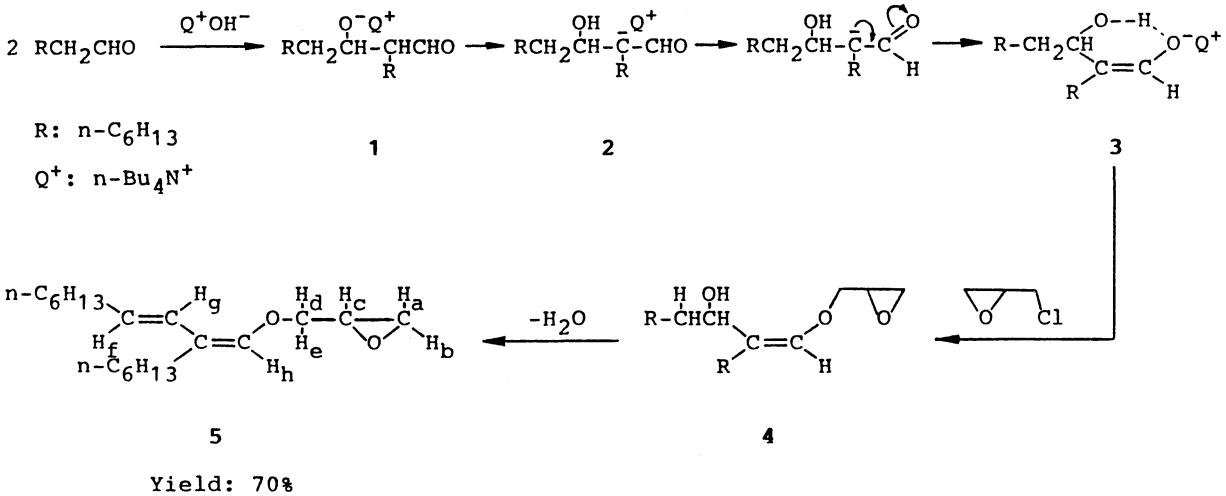
Aldol condensation is a basic and useful reaction of aldehydes, and plays an important role in organic synthesis.[1-3] Recently, direct alkylation of aldehyde has also attracted attention. The aldehydes having one α-hydrogen atom[4] or an α,β-unsaturated group[5] have been directly alkylated to afford alkylated aldehydes such as α-, γ-, or *O*-alkyl products.

During the course of investigations regarding the reactivity of epichlorohydrin under phase transfer (PT) catalytic conditions, we have recently found a simple synthetic method for the preparation of oligoethylene glycol diglycidyl ethers in good yields,[6] and also the regioselective addition of organic chlorides to epoxides under mild conditions.[7] Now we wish to report a regio- and stereoselective alkylation of aliphatic aldehydes with epichlorohydrin or other organic halides during the course of aldol condensation in the presence of PT catalyst and solid sodium hydroxide.

The reaction of octanal with epichlorohydrin was carried out at 55 °C for 2 h in the presence of solid sodium hydroxide and tetrabutylammonium hydrogensulfate in dioxane. The reaction was very clean judging from inspection by GLC. Only two peaks were observed. The main peak was characterized as (5*Z*, 7*E*)-1,2-epoxy-6-hexyl-4-oxatetradeca-5,7-diene (**5**) by spectral analyses: absorptions due to conjugated carbon-carbon double bonds and an ether linkage were observed in the infrared spectra (1660, 1640, 1120 cm^{-1}). The presence of an epoxide ring and two kinds of olefinic moieties in *E* and *Z* forms respectively were deduced from chemical shift values and coupling constants in ^1H NMR. Especially H_h was characterized by Pascual's empirical equation[8] to support the structure of **5** (δ=2.52—2.70 (m, H_a), 2.70—2.90 (m, H_b), 3.04—3.28 (m, H_c), 3.40—4.08 (m, $H_{d,e}$), 5.30—5.70 (m, *J*=17.2 Hz, H_f), 5.70—5.95 (d, *J*=17.2 Hz, H_g), 6.10 (s, H_h)). A conspicuous component of short retention time was identified as *trans*-3-chloroallyl glycidyl ether, which was formed by the isomerization of epichlorohydrin under PT catalytic conditions followed by the condensation with another molecule of epichlorohydrin.[9]

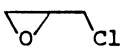
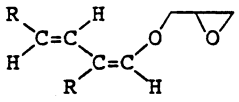
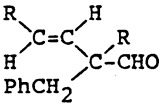
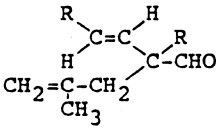
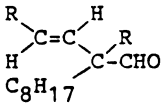
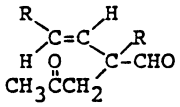
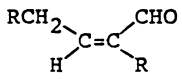
In the absence of PT catalyst, the reaction mentioned above is different. The main product isolated is 2-hexyl-2-decenal (**8**) resulting from the aldol condensation. The alkylated product, **5**, formed only in a small amount in this case.

The stereospecific formation of product **5** under PT catalytic conditions can be explained reasonably by the postulation shown in Scheme 1: the intermediate **1** formed by aldol condensation of two aldehyde molecules rearranges to the intermediate **2**, which further changes to the enolate **3** forming a six-membered ring stabilized by the intramolecular hydrogen bonding. This structure of enolate **3** may cause the formation of a *Z* conformation at one of the two double bonds in **5**. Finally, the enolate **3** attacks epichlorohydrin to produce compound **4**, which is then dehydrated under alkaline conditions to form the conjugated dienyl glycidyl ether **5** with the thermodynamically stable *E*

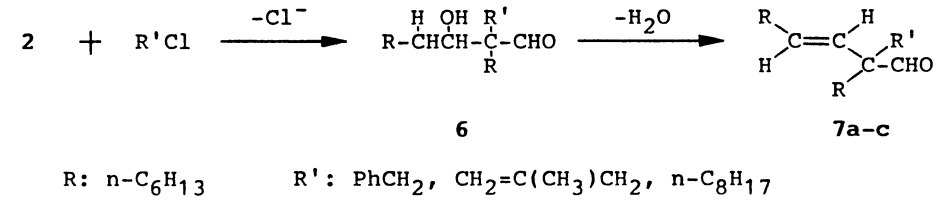


Scheme 1.

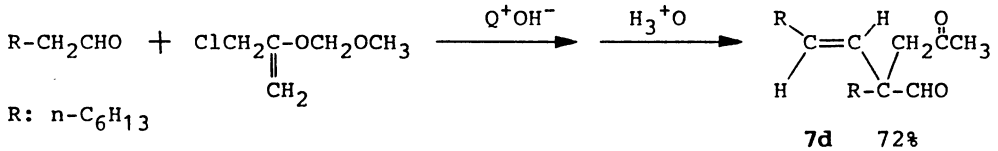
Table 1. Results of Alkylation during the Course of Aldol Condensation under PT Catalytic Conditions[a)]

Alkylating reagent	Product (R: n-C_6H_{13})		Yield %	Bp θ_m[b)] °C/Torr
		(**5**)	70	130/0.05
$PhCH_2Cl$		(**7a**)	66	130/0.02
$CH_2=C(CH_3)-CH_2Cl$		(**7b**)	68	120/0.02
n-$C_8H_{17}Cl$		(**7c**)	31	135/0.02
$ClCH_2C(=CH_2)-OCH_2OCH_3$		(**7d**)	72	125/0.05
 (without PT catalyst)		(**8**)	30	115/0.05

a) Octanal was used in all cases, and the reaction was carried out at 55 °C for 2 h in the presence of PT catalyst and solid sodium hydroxide. b) By Kugelrohr distillation.



Scheme 2.



Scheme 3.

conformation.

However, the reaction of octanal with benzyl, methallyl, or octyl chlorides afforded different products even under the same PT catalytic conditions, as reported by Suyama and Shimizu.[10] The sole product isolated was an α-substituted β,γ-olefinic aldehyde **7a—c** (Scheme 2). The distinguishing spectral feature of products **7** are the following: no infrared absorption due to conjugated carbon-carbon double bonds nor ether linkage appeared, while absorption due to isolated double bond and carbonyl group was observed in the IR spectra (1460, 1720 cm^{-1}, respectively). The signal of the aldehyde proton was clearly seen in the ^1H NMR spectra (δ 9.30). In these cases, the following reaction route is indicated. The intermediate **2** attacks organic chloride directly to afford compound **6** before rearrangement to the intermediate **3** (or even if **2** exists in equilibrium with **3**), **6** is then further dehydrated to **7a—c** (Scheme 2). Judging from the GLC, this reaction was also selective, and the yields of these products were 66, 68, and 31% for benzyl (**7a**), methallyl (**7b**), and octyl (**7c**) derivatives, respectively. Without PT catalyst, the main product in these cases was also an aldol condensation product **8** instead of **7**. The results of alkylation during the course of the aldol condensation are summarized in Table 1.

The reaction of octanal with 2-(chloromethyl)-3,5-dioxahex-1-ene, which was developed recently as an effective acetonylating reagent,[11] afforded γ-keto aldehyde **7d** in yield of 72% after hydrolysis in acidic medium (Scheme 3). It has been reported that γ-keto aldehydes are an important class of compounds especially as intermediates for the preparation of cyclopentenones.[12]

It is well-known that PT catalyst often modifies the mode of chemical reaction or changes the selectivity of the reaction.[13] The title alkylation during the course of aldol condensation under PT catalytic conditions provided additional highly selective examples. It is difficult properly to account for the different selectivities depending on the organic chloride observed in this study. The results of this alkylation reaction, however, agree with those for alkylation of ambident anions reported in the references.[4,14]

In the case of 2-octanone, the reaction with epichlorohydrin did not proceed under the same reaction conditions as those for octanal even at 80 °C for 2 h. The raw material, 2-octanone, was recovered almost quantitatively, except for the formation of a small amount of 3-chloroallyl glycidyl ether.

Experimental

^{1}H NMR spectra were recorded on a JEOL-PS-100 instrument in $CDCl_3$ with Me_4Si as an internal standard. Mass spectra were measured on a Hitachi RMU-6E spectrometer. HRMS were measured on a JMS-DX300 spectrometer. All the reagents were of reagent grade and were used without further purification. Evaporative distillation was performed from bulb to bulb distillation by a glass tube oven model GTO-250RS (Kugelrohr distillation).

Typical Procedure: Synthesis of (5*Z*, 7*E*)-1,2-Epoxy-6-hexyl-4-oxatetradeca-5,7-diene (5). A mixture of octanal (12.8 g, 0.1 mol), epichlorohydrin (9.2 g, 0.1 mol), sodium hydroxide (8 g, 0.2 mol, pellet), tetrabutylammonium hydrogensulfate (1.7 g, 0.005 mol) and dioxane (30 ml) was stirred with a magnetic stirrer at 55 °C for 2 h. After removing the solid materials by filtration through a short column filled with silica gel, and evaporating off the solvent, product **5** was obtained by Kugelrohr distillation under reduced pressure in 70% yield as a colorless oil; bp 130 °C/0.05 Torr (1 Torr≈133.322 Pa). ^{1}H NMR ($CDCl_3$) δ=0.72—1.10 (t, 6H), 1.30 (s, 16H), 1.90—2.36 (m, 4H), 2.52—2.70 (m, 1H), 2.70—2.90 (m, 1H), 3.04—3.28 (m, 1H), 3.40—4.08 (m, 2H), 5.30—5.70 (m, *J*=17.2 Hz, 1H), 5.70—5.95 (d, *J*=17.2 Hz, 1H), and 6.10 (s, 1H); MS *m/z* (relative intensity) 294 (M^+, 80), 223 (50), and 57 (100); IR (neat) 2950, 1660, 1480, 1640, 1180, 1120, 970, and 860 cm^{-1}; Found: *m/z* 294.2549. Calcd for $C_{19}H_{34}O_2$: M, 294.2557.

2-Benzyl-2-hexyl-3-decenal (7a). With the general procedure described above, **7a** was isolated as a colorless liquid in yield of 66%; bp 130 °C/0.02 Torr. ^{1}H NMR ($CDCl_3$) δ= 0.76—1.08 (t, 6H), 1.28 (s, 18H), 1.90—2.24 (m, 2H), 2.94 (s, 2H), 5.28—5.50 (m, *J*=17 Hz, 2H), 7.00—7.40 (m, 5H), and 9.45 (s, 1H); MS *m/z* (relative intensity) 328 (M^+), 237 (50), and 91 (100); IR (neat) 2950, 1735, 1460, 980, and 705 cm^{-1}; Found: *m/z* 328.2760. Calcd for $C_{23}H_{36}O$: M, 328.2764.

2-(2-Methylallyl)-2-hexyl-3-decenal (7b). With the general procedure described above, **7b** was obtained as a colorless oil in yield of 68%; bp 120 °C/0.02 Torr. ^{1}H NMR ($CDCl_3$) δ= 0.72—1.04 (t, 6H), 1.25 (s, 18H), 1.64 (s, 3H), 1.92—2.24 (m, 2H), 2.37 (s, 2H), 4.62—5.00 (d, 2H), 5.20—5.60 (m, *J*=17 Hz, 2H), and 9.34 (s, 1H); MS *m/z* (relative intensity) 292 (M^+), 237 (50), 179 (80), 55 (100), and 43 (90); IR (neat) 2950, 1720, 1460, 980, and 900 cm^{-1}. Found: C, 82.19; H, 12.70%. Calcd for $C_{20}H_{36}O$: C, 82.13; H, 12.41%.

2-Octyl-2-hexyl-3-decenal (7c). With the general procedure described above, **7c** was isolated in yield of 31% as a colorless liquid; bp 132 °C/0.02 Torr. ^{1}H NMR ($CDCl_3$) δ=0.76—1.04 (t, 9H), 1.10—1.80 (m, 32H), 1.96—2.25 (m, 2H), 5.20—5.60 (m, 2H), and 9.30 (s, 1H); MS *m/z* (relative intensity) 350 (M^+), 321 (83), 69 (100), 55 (100), and 43 (100); IR (neat) 2900, 1720, 1460, and 970 cm^{-1}; Found: *m/z* 350.3577. Calcd for $C_{24}H_{46}O$: M, 350.3546.

2-Acetonyl-2-hexyl-3-decenal (7d). A mixture of octanal (12.8 g, 0.1 mol), 2-(chloromethyl)-3,5-dioxahex-1-ene[11] (9.5 g, 0.075 mol), sodium hydroxide (8 g, 0.2 mol, pellet), tetrabutylammonium hydrogensulfate (1.7 g, 0.005 mol) and dioxane (30 ml) was stirred with a magnetic stirrer at 55 °C for 2 h. After removing the solid material by filtration through a short column filled with silica gel, the solvent was evaporated off. Then, 1% aqueous sulfuric acid 10 ml and dioxane 10 ml were added to the residue, and the mixture was stirred at 60 °C for 1 h. The organic components were extracted with ether and dried over anhydrous magnesium sulfate, then the solid material was removed by filtration and the solvent evaporated off. By Kugelrohr distillation of the resulting oil under reduced pressure, **7d** was isolated in yield of 72% (10.6 g) as a colorless liquid; bp 125 °C/0.05 Torr. ^{1}H NMR ($CDCl_3$) δ=0.76—1.00 (t, 6H), 1.24 (s, 20H), 1.90—2.20 (m, 5H), 2.84 (s, 2H), and 5.38—5.50 (m, 2H); MS *m/z* (relative intensity) 294 (M^+), 208 (25), and 43 (100); IR (neat) 2950, 1730, 1470, 1370, 1180, and 900 cm^{-1}; Found: *m/z* 294.2539. Calcd for $C_{19}H_{34}O_2$: M, 294.2557.

2-Hexyl-2-decenal (8): With the procedure similar to the preparation of **5** but in the absence of PT catalyst, **8** was obtained in yield of 30% as a colorless liquid; bp 115 °C/0.05 Torr. ^{1}H NMR ($CDCl_3$) δ=0.80—1.00 (t, 6H), 1.30 (s, 18H), 2.20—2.50 (m, 4H), 6.40—6.60 (t, 1H), and 9.40 (s, 1H); MS *m/z* (relative intensity) 238 (M^+), 55 (100), and 43 (100); IR (neat) 2950, 1700, and 1480 cm^{-1}.

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