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Enantioselective Alkylation Using Optically Active Phase Transfer Catalyst

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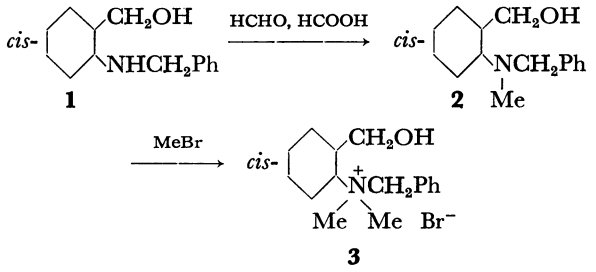
Synopsis. Synthesis of optically active benzyl[*cis*-2-(hydroxymethyl)cyclohexyl]dimethylammonium bromide (**3**) and its application to asymmetric synthesis were studied. It was found that **3** was as effective as (−)-*N*-benzyl-*N*-methylephedrinium bromide in the enantioselective alkylation of active methylene compounds when it was employed as a chiral phase transfer catalyst.

As part of ongoing program of study on the use of optically active benzyl[*cis*-2-(hydroxymethyl)cyclohexyl]amine (**1**), prepared by the lithium aluminium hydride reduction[1] of optically active *cis*-2-benzamidocyclohexanecarboxylic acid,[2] application of **1** to the asymmetric synthesis and induction was initiated. Among many papers about asymmetric synthesis and induction, there is only one report concerning enantioselective alkylation of active methylene compounds using a chiral phase transfer catalyst.[3] This prompted us to prepare a new chiral catalyst from **1** and to employ it in the enantioselective alkylation.

Both enantiomers, (+)- and (−)-**1**, were prepared in 30—40% overall yields and in high optical purities from commercially available *cis*-1,2-cyclohexanedicarboxylic anhydride *via* six steps as reported.[1,2]

Treatment of **1** with aq formaldehyde and formic acid under gentle refluxing gave *N*-methylated product, namely, benzyl[*cis*-2-(hydroxymethyl)cyclohexyl]methylamine (**2**) in a good yield. By the quaternization of **2** with methyl bromide, benzyl[*cis*-2-(hydroxymethyl)-cyclohexyl]dimethylammonium bromide (**3**) was obtained in a moderate yield.



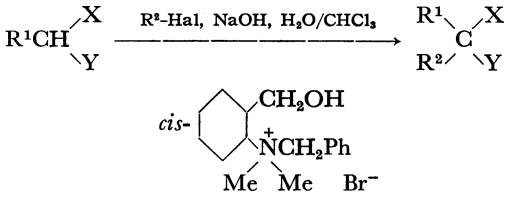
1 2 3

These reaction conditions are completely free from epimerization and/or racemization. Therefore, (+)- and (−)-**3** are considered to be optically pure when optically pure **1** is used as a starting material.

In the next stage, the enantioselective alkylation of active methylene compounds (**4**) was carried out using (+)- or (−)-**3** as an asymmetric phase transfer catalyst.

The solvent effect on the alkylation of ethyl 2-oxocyclohexanecarboxylate (**4a**) with allyl bromide was studied in ether, benzene, dichloromethane, and chloroform, and chloroform was found to be a suitable solvent. Both chemical yield and optical purity of ethyl 1-allyl-2-oxocyclohexanecarboxylate (**5a**) were fairly improved when the alkylation was carried out in

TABLE 1. ENANTIOSELECTIVE ALKYLATION OF ACTIVE METHYLENE COMPOUNDS



Run	Active Methylene Compound	Halide	3/4 Ratio mol%	Solvent	Temp	Product	Yield/%	$[\alpha]_D$/°
1	**4a**	CH_2=$CHCH_2Br$	3	Et_2O	r.t.	**5a**	0	—
2[a]	**4a**	CH_2=$CHCH_2Br$	3	C_6H_6	r.t.	**5a**	18	+0.1
3	**4a**	CH_2=$CHCH_2Br$	3	CH_2Cl_2	r.t.	**5a**	54	−0.9
4	**4a**	CH_2=$CHCH_2Br$	3	$CHCl_3$	r.t.	**5a**	60	−3.3
5	**4a**	CH_2=$CHCH_2Br$	3	$CHCl_3$	0 °C	**5a**	74	−7.0
6	**4a**	CH_2=$CHCH_2Br$	5	$CHCl_3$	0 °C	**5a**	84	−7.4
7[a]	**4a**	CH_2=$CHCH_2Br$	5	$CHCl_3$	0 °C	**5a**	79	+7.7
8[a]	**4a**	CH_3CH_2Br	5	$CHCl_3$	0 °C	**5a′**	71	+4.7
9[a]	**4b**	CH_2=$CHCH_2Br$	5	$CHCl_3$	0 °C	**5b**	68	+18.2
10[b]	**4c**	CH_3I	5	$CHCl_3$	0 °C	**5c**	65	+1.7
11[b]	**4d**	CH_2=$CHCH_2Br$	5	$CHCl_3$	0 °C	**5d**	86	+0.4

a) (+)-Ammonium bromide, (+)-**3**, was used, and in the other runs (−)-**3** was employed. b) 5% Aq NaOH (40 ml) was used. Runs (5—11) were carried out twice, and comparing their specific rotations lower ones are listed.

chloroform at 0 °C. No reaction proceeded when allyl chloride was employed as an alkylating agent.

Under optimum conditions, the enantioselective alkylation of ethyl 2-oxocyclohexanecarboxylate (**4a**), 2-acetylcyclohexanone (**4b**), ethyl 2-oxocyclopentanecarboxylate (**4c**), and ethyl 2-cyano-2-phenylacetate (**4d**) was carried out giving ethyl 1-allyl-2-oxocyclohexanecarboxylate (**5a**), ethyl 1-benzyl-2-oxocyclohexanecarboxylate (**5a'**), 2-acetyl-2-allylcyclohexanone (**5b**), ethyl 1-methyl-2-oxocyclopentanecarboxylate (**5c**),[4] and ethyl 2-cyano-2-phenyl-4-pentenoate (**5d**).[5] The results are summarized in Table 1.

Fiaud reported that specific rotations of **4a** and **4b** were −8.2° and −23.5°, respectively, when (−)-*N*-benzyl-*N*-methylephedrinium bromide (**6**) was used as a catalyst.[3] Thus, **3** is considered to be as effective as **6** in the enantioselective alkylation of active methylene compounds. In contrast to that only one enantiomer, namely, (−)-**6** is usually available because it is derived from a natural product, both enantiomers of **3** are conveniently prepared, and alkylated products having the desired configuration are easily given choosing the suitable enantiomer. In this respect, **3** is considered to be advantageous as a chiral phase transfer catalyst.

Experimental

The melting points were determined on a Laboratory Devices Mel-Temp apparatus and are uncorrected. The boiling points are also uncorrected. The NMR spectra were recorded on a Varian A-60 spectrometer at 60 MHz using Me_4Si as an internal standard. The IR and MS spectra were determined on a JASCO IR-2A spectrometer and on a JEOL-01SG instrument, respectively. The values of specific rotation were obtained on JASCO DIP-181 digital polarimeter. Optically active **1** was prepared as reported.[1,2] (+)-Form: mp 68—69 °C, $[\alpha]_D^{32}$ +40.4° (*c* 1.00, dry Et_2O). (−)-Form: mp 68—69 °C, $[\alpha]_D^{24}$ −40.6° (*c* 1.00, dry Et_2O).

Benzyl[cis-*2-(hydroxymethyl)cyclohexyl*]*methylamine (2)*. To (+)-**1** (5.48 g, 25 mmol) was added under cooling with an ice bath 35% aq formaldehyde (2.15 g, 25 mmol) followed by dropwise addition of formic acid (4.14 g, 90 mmol). Then, the mixture was allowed to stand at room temperature for 15 min, and was gently refluxed for 8 h. To the ice cooled reaction mixture was added concd HCl (13 ml), and the solution was concentrated under reduced pressure to give viscous brown residue. The residue was treated with 4 M NaOH (50 ml) and was extracted with three 30 ml portions of ether. The ethereal extract was dried ($MgSO_4$), concentrated, and distilled giving 4.59 g (79%) of (+)-**2**: bp 141—142 °C/0.2 Torr; $[\alpha]_D^{30}$ +22.8° (*c* 1.14, $CHCl_3$); IR (neat) 3300 (OH), 1030 (OH), 740 (Ph), and 695 cm^{-1} (Ph); NMR (CCl_4) δ=1.1—2.1 (8H, m), 2.10 (3H, s), 2.2—2.7 (2H, m), 3.3—4.3 (4H, m), 4.87 (1H, *quasi* s) and 7.22 (5H, s); MS *m/e* 233 (M^+); Found: N, 6.31%. Calcd for $C_{15}H_{23}NO$: N, 6.00%.

In a similar manner, (−)-**2** was obtained in 75% yield: bp 130—132 °C/0.08 Torr; $[\alpha]_D^{24}$ −22.4° (*c* 0.98, $CHCl_3$); MS *m/e* 233 (M^+).

Benzyl[cis-*2-(hydroxymetyl)cyclohexyl*]*dimethylammonium Bromide (3)*. To a solution of (+)-**2** (4.00 g, 17 mmol) in methanol (30 ml) was bubbled methyl bromide gas for about 8 h at 0 °C. After removal of the solvent, the residual crystals were recrystallized from 2-propanol giving 3.87 g (69%) of (−)-**3**: mp 176—177 °C; $[\alpha]_D^{29}$ −34.6° (*c* 1.00, $CHCl_3$); IR (KBr) 3450 (OH), 1040 (OH), 730 (Ph) and 700 cm^{-1} (Ph); NMR ($CDCl_3$) δ=1.1—2.5 (8H, m), 2.6—3.0 (1H, bs), 3.17 (3H, s), 3.67 (3H, s), 3.7—4.2 (3H, m), 4.7—5.2 (3H, m) and 7.2—7.7 (5H, m); Found: N, 4.29%. Calcd for $C_{16}H_{26}BrNO$: N, 4.27%.

Similarly, (+)-**3** was prepared from (−)-**2** in 54% yield: mp 175—176 °C; $[\alpha]_D^{21}$ +34.6° (*c* 1.04, $CHCl_3$); Found: N, 4.21%. Calcd for $C_{16}H_{26}BrNO$: N, 4.27%.

General Procedure for the Alkylation of Active Methylene Compounds (4). To an ice cooled solution of active methylene compound (**4**) (20 mmol), alkylating agent (22 mmol), and (+)- or (−)-**3** (328 mg, 1.0 mmol) in chloroform (20 ml) was added 10% NaOH (20 ml), and the mixture was stirred overnight at 0 °C. After separation of the chloroform layer, the aqueous layer was extracted with three 40 ml portions of chloroform. The chloroform solution combined was concentrated under reduced pressure. Ether (about 100 ml) was added to the concentrated oily product, and residue was separated by decantation. The ethereal solution was dried (Na_2SO_4), evaporated, and distilled giving **5**.

5a: Yield 3.53 g (84%); bp 84—85 °C/2 Torr; $[\alpha]_D^{25}$ −7.4° (*c* 1.51, $CHCl_3$); IR (neat) 1740 (shoulder, C=O), 1705 (C=O) and 1200 cm^{-1} (C–O–C); NMR (CCl_4) δ=1.23 (3H, t, *J*=7 Hz), 1.4—2.2 (6H, m), 2.2—2.7 (4H, m), 4.15 (2H, q, *J*=7 Hz), 4.7—5.0 (1H, m), 5.0—5.2 (1H, m), and 5.4—6.1 (1H, m).

5a': Yield 3.69 g (71%); bp 140—141 °C/3 Torr; $[\alpha]_D^{25}$ +4.7° (*c* 1.15, $CHCl_3$); IR (neat) 1730 (C=O), 1710 (C=O), 1190 (C–O–C), 740 (Ph) and 700 cm^{-1} (Ph); NMR (CCl_4) δ=1.12 (3H, t, *J*=7 Hz), 1.4—2.2 (6H, m), 2.2—2.6 (2H, m), 2.77 (1H, d, *J*=13.5 Hz), 3.19 (1H, d, *J*=13.5 Hz), 4.01 (2H, q, *J*=7 Hz) and 7.10 (5H, s).

5b: Yield 2.44 g (68%); bp 119—120 °C/11 Torr; $[\alpha]_D^{28}$ +18.2° (*c* 1.48, $CHCl_3$); IR (neat) 1710 (C=O) and 1695 cm^{-1} (C=O); NMR (CCl_4) δ=1.3—2.2 (6H, m), 1.99 (3H, s), 2.2—2.6 (4H, m), 4.8—5.0 (1H, m), 5.1 (1H, *quasi* s) and 5.2—5.8 (1H, m).

5c: yield 2.21 g (65%); bp 101—102 °C/14 Torr; $[\alpha]_D^{22}$ +1.7° (*c* 10.33, $CHCl_3$); IR (neat) 1745 (C=O) and 1725 cm^{-1} (C=O); NMR (CCl_4) δ=1.22 (3H, s), 1.25 (3H, t, *J*=7 Hz), 1.6—2.6 (6H, m) and 4.08 (2H, q, *J*=7 Hz).

5d: yield 3.95 g (86%); bp 111—112 °C/1 Torr; $[\alpha]_D^{20}$ +0.4° (*c* 10.0, $CHCl_3$); IR (neat) 2250 (C≡N) and 1740 cm^{-1} (C=O); NMR (CCl_4) δ=1.17 (3H, t, *J*=7 Hz), 2.5—3.3 (2H, m), 4.15 (2H, q, *J*=7 Hz), 5.0—6.1 (3H, m) and 7.2—7.7 (5H, m).

References

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2) J. Nishikawa, T. Ishizaki, F. Nakayama, H. Kawa, K. Saigo, and H. Nohira, *Nippon Kagaku Kaishi*, **1979**, 754.

3) J.-C. Fiaud, *Tetrahedron Lett.*, **1975**, 3495.

4) This compound is expected to be applicable in optically active illudin S synthesis.

5) Disubstituted cyanoacetate is employed to synthesize barbital.