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Enantioselective synthesis of β-hydroxy esters by Reformatsky reactions in chiral micelles

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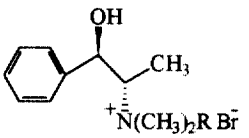
Abstract: Chiral β-hydroxy esters were obtained enantioselectively from ethyl bromoacetate and aldehydes (Reformatsky reaction) in the presence of chiral micelles. The highest enantioselectivity was 33.7%. Meanwhile, we have found that the asymmetric induction depends on the reaction temperature, the alkyl chain length of surfactant and the type of surfactant. © 1997 Published by Elsevier Science Ltd

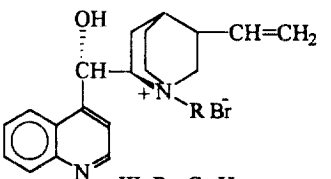
Chiral micelles are very important in enantioselective reactions, for instance, the hydrolysis of enantiomeric p-nitrophenyl esters.[1,2] However, asymmetric synthesis using chiral micelles as an asymmetric environment to induce the formation of a new stereogenic center is a relatively new area.

Goldberg[3] first reported the reduction of prochiral ketones in an aqueous micellar solution of (+)-(*R*)-*N*-dodecyl-*N*,*N*-dimethyl-phenylethylammonium bromide to give chiral alcohols, but the enantiomeric excess was only 1.7%. Recently we have utilized chiral micelles as an asymmetric environment in the reactions of various prochiral substrates, such as reduction of ketones,[4] oxidation of sulfides[5] and epoxidation of chalcones.[6]

Here we wish to report the enantioselective synthesis of β-hydroxy esters by Reformatsky reactions within chiral micellar systems. This work is one application of the known reaction in water medium.[7] For our work chiral surfactants I and II were synthesized from (−)-(1*S*,2*R*)-ephedrine[8] and III was obtained from (+)-(8*R*,9*S*)-cinchonine.[9]

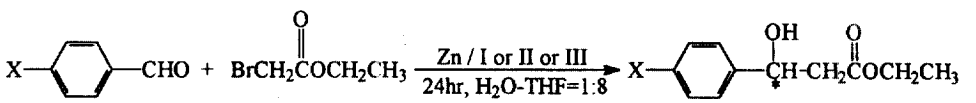


I : R= $C_{12}H_{25}$-n
II: R= $C_{16}H_{33}$-n



III: R= $C_{12}H_{25}$-n

The micelles which were produced by certain compositions of surfactants I, II, III and THF–H_2O provided the asymmetric microenvironments for enantioselective β-hydroxy ester synthesis. The reactions are as follows.



We investigated the influence of reaction temperature and the results are listed in Table 1.

From Table 1, it can be seen that temperature influenced the enantiomeric excess and relatively higher e.e. was obtained at lower temperature. In addition, when the temperature was 0°C or below 0°C, e.e.% was almost the same. Therefore 0°C was chosen as the reaction temperature in order to control reaction conditions more easily.

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Table 1. The influence of reaction temperature[a,b]

Temperature (℃)	Yield (%)	$[\alpha]^{25}_D$	e.e.%
20	66	+9.2	19
10	62	+10 0	20
0	60	+12 7	26
-10	56	+12 8	26
-20	59	+12 8	26

a) Surfactant is I and concentration of it is 0.056M b)Substrate is benzaldehyde.

Table 2. The Reformatsky reactions of ethyl bromoacetate and aldehydes in chiral micelles

X	Surfactant[a]	Yield (%)	$[\alpha]^{25\ b)}_D$	e.e.%[c]	Absolute configuration[d]
H	I	60	+12.7	26	R
	II	55	+14.6	30	R
	III	49	-16.7	34	S
Cl	I	51	+6.5	15	R
	II	46	+8.3	19	R
	III	51	-10.9	24	S
OMe	I	57	+7.1	17	R
	II	52	+8.0	19	R
	III	56	-9.6	23	S

a) Concentration of chiral surfactants are 0.056M. b) $CHCl_3$ is used as solvent c) Obtained from $[\alpha]^{25}_D$ /$[\alpha]^{25}_{D.max}$, $[\alpha]^{25}_{D.max}$ are cited from the lit. 10. d) Absolute configurations were determined by the sign of specific rotation according to the reported[10].

We then studied these Reformatsky reactions when X is H, Cl or OCH_3 and surfactant is I, II or III. The results are listed in Table 2.

The results shown in Table 2 clearly demonstrate that enantioselectivity was achieved in all chiral micelles employed. The micelle formed from III provided better enantioselectivity than I and II. It might be explained that the polar head group of III has higher rigidity. At the same time, all the enriched enantiomers of β-hydroxy esters when surfactant is I or II have the same absolute configuration (*R*), However, when surfactant III is employed, the absolute configuration is *S*. From this, we could draw the conclusion that there is a relationship of configuration between chiral surfactant and product. On the other hand, the micelle formed from surfactant with longer alkyl chain II provided better enantioselectivity than the shorter chain analogue I. Evidently, these results can be attributable to hydrophobic–lipophilic interactions between the substrate and the micelle. The binding of the substrate by the chiral micelle is a dynamic process; micelles and their monomeric surfactants are also in a

dynamic equilibrium. Therefore by increasing the alkyl chain length in surfactants of chiral micelles, better enantioselectivity would be obtained. This was identical with the results of our previous work.[4–6]

Experimental

The optical rotations were obtained from a WZZ-1 automatic rotation detector (Shanghai). The ^1H NMR was recorded on a JEOL JUM-PMX 60 SI (60 MHz) spectrometer using CCl_4 as the solvent and TMS as the internal standard. The IR were recorded on a Perkin–Elmer 683 spectrometer.

General procedure

Preparation of Reformatsky reagent (ethyl bromozincacetate)

Chlorotrimethylsilane (0.037 mL, 0.29 mmol) was added to a suspension of Zn dust (261 mg, 4 mmol) in anhyd. THF (1 mL). The mixture was refluxed for 15 min, the heating was stopped, and a solution of ethyl bromoacetate (0.45 mL, 4 mmol) in anhyd. THF (7 mL) was added. The mixture was heated at 50–55°C for 20 min, and then the dark green solution was cooled to r.t.

Enantioselective Reformatsky reaction

2 mL H_2O was added in 8 mL THF, then 1 mmol of surfactant was added under vigorous stirring for 40 min at 30°C, to form a homogeneous system. Then aldehydes (1 mmol) were added, cooled to 0°C and stirred for 20 min. After that, the Reformatsky reagent prepared as described above was added via syringe, and the mixture was stirred for 24 h at that temperature under a nitrogen atmosphere, then quenched with a 10% solution of HCl (8 mL). The reaction mixture was extracted with EtOAc. The extract was washed with brine, and dried over anhyd. Na_2SO_4. The solvent was evaporated and the crude product was purified by TLC (silica gel, EtOAc/n-hexane: 1/5, R_f 0.6). The structures of products were all identified by ^1H NMR and IR.

Ethyl 3-hydroxy-3-phenylpropanoate. ν_{max}/cm^{-1} 3450 (OH) and 1720 (C=O); δ_H 1.1 (3H, t, J=7 Hz, CH_3), 2.5 (2H, m, CH_2), 3.30 (1H, s, OH), 3.95 (2H, q, J=7 Hz, CH_2), 4.93 (1H, m, CH) and 7.15 (5H, m, C_6H_5).

Ethyl 3-hydroxy-3-(p-chlorophenyl)propanoate. ν_{max}/cm^{-1} 3445 (OH) and 1720 (C=O); δ_H 1.1 (3H, t, J=7 Hz, CH_3), 2.45 (2H, m, CH_2), 3.34 (1H, s, OH), 3.96 (2H, q, J=7 Hz, CH_2), 5.10 (1H, m, CH) and 7.13 (4H, m, C_6H_5).

Ethyl 3-hydroxy-3-(p-methoxyphenyl)propanoate. ν_{max}/cm^{-1} 3450 (OH) and 1722 (C=O); δ_H 1.1 (3H, t, J=7 Hz, CH_3), 2.51 (2H, m, CH_2), 3.35 (1H, s, OH), 3.70 (3H, s, OMe), 3.98 (2H, q, J=7 Hz, CH_2), 4.98 (1H, m, CH), 6.77 (2H, d, J=9 Hz, ArH) and 7.15 (2H, d, J=9 Hz, ArH).

Acknowledgements

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