Stereochemistry of Friedel-Crafts Alkylation of Benzene with Optically Active 2-Chlorobutane

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Synopsis. The alkylation of benzene with (+)-2-chlorobutane (**1**) by Lewis acid catalyst gave stereospecifically (−)-2-phenylbutane (**2**) with inversion of configuration at low temperature for short reaction times. A lowering of the stereospecificity of the reaction was found to be partly due to the racemization of (+)-**1** and (−)-**2**.

Friedel-Crafts alkylation has long been pointed out to proceed with almost complete racemization when an optically active alkylating reagent was used. For example, Price, Burwell, and Streitwieser reported that the alkylation of benzene with optically active 2-butanol and propan-1,1,1-d_3-2-ol gave almost racemic 2-phenylbutane and 2-phenylpropane-1,1,1-d_3, respectively, and concluded that these alkylations proceeded *via* a free carbonium ion intermediate.[1–3] However, some examples of the highly stereospecific reactions have been reported; the high degree of stereospecificity of the reactions was explained on the basis of the cyclic nature of the alkylating reagents or the formation of the cyclic intermediates.[6]

Recently, Rosenberg reported that the Friedel-Crafts alkylation of benzene with (+)-2-butanol by $AlBr_3$ catalyst gave (−)-2-phenylbutane with 27% inversion of configuration.[4] This is the only example of stereospecific Friedel-Crafts alkylation with such a simple alkylating reagent. On the other hand, Eliel reported that an optically active 2-phenylbutane was readily racemized under the influence of $AlCl_3$ at 0 °C.[5] These results prompted us to investigate the reaction with a simple acyclic reagent, optically active 2-chlorobutane (**1**).

Results and Discussion

Optically pure (*S*)-(+)-**1** was easily prepared from (+)-propylene oxide *via* (−)-2-butanol. The alkylation of benzene with (+)-**1** was carried out using a variety of Lewis acids as the catalyst. These reactions gave 2-phenylbutane (**2**) mainly and few by-products (<1%). The **2** produced was separated and its optical rotation was determined. The results are summarized in Table 1. The alkylations by $AlCl_3$, $FeCl_3$, and $AlCl_3$–CH_3NO_2 catalysts proceeded with inversion of configuration to give (*R*)-(−)-**2**. In the case of $AlBr_3$ catalyst the product was an almost racemic **2**.

In the case of the alkylation by $AlCl_3$ catalyst at −30 °C, the optical yield of the reaction decreased from 24%(50 s) to 14%(100 s) or 12%(120 s) with increasing reaction time. The product given at −10 °C for 20 min was completely racemic. The decrease of the optical yield appears to be due to a great extent to the racemization of (−)-**2** produced, because the alkylation proceeds to completion within 30 s even at −30 °C.

In the presence of $FeCl_3$ the racemization of (−)-**2** scarcely occurred for 60 min at 0 °C (Table 2). On the other hand, the starting (+)-**1** was racemized from $[\alpha]_D$ +27.0° to +6.1° by $FeCl_3$ catalyst in 1,2-dichloroethane for 4 min at 0 °C.

In the preceding paper,[6] we attempted to evaluate the net stereospecificity in the alkylation from the extent of alkylation and the remaining optical activity of the starting material by considering a kinetic model.[7] In the alkylation with (+)-**1** at 0 °C (4 min), **2** was obtained in 70% yield and in 24% optical yield, and the optical activity of the starting chloride was depressed to 22% of the initial value. The rate of alkylation and racemization of the chloride were calculated to be $5.0\times10^{-3}\ s^{-1}$ and $6.3\times10^{-3}\ s^{-1}$, respectively. Therefore, the net stereospecificity in the

Table 1. Alkylation of benzene with (*S*)-2-chlorobutane (**1**) in the presence of lewis acids[a)]

Lewis acid	Temp °C	Time min	Conv.[b)] %	(*R*)-2-Phenylbutane (**2**) $[\alpha]_D$ (*c* 5, $CHCl_3$)	(*R*)-2-Phenylbutane (**2**) O.Y.[c)] %
$AlCl_3$[d)]	−30	0.8	100	−4.7°	24
$AlCl_3$[d)]	−30	1.6	100	−2.8°	14
$AlCl_3$[d)]	−30	2.0	100	−2.4°	12
$AlCl_3$[d)]	−10	20	100	0.0°	0
$FeCl_3$[e)]	0	4.0	70	−4.6°	24
$AlCl_3$-CH_3NO_2 (1:15)	30	15	30	−2.5°	13
$AlBr_3$[d)]	−30	1.0	100	0.0°	0

a) Mole ratio is (*S*)-1: Lewis acid:benzene=1:0.15:30. The optical rotation of (*S*)-1 used was $[\alpha]_D$ +28.0° (neat). b) Determined by GLC. c) Calculated from the reported rotations of (*S*)-1 (+34.8°)[8)] and (*R*)-2 (−23.6°).[9)] d) A small amount of carbon disulfide was added. e) A small amount of 1,2-dichloroethane was added.

Table 2. Reaction of (R)-2-phenylbutane (**2**) in the presence of iron(III) chloride at 0 °C[a)]

Time / min	Recovered (R)-**2**	
	$[\alpha]_D$	O.P./%[d)]
0	$-2.8°$[b)]	12
5	$-2.5°$[b)]	10
60	$-2.6°$[c)]	11

a) Mole ratio is (R)-**2**: $FeCl_3$:benzene=1:0.15:30. A small amount of carbon disulfide was added. b) Measured in benzene (c 5.0). c) Measured in benzene (c 3.0). d) Calculated from the reported rotation $[\alpha]_D$ −23.6° (neat).[9)]

alkylation step was calculated to be 40%.

Friedel-Crafts reactions of primary halides are thought to proceed in part by a displacement process.[10,11)] Such views are consistent with our stereochemical results about the reaction of 2-chlorobutane. However, the possibility of a carbonium ion character in the alkylating intermediate is not excluded. In addition, the lesser stereospecificity in the alkylations reported in the literature[1–3)] may be attributed in part to the successive racemization of the product and the simultaneous racemization of the starting material, which are caused by raising the reaction temperature and prolonging the reaction time.

Experimental

GLC analysis was carried out on a 2 m column of 10% Carbowax 20 M on Diasolid L with a Shimadzu GC-3BT instrument. Optical rotations were taken with a JASCO DIP-SL polarimeter using 1 or 0.5 cm tubes.

Benzene was washed with concentrated sulfuric acid and water, and distilled after drying on sodium ribbon. Other solvents were dried[12)] and distilled before use. Aluminium chloride was purified by sublimation under nitrogen. Other Lewis acids of commercial GR grade were used without further purification.

*(+)-2-Chlorobutane (**1**).* (+)-Propylene oxide[6)] (20 g, 0.35 mol) was added to an ethereal solution (400 ml) of methyllithium (1.0 mol) at 0 °C. After the addition, the reaction mixture was refluxed for 12 h, decomposed with water (50 ml), and extracted three times with 100 ml of ether. The extracts were fractionally distilled to give 19 g of (−)-2-butanol, $[\alpha]_D$ −11.8°(neat). Dichlorophenylphosphine (12.2 g, 0.0682 mol) and (−)-2-butanol (10 g, 0.137 mol) were mixed at 0 °C, stirred for 1 h, then distilled on a cooled trap *in vacuo*. The distillate was fractionated by a column to yield 4 g of (+)-**1**, bp 68 °C, $[\alpha]_D$ +28.0°(neat), [Lit,[8)] $[\alpha]_D$ +34.8°(neat)].

Alkylation. To a stirred mixture of benzene (13 g, 160 mmol), Lewis acid (0.81 mmol), and carbon disulfide (4 ml), (+)-**1** (500 mg, 5.4 mmol) was added at the prescribed temperature. The resulting mixture was allowed to stand at the above temperature for the prescribed period with stirring, then quenched with ice water (5 ml). The organic layer was separated, washed with water, and dried over anhydrous sodium sulfate. After the removal of solvent, the residue was distilled by fractionating column to give (−)-**2**, bp 68—70 °C/20 mmHg.

*Racemization of (+)-**1** or (−)-**2**.* A stirred mixture of (+)-**1** (500 mg, 5.4 mmol), iron (III) chloride (130 mg, 5.4 mmol), and 1,2-dichloroethane (14 ml) was treated at 0 °C for 4 min. After the usual work-up, the optical rotation of the recovered **1** was measured. Racemization of (−)-**2** was also carried out in a similar manner.

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