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Stereochemical Studies in Friedel-Crafts Reactions. II. The Reactions of 4-Substituted Cyclohexenes with Benzene

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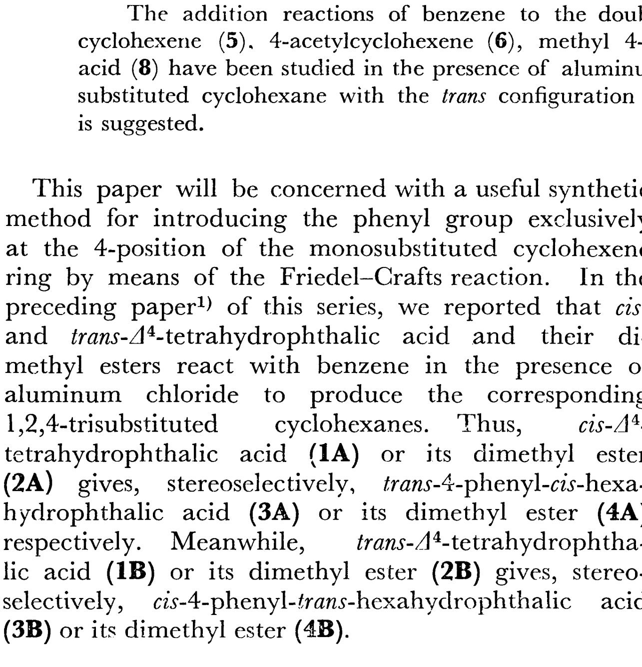
The addition reactions of benzene to the double bonds of 4-substituted cyclohexenes, such as 4-benzoylcyclohexene (**5**), 4-acetylcyclohexene (**6**), methyl 4-cyclohexenecarboxylate (**7**), and 4-cyclohexenecarboxylic acid (**8**) have been studied in the presence of aluminum chloride. In all cases, the reactions gave mainly 1,4-disubstituted cyclohexane with the *trans* configuration stereoselectively. A possible mechanism for this reaction is suggested.

This paper will be concerned with a useful synthetic method for introducing the phenyl group exclusively at the 4-position of the monosubstituted cyclohexene ring by means of the Friedel-Crafts reaction. In the preceding paper1) of this series, we reported that *cis*- and *trans*-Δ^4-tetrahydrophthalic acid and their dimethyl esters react with benzene in the presence of aluminum chloride to produce the corresponding 1,2,4-trisubstituted cyclohexanes. Thus, *cis*-Δ^4-tetrahydrophthalic acid (**1A**) or its dimethyl ester (**2A**) gives, stereoselectively, *trans*-4-phenyl-*cis*-hexahydrophthalic acid (**3A**) or its dimethyl ester (**4A**) respectively. Meanwhile, *trans*-Δ^4-tetrahydrophthalic acid (**1B**) or its dimethyl ester (**2B**) gives, stereoselectively, *cis*-4-phenyl-*trans*-hexahydrophthalic acid (**3B**) or its dimethyl ester (**4B**).



Scheme 1

This finding prompted us to explore the reaction of benzene with carbonium ions which are derived from 4-negatively substituted cyclohexenes. The present paper will describe some addition reactions of benzene to 4-benzoylcyclohexene (**5**), 4-acetylcyclohexene (**6**), methyl 4-cyclohexenecarboxylate (**7**), and 4-cyclohexenecarboxylic acid (**8**) in the presence of aluminum chloride.

Results and Discussion

The results of the reactions of various 4-substituted cyclohexenes with benzene have been summarized in Table 1. The products obtained from 4-substituted cyclohexenes and benzene were found by gas-chromatographic analysis to be composed of two components in all cases. The major components were *trans*-1,4-disubstituted cyclohexanes, whereas the minor components were the *cis*-1,4-disubstituted isomers. All the *trans*-products were identified by a comparison of the spectral and physical data with those of an authentic sample.2) No 1,3-disubstituted product could be detected.3)

The semi-crystalline solid obtained from the reaction of 4-benzoylcyclohexene (**5**) and benzene was found to be a mixture of *trans*-4-benzoyl-1-phenyl4) cyclohexane (**9A**)(96%) and its *cis*-isomer (**9B**)(4%). Since no epimerization of **9A** by sodium ethoxide occurred, the phenyl and benzoyl groups must be diequatorial, *i.e.*, in the *trans* position5) with respect to each other. On the other hand, the mother-liquid obtained from the reaction of **5** with benzene was converted to pure **9A** by the action of sodium ethoxide. This indicates that **9B** must be the *cis*-isomer. An oily product obtained from the reaction of 4-acetylcyclohexene (**6**) and benzene was found to be a mixture of *trans*-4-acetyl-1-phenylcyclohexane (**10A**) (95%) and its *cis*-isomer (**10B**)(5%). Likewise, methyl 4-cyclohexenecarboxylate (**7**) and benzene were found to be methyl *trans*-4-phenylcyclohexane-1-carboxylate (**11A**)(85%) and its *cis*-isomer (**11B**) (15%).

Thus, the above-mentioned reaction provides a useful method of preparing **9A**, **10A**, and **11A** in good yields. For example, the Friedel-Crafts reaction of **5**, followed by epimerization, gives **9A** in a 90% overall yield.

The reaction of 4-cyclohexenecarboxylic acid (**8**) with benzene gave a mixture of crystalline carboxylic acids in a 94% yield. The mixture of methyl esters obtained by treatment with diazomethane in ether consisted of the *trans* ester (**11A**)(67%) and its *cis*-isomer (**11B**)(33%). When the epimerization of

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1) K. Sugita and S. Tamura, This Bulletin, **44**, 3383 (1971).

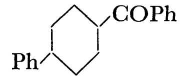
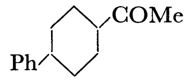
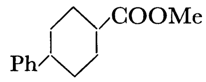
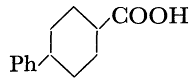
2) W. S. Johnson and R. D. Offenhauer, *J. Amer. Chem. Soc.*, **67**, 1045 (1945).

3) The results obtained in subsequent experiments suggest that the carbonium ion is formed at the 4-position. Therefore, the carbonium ion is not formed at the 3-position.

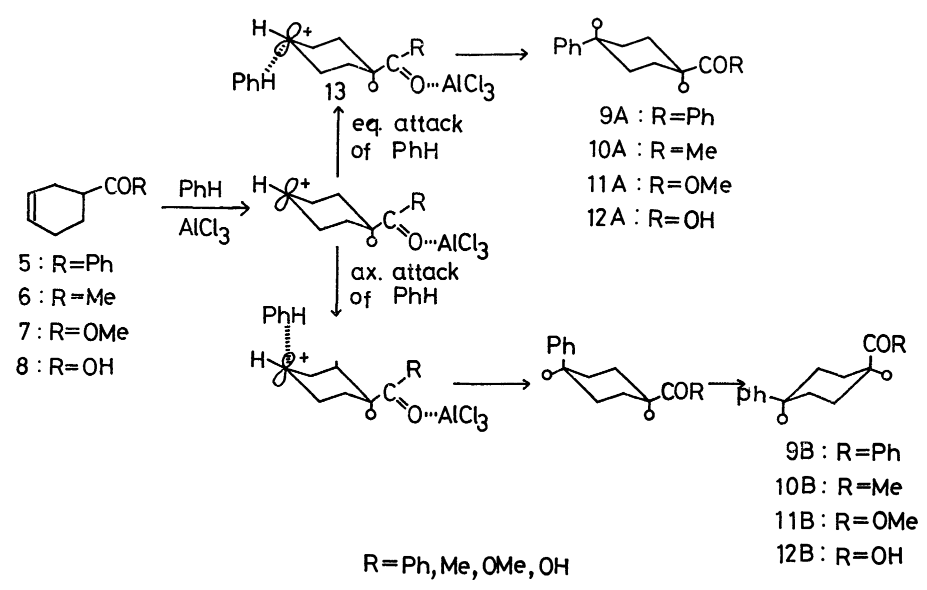
4) Since it has been reporteda,b) that the phenyl group has a substantially greater A value than the benzoyl, acetyl, and methoxycarbonyl groups, it is supposed that the phenyl group in this paper has an equatorial conformation. a) E. L. Eliel, N. L. Allinger, S. T. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y. (1965), p. 236. b) E. W. Grabish, Jr., and D. B. Patterson, *J. Amer. Chem. Soc.*, **85**, 3228 (1963).

5) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955).

Table 1. ALUMINUM CHLORIDE-CATALYZED ALKYLATION REACTION OF BENZENE WITH 4-SUBSTITUTED CYCLOHEXENE

Cyclohexene	Product	Bp	Yield (%)	Product distribution,[a] *trans* : *cis*
(**5**)		b)	90	96 (54)[d] : 4 (49)
(**6**)		144—148°C/5—6 mmHg	81	95 (28) : 5 (25)
(**7**)		118—121°C/5 mmHg	79	85 (27) : 15 (23)
(**8**)		b)	94[c]	67 (26.5) : 33 (24.5)

a) By gas chromatographic analysis. The product ratio was calculated from the peak areas. Dimethyl *cis*-Δ^4-tetrahydrophthalate[1] was used as an internal standard for determination of yields.
b) Semi-crystalline solid.
c) The ratio of the acid was determined as the corresponding methyl ester.
d) Retention time (min).



Scheme 2.

the methyl ester was carried out in a manner similar to that described above, the **12A** acid was obtained. The **12A** acid was identified as being in a *trans*-isomer.

Thus, the addition of benzene to the double bond of 4-substituted cyclohexenes (**5**, **6**, **7**, **8**) in the presence of aluminum chloride selectively occurred at the 4-position to the substituent, as is shown in Table 1. These results indicate that the carbonium ion must be produced at the 4-position in these reactions. The equatorial attack of benzene on the carbonium ion should be more favorable than an axial attack, since it leads to a more favorable transition state (**13**) in which the substituent and attacking benzene are both equatorial. Thus, these reactions give rise to predominantly *trans*-1,4-disubstituted products.[6]

Experimental[7]

Materials. 4-Acetylcyclohexene (**6**) was prepared by the procedure reported by Petrov.[8] Methyl 4-cyclohexenecarboxylate (**7**) and 4-cyclohexenecarboxylic acid (**8**) were prepared by the procedure reported by Klein, Dunkelblum, and Avrahami.[9]

*4-Benzoylcyclohexene (**5**).* This was obtained as follows. To a mixture of β-Chloropropiophenone (34 g),

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[6] It may be considered that the result obtained in the present work support the mechanism.

[7] All the melting points and boiling points are uncorrected. The IR spectra were taken on a Hitachi EPI-S spectrometer. The NMR spectra were obtained on a Japan Electron Optics C-60-H spectrometer. The glpc analyses were carried out with a Shimazu GC-4AP appratus using Silicone Grease as the stationary phase.

[8] A. A. Petrov, *J. Gem. Chem.*, **11**, 309(1941): *cf. Chem. Abstr.*, **35**, 5873 (1941).

[9] J. Klein, E. Dinkelblum, and D. Avrahami, *J. Org. Chem.*, **32**, 935 (1967).

potassium acetate (30 g), and toluene (30 m*l*), butadiene (34 m*l*) was added in an autoclave. The solution was heated with stirring at 90—92°C for 24 hr. Then the inorganic salt was filtered off after adding toluene. The toluene solution was washed with water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The distillation of the reaction residue gave **5**; bp 125—126°C/5 mmHg (24 g, 63% yield). IR: (neat) 1670 (benzoyl) and 1645 cm^{-1} (olefin). NMR: δ(CDCl$_3$) 2.45—1.50 (m, 6, 3CH$_2$), 3.50—3.00 (m, 1, CH), 5.80 (t, 2, CH=CH), 7.50—7.25 (m, 3, aromatic), and 8.10—7.75 ppm (m, 2, aromatic). Found: C, 84.45; H, 7.69%. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58%.

4-Acetyl-1-phenylcyclohexane. This was prepared by the procedure reported by Johnson and Offenhauer;[2] mp 55—56°C (lit,[2] 55.1—55.6°C). IR: (Nujol) 1700 (Ketone) and 1600 cm^{-1} (aromatic). NMR: δ(CDCl$_3$) 2.05—1.25 (m, 8, 4CH$_2$), 2.18 (s, 3, CH$_3$), 2.75—2.25 (m, 2, 2CH) and 7.20 ppm (s, 5, aromatic).

Methyl 4-Phenylcyclohexane-1-carboxylate. This was prepared by the procedure reported by Johnson and Offenhauer;[2] mp 28—30°C (lit,[2] 29—30°C). IR: (Nujol) 1730 (ester) and 1600 cm^{-1} (aromatic). NMR: δ(CDCl$_3$) 2.90—1.20 (m, 10, 4CH$_2$ and 2CH), 3.68 (t, 3, CH$_3$) and 7.22 ppm (s, 5, phenyl).

4-Phenylcyclohexane-1-carboxylic Acid. This was prepared by the procedure reported by Johnson and Offenhauser;[2] mp 200—201°C (lit,[2] 203—204°C).

4-Benzoyl-1-phenylcyclohexane from 4-Phenylcyclohexane-1-carboxylic Acid. A mixture of 4-phenylcyclohexane-1-carboxylic acid (3.3 g) and thionyl chloride (3.5 g) was refluxed for 2 hr and then cooled. The excess thionyl chloride in the reaction mixture was removed under an atmosphere of nitrogen at 30—40°C under reduced pressure. 4-Phenyl-1-chloroformylcyclohexane as a liquid was obtained quantitatively and was used directly, without distillation. To a suspension of aluminum chloride (2.5 g) in dry benzene (17 m*l*), we vigorously stirred in 4-phenyl-1-chloroformylcyclohexane (3.8 g), drop by drop, below 10°C. Stirring was continued for one hour without further cooling, and then for two more hours under reflux. Then the reaction mixture was poured onto icewater. The benzene solution was separated, washed with water, 5% sodium hydrogencarbonate, and water, dried over anhydrous magnesium sulfate, and evaporated to dryness. A semi-crystalline solid was dissolved in hot *n*-hexane. The solvent was then removed to give *trans*-4-benzoyl-1-phenylcyclohexane (1.0 g, 23% yield); mp 73—79°C. Recrystallization from *n*-hexane gave colorless prisms (0.7 g, 16% yield); mp 95—96°C. IR: (Nujol) 1670 (benzoyl) and 1600 cm^{-1} (aromatic). NMR: δ(CDCl$_3$) 2.25—1.40 (m, 8, 4CH$_2$), 2.75—2.35 (m, 1, CH), 3.60—3.05 (m, 1, CH), 7.22 (s, 5, aromatic), 7.60—7.35 (m, 3, aromatic), and 8.15—7.80 ppm (m, 2, aromatic). Found: C, 86.33; H, 7.68%. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63%.

Aluminum Chloride-catalyzed Reaction of 4-Substituted Cyclohexene with Benzene. General Procedure: Into a solution of 4-substituted cyclohexene (0.05 mol) in dry benzene (0.5 mol) we stirred aluminum chloride (0.06 mol) over a five-minute period below 10°C. Stirring was continued for one hour without further cooling, and then for two additional hours under reflux. Then the reaction mixture was poured onto icewater. The benzene solution was separated, dried over anhydrous magnesium sulfate, and evaporated to dryness. The product was purified by recrystallization or distillation.

trans-*4-Benzoyl-1-phenylcyclohexane* (***9A***) *from 4-Benzoylcyclohexene* (***5***). The reaction product was recrystallized from *n*-hexane to give **9A** as colorless prisms; mp 96—98°C, 74% yield. The mother liquid was used as the epimerization sample. **9A** was identified as 4-benzoyl-1-phenylcyclohexane by a mixed-melting-point determination and by a comparison of its IR and NMR spectra with those of an authentic sample.

trans-*4-Acetyl-1-phenylcyclohexane* (***10A***) *from 4-Acetylcyclohexene* (***6***). The product was kept standing in an ice-box for 10 days to separate a crystalline solid (**10A**) (62% yield) from the mother liquid. The mother liquid was used as the epimerization sample. The recrystallization of **10A** from light petroleum ether (bp 30—70°C) gave colorless prisms; mp 54—55°C. **10A** was identified as 4-acetyl-1-phenylcyclohexane by a mixed-melting-point determination and by a comparison of its IR and NMR spectra with those of an authentic sample (Found: C, 82.96; H, 9.12%).

Methyl trans-*4-Phenylcyclohexane-1-carboxylate* (***11A***) *from Methyl 4-Cyclohexenecarboxylate* (***7***). The product was kept standing in an ice-box for 10 days to separate a crystalline solid (**11A**) (27% yield) from the mother liquid (52% yield). The mother liquid was used as the epimerization sample. The recrystallization of **11A** from *n*-hexane gave colorless prisms; mp 29—30°C. **11A** was identified as methyl 4-phenylcyclohexane-1-carboxylate by a mixed-melting-point determination and by a comparison of its IR and NMR spectra with those of an authentic sample (Found: C, 77.20; H, 8.29%).

trans-*4-Phenylcyclohexane-1-carboxylic Acid* (***12A***) *from* 4-*Cyclohexenecarboxylic Acid* (***8***). The reaction product was recrystallized from 60% aqueous acetic acid to give a crystalline solid; mp 79—124°C. The recrystallization of the crystalline solid from 60% acetic acid gave colorless needles (**12A**) (3% yield); mp 199—200°C. **12A** was identified as 4-phenylcyclohexane-1-carboxylic acid by a mixed-melting-point determination and by a comparison of its IR and NMR spectra with those of an authentic sample. IR: (KBr) 2400—2700 (-OH), 1685 (carboxyl) and

TABLE 2. EPIMERIZATION OF 1,4-DISUBSTITUTED CYCLOHEXANE

Sample	Product	Mp(°C)	Yield	
			mg[f]	%
9A	9A	94— 98	450	90
Mother liquid[a]	9A	92— 96	400	80
10A	10A	51— 55	450	90
Mother liquid[b]	10A[e]	54— 55	400	80
11A	12A	197—200	400	90
Mother liquid[c]	12A	198—201	400	90
d)	12A	195—199	350	80

In all cases, the product obtained was identified by mixed melting point and by comparison of IR spectra with that of authentic sample.

a) From the reaction of **5** with benzene.
b) From the reaction of **6** with benzene.
c) From the reaction of **7** with benzene.
d) Crude product obtained from the reaction of **8** with benzene was converted into its methyl ester by esterification of diazomethane.
e) The product obtained crystallized upon standing in an ice-box. Recrystallization from petroleum ether (bp 30—70°C) gave colorless prisms.
f) Yield from 500 mg of the sample.

1600 cm^{-1} (aromatic) (Found: C, 76.33; H, 7.82%).

General Epimerization Procedure. To a sodium ethoxide solution prepared from absolute ethanol (50 m*l*) and sodium (100 mg), we added the sample (500 mg). The solution was refluxed for five hours and then cooled. After the addition of water (100 m*l*) to the reaction mixture, the resulting mixture was acidified and filtered. The results are shown in Table 2.

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