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Stereochemistry of Friedel-Crafts Reaction of Benzene with Optically Active 2-Methyloxetane

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The Friedel-Crafts alkylation of benzene with (+)-2-methyloxetane in the presence of Lewis acids ($AlCl_3$, $SnCl_4$, and $TiCl_4$) gave 3-phenyl-1-butanol with 20—60% inversion of configuration at the reaction center and a mixture of 4-chloro-2-butanol and 3-chloro-1-butanol in optically active form as the by-products. These by-products were formed by the attack of the chlorine atom in Lewis acid. The stereochemical course of the reaction to 3-chloro-1-butanol varied with the kind of catalyst, *i.e.*, inversion with $AlCl_3$ or $TiCl_4$ and retention with $SnCl_4$. The addition of nitromethane to the reaction system promoted the retentive ring-opening to 3-chloro-1-butanol.

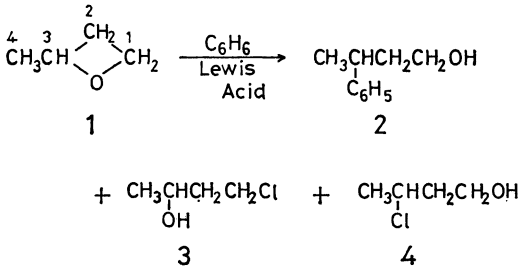
Although the entire field of Friedel-Crafts chemistry has been reviewed in great detail,[1] the stereochemical view has been limited because of the long-standing acceptance of the free carbonium ion mechanism in the aromatic alkylation.[2] Some examples of Friedel-Crafts reactions with extensive stereochemical integrity have appeared during this decade. Brauman and his co-workers reported that the alkylation of benzene with (+)-γ-valerolactone[3] or (+)-2-methyltetrahydrofuran[4] proceeded with some inversion (47 or 35%) of configuration, and concluded that the stereospecificity was due to the cyclic nature of the alkylating reagent or the enforced proximity of ion-pairs produced from the ring opening. Previous studies in our laboratory demonstrated that optically active oxiranes reacted with benzene in the presence of Lewis acid to give the corresponding 2-phenyl-1-propanols with complete inversion of configuration.[5]

The difference in the degree of stereospecificity between the above reactions with five- and with three-membered ether prompted us to study the stereochemistry of the similar alkylation with oxetane. There have been few reports on the reaction of oxetane in the presence of Lewis acid,[6] but no stereochemical information is obtained even in the ring-opening of oxetane.

This paper describes the alkylation of benzene with (+)-2-methyloxetane in the presence of Lewis acid and the stereochemistry of the ring-opening reaction.

Results and Discussion

Treatment of (+)-2-methyloxetane (**1**) with Lewis acid in benzene below 0 °C gave 3-phenyl-1-butanol (**2**) as the alkylated product, and a mixture of 4-chloro-2-butanol (**3**) and 3-chloro-1-butanol (**4**). No 4-phenyl-2-butanol was obtained under these conditions. The structures of **2**, **3**, and **4** were identified by IR and NMR spectroscopy, and by comparison of the retention time of gas chromatography (GLC) with those of authentic samples. The yield and isomer distribution were determined by GLC analysis. The results under various conditions are summarized in Tables 1 and 2.



(+)-2-Methyloxetane (**1**) has S configuration, since it was prepared from (*S*)-(+)-ethyl-3-hydroxybutanoate by a series of chemical interconversions not affecting bonds to the asymmetric center, as mentioned in the experimental section. The absolute configurations of (−)-**2**, (+)-**3**, and (+)-**4** have been established to be R,[7] S,[8] and S,[9] respectively. Accordingly, it is apparent that the alkylation of benzene with (+)-**1** to (−)-**2** and the ring-opening reaction of the oxetane (formation of **4**) by aluminium chloride proceeded with inversion of configuration at the reaction center. Aluminium chloride at first coordinates with the oxygen atom of oxetane, which would result in appreciable polarization of the C_3–O bond, and then benzene attacks the C_3 atom from the back-side of the C_3–O bond.

In the case of $AlCl_3$ catalyst, as shown in Table 1, the alkylation exhibited less stereospecificity than that using propylene oxide[5a] or γ-valerolactone.[3] The optical yield of **2** increased slightly with decreasing reaction temperature. The following interpretations can be given for the less stereospecificity in the formation of **2** from **1**: first, the racemization *via* a carbonium ion intermediate and, secondly, the apparent racemization owing to the competitions between two reactions (path a and b in Scheme 1) which result in the alkylated products having the opposite configuration. Accordingly, the two-step reaction mechanism *via* (*R*)-**4** becomes significant along with the direct substitution. In fact, (*S*)-**4** reacted with benzene in the presence of $AlCl_3$ to give (*R*)-**2** with 46% inversion of configuration.[10]

When $SnCl_4$ or $TiCl_4$ was used as a catalyst, the alkylation of benzene exhibited a moderate stereospecificity with 62 and 55% optical yield, respectively. This seems to mean that the racemization mechanism through carbonium ion was depressed because of the weaker catalytic ability of $SnCl_4$ compared with that

Table 1. Friedel-crafts reaction of benzene with (+)-2-methyloxetane (**1**)[a]

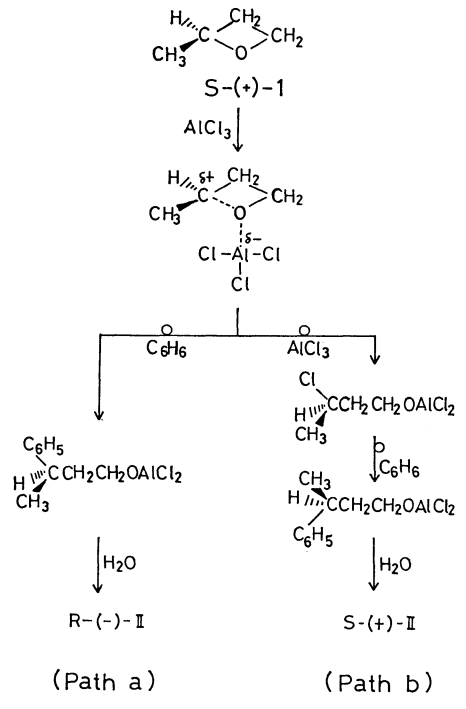
Run	$[\alpha]_D$[b] of **1** °	Lewis acid	Temp °C	Time h	3-Phenyl-1-butanol (**2**) Yield[c] %	$[\alpha]_D$[d] °	Optical yield[e] %
1	+33.0	$AlCl_3$	0	0.5	62.4	−8.7	19.5
2	+33.0	$AlCl_3$	−10	0.5	36.7	−8.7	19.5
3	+33.0	$AlCl_3$	−20	0.5	5.9	−10.8	24.2
4	+33.0	$AlCl_3$	−30	2.0	8.3	−13.5	30.3
5	+33.5	$AlCl_3$-CH_3NO_2	0	2.5	7.7	−10.1	22.3
6	+31.2	$SnCl_4$	0	4.0	13.5	−26.3	62.3
7	+32.8	$SnCl_4$	−10	5.0	11.9	−27.7	62.4
8	+33.5	$SnCl_4$-CH_3NO_2	0	2.5	22.7	−18.9	41.7
9	+31.2	$TiCl_4$	0	2.5	22.9	−23.3	55.2

a) Molar ratio: (+)-**1**: Lewis acid:C_6H_6:CS_2 (or CH_3NO_2)=1:1.2:16:10(16); max$[\alpha]_D$ of *S*-(+)-**1** is +33.5°. b) Measured in chloroform (*c* 5.0). c) Based on (+)-**1** used. Determined by GLC. d) Measured in ethanol (*c* 2.4—5.0). e) Calculated from the maximum rotations of (+)-**1** and (−)-**2**. Max$[\alpha]_D$ of *R*-(−)-**2** is −45.3°.[19]

Table 2. The isomer distribution and the specific rotations of chlorobutanols (**3** and **4**) as by-products

Run	Yield[a] %	Isomer ratio[a]/% **3** : **4**	$CH_3CH(OH)CH_2CH_2Cl$ (**3**) $[\alpha]_D$[b] °	Optical yield[c] %	$CH_3CHClCH_2CH_2OH$ (**4**) $[\alpha]_D$[b] °	Optical yield[c] %
1	2.7	69 : 31	—	—	—	—
2	2.5	45 : 55	—	—	—	—
3	6.2	63 : 37	+44.0	100	−49.0	91.6
4	7.4	64 : 36	+44.0	100	−53.0	99.1
5	48.3	1 : 99	—	—	+9.6	17.7
6	32.7	8 : 92	+41.4	100	+15.2	28.0
7	30.0	4 : 96	—	—	+19.3	35.5
8	44.3	0 : 100	—	—	+17.3	31.9
9	27.8	22 : 78	+46.9	100	−20.0	39.5

a) Determined by GLC. b) Measured in chloroform (*c* 1.3—5.0). c) Calculated from the maximum rotations of (+)-**1** and (+)-**3** or (−)-**4**. Max$[\alpha]_D$ of *S*-(+)-**3** is +44.7°[20] and max$[\alpha]_D$ of *R*-(−)-**4** is −54.3°.



Scheme 1.

of $AlCl_3$. Furthermore, benzene did not react with 3-chloro-1-butanol in the presence of $SnCl_4$ or $TiCl_4$, so that path b in Scheme 1 should be excluded. In order to examine the possibility of racemization of the product during the reaction, (+)-**2** was treated with these Lewis acids in benzene under the same conditions as those of the alkylation. The specific rotation of this compound remained almost unchanged before and after the treatment (Table 3). Thus, it turns out that the optical yield in the presence of $SnCl_4$ or $TiCl_4$ shows a net stereospecificity in this alkylation (Table 1).

Chlorobutanol isomers (**3** and **4**), which were by-products, were separated by preparative GLC and their specific rotations were determined. As shown in Table 2, the ring-opening reaction toward **4** involves two opposite stereochemical courses: inversion with $AlCl_3$ or $TiCl_4$ and retention with $SnCl_4$. It is interesting that the formation of **4** took place with complete inversion in the presence of $AlCl_3$, despite the less stereospecificity in the alkylation (runs 1—4 in Table 1). On the other hand, the retentive ring-opening in the presence of $SnCl_4$ was observed. This retentive result was not observed in the reaction with three-membered ring oxiranes.[5] This result could be

Table 3. Treatment of (+)-3-phenyl-1-butanol (**2**) or (−)-3-chloro-1-butanol (**4**) with lewis acid in benzene[a)]

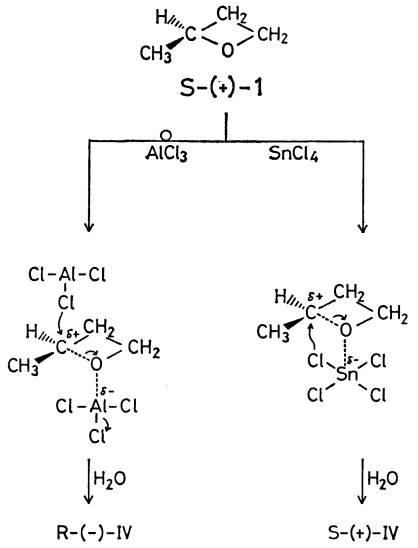
Run	Substrate	Lewis acid	Temp °C	Time h	Specific rotation[b)]/° Before reaction	After reaction
10	(+)-**2**	$SnCl_4$	0	4.0	+6.9	+6.9
11	(+)-**2**	$TiCl_4$	0	3.0	+6.9	+6.8
12	(−)-**4**	$SnCl_4$	20	4.5	−54.0	−53.5
13	(−)-**4**	$TiCl_4$	0	2.5	−52.1	−53.0

a) Molar ratio: (+)-**2** or (−)-**4**: Lewis acid: C_6H_6:CS_2=1:1.2:16:10. b) Measured in ethanol.

Table 4. Ring-opening reaction of (+)-2-methyloxetane (**1**) with lewis acid or hydrochloric acid[a)]

Run	$[\alpha]_D$[b)] of **1** °	Acid	Temp °C	Time h	Yield[c)] %	Isomer ratio[c)]/% **3** : **4**	$CH_3CH(OH)CH_2$-CH_2Cl (**3**) $[\alpha]_D$[b)] °	O.Y.[d)] %	$CH_3CHClCH_2CH_2$-OH (**4**) $[\alpha]_D$[b)] °	O.Y.[d)] %
14	+33.0	concd HCl	0	1.0	50.7	81 : 19	+44.1	100	−46.7	86.0
15	+32.2	$AlCl_3$	0	2.5	48.8	10 : 90	+46.3	100	−17.4	33.3
16	+33.5	$SnCl_4$	0	4.0	67.0	5 : 95	—	—	−25.0	46.0

a) Molar ratio: (+)-**1**: Lewis acid (or HCl):CS_2=1:1.2:18. b) Measured in chloroform (*c* 5.0). c) Determined by GLC. d) Optical yield.



Scheme 2.

explained by considering that the conformation of the transition state fits a steric requirement which gives rise to the internal attack of the chlorine atom on the secondary carbon (Scheme 2). The configuration of 4-chloro-2-butanol (**3**) was completely retained. This shows that the successive racemization of the starting oxetane did not occur in all reactions. Further, the ring-opening of (+)-**1** with $SnCl_4$ yielded regioselectively **4** with C_3–O bond cleavage (runs 6 and 7 in Table 2).

In connection with the reaction under Friedel-Crafts condition, we examined the ring-opening reaction of (+)-**1** with aqueous hydrogen chloride or Lewis acids in CS_2 solvent. The results are presented in Table 4. The direction of ring-opening with Lewis acid differed from that with aqueous hydrogen chloride. This result is similar to that of the ring-opening reaction of propylene oxide with acids.[5a)] Under Lewis acid catalyst both the C_1 and the C_3 atom adjacent to oxygen atom of **1** would develop a cationic nature to a certain extent by coordination of the Lewis acid, but especially the C_3 atom would be further stabilized because of an electron-releasing effect or a hyperconjugation of a methyl group.[11)] Thus, it seems that the nucleophilic attack of the chlorine atom should take place at the C_3 atom preferentially.

Finally, some interesting results were obtained when nitromethane was added in a reaction system. $AlCl_3$–CH_3NO_2 catalyst had no influence on the stereochemistry of alkylated product, but promoted the retentive reaction of **1** to **4**, as in the case of $SnCl_4$ catalyst. The high regioselective ring-opening with C_3–O bond cleavage was observed. Similar results have been observed in the reaction of oxiranes, in which $AlCl_3$–CH_3NO_2 1:1 addition compound[12)] in solution was concluded to be important for the retentive reaction and the direction of ring-opening.[13)] This consideration may explain the result in the case of oxetane.

Experimental

The optical rotations were measured on a JASCO DIP-SL polarimeter with use of a 0.1 dm tube. The IR and ^{1}H-NMR spectra were recorded on a JASCO DS-301 spectrometer and a JEOL PS-100 spectrometer, respectively. Chemical shifts are given in ppm downfield from internal TMS. GLC analyses were carried out on a 2 m column of 10% Carbowax 20 M on Diasolid L with a Shimadzu GC-3A instrument.

Benzene was washed with concentrated sulfuric acid and distilled after drying on sodium ribbon. Carbon disulfide and nitromethane were dried over phosphorus pentachloride and distilled prior to use. Commercial grade aluminium chloride was purified by sublimation under a nitrogen gas stream. Commercial grade tin(IV) chloride and titanium (IV) chloride were used without further purification.

Substrate. *(+)-2-Methyloxetane (1)*: Ethyl acetoacetate was reduced microbiologically by the reductase of baking yeast to (+)-ethyl-3-hydroxybutanoate,[14] bp 78—81 °C/17 mmHg,† $[\alpha]_D$ +36.5° (*c* 5.5, $CHCl_3$) [Lit,[14] $[\alpha]_D$ +38.5° (*c* 1.0, $CHCl_3$)], yield 73%. The hydroxybutanoate was heated under reflux with lithium aluminium hydride in THF for 30 hours and converted to (+)-1,3-butanediol, bp 108 °C/17 mmHg, $[\alpha]_D$ +32.3° (*c* 5.0, EtOH) [Lit,[15] $[\alpha]_D$ −29.6° (*c* 10, EtOH)], yield 89%. The treatment of (+)-1,3-butanediol and acetyl chloride gave a mixture of 1-chloro-3-acetoxybutane and 3-chloro-1-acetoxybutane.[16] This mixture was converted to (+)-**1** with concentrated alkali solution according to the procedure of Searles,[17] bp 60 °C, $[\alpha]_D$ +33.5° (*c* 5.0, $CHCl_3$) (Lit,[18] $[\alpha]_D$ +20.2°], yield 25%. (+)-**1** obtained in this manner seems optically pure. NMR (CCl_4, 10%): δ 1.33 (d, J=6.4Hz, 3H, $-CH_3$), 1.91—2.83 (m, 2H, $-CH_2-$), 4.19—4.63 (m, 2H, $-CH_2O-$), and 4.66—5.03 ppm (sex, J=7.2 Hz, 1H, $-CH=$).

Reaction of (+)-2-Methyloxetane (1) with Benzene in the Presence of Lewis Acid. The following example shows a typical experimental procedure. To a stirred mixture of dry benzene (18 ml) containing tin(IV) chloride (4.3 g, 16.6 mmol) and carbon disulfide (7 ml), cooled in an ice bath, a mixture of (+)-**1** (1.0 g, 13.9 mmol), benzene (2 ml), and carbon disulfide (1 ml) was added at a rate sufficient to maintain the reaction temperature. After an additional 4.0 h at 0 °C, the reaction was quenched with cooled 5% hydrochloric acid (40 ml). The organic layer was neutralized with 5% sodium hydrogencarbonate and then dried over anhydrous sodium sulfate. The yield of alkylated product was determined by GLC. After the removal of solvent, the residue was fractionated *in vacuo* to give chlorobutanol isomers (bp 70 °C/17 mmHg) and 3-phenyl-1-butanol (**2**) (bp 125 °C/17 mmHg). The water layer was extracted five times with 20 ml portions of ether. The combined organic layers were washed with water and dried over anhydrous sodium sulfate. After the removal of solvent, the residue was distilled *in vacuo* to give chlorobutanols (**3** and **4**), bp 70 °C/17 mmHg. The isomers could be separated by preparative GLC. The results are summarized in Tables 1 and 2.

Ring-opening Reaction of (+)-2-Methyloxetane (1) with Lewis Acid or Hydrochloric Acid. To a cooled and stirred mixture of carbon disulfide (12 ml) and Lewis acid or concentrated hydrochloric acid (16.6 mmol) was added a solution of (+)-**1** (1.0 g, 13.9 mmol) in carbon disulfide (2 ml) at 0 °C. The reaction mixture was worked up as mentioned above. The results are summarized in Table 4.

† 1 mmHg≈133.322 Pa.

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8) (*S*)-2-Methyloxetane reacted with aqueous hydrogen chloride in CS_2 solvent to give the dextrorotatory chloride (**3**), which retains the configuration of the asymmetric center because of C_1–O bond cleavage, as shown in Table 4.

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20) The maximum rotation of **3** was calculated based on +20.2° of **1** (optical purity 60.3%) obtained by cyclization of (+)-**3** ($[\alpha]_D$ +26.98°) without a racemization. See Ref. 19.