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Preparation of Rearranged Allylic Isocyanates from the Reaction of Allylic Alkoxides with Cyanogen Chloride

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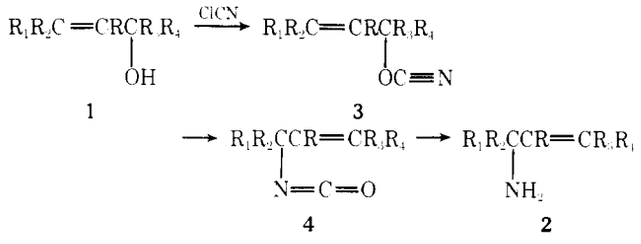
As a potential room temperature method for allylically transposing hydroxyl and amino functions, the reaction of cyanogen chloride with the lithium salt of four representative allylic alcohols was examined. Such treatment results in the formation, in good yield, of a mixture of the allylically rearranged isocyanate and a dimeric carbamate. The allylic isocyanate **4** results from rapid [3,3] sigmatropic rearrangement of the initially formed allylic cyanate **3**, and the dimeric carbamate results from the addition of the starting alkoxide to **4**. Similar treatment of the propargylic alcohol, 2-octyn-1-ol, did not result in the formation of the allenyl isocyanate **19**, but afforded 1-chloro-2-octyne in 70% yield.

Previous reports from our laboratory have demonstrated that the [3,3] sigmatropic rearrangement of allylic trichloroacetimidates[2,3] is a superior method for the 1,3 transposition[4] of alcohol and amine functions (**1** → **2**). With a goal of developing similar methodology in which the thermal rearrangement[5] could be accomplished at or below room temperature, we were attracted to the procedure of Scheme I. Attempts[6] to prepare allylic cyanic esters[7] have invariably led to the formation of allylic isocyanates, and such results have been interpreted to mean that the allyl cyanate to allyl isocyanate rearrangement (**3** → **4**)[8] occurs rapidly at room temperature. The direct synthesis of alkyl cyanates from the reaction of alkoxides and cyanogen halides has been reported.[7,10] However, good yields have been obtained by this procedure with bridgehead[10a] and acidic alcohols[10b,c] only. Typically encountered[11] problems are further transformations of the initially formed alkyl cyanates,[11] leading to the formation of iminocarbonates,[12] isocyanates,[10a,13] cyanate or isocyanate trimers, and alkenes. We anticipated that many of these problems would be avoided in the reaction of an allylic alkoxide with a cyanogen halide if the initially formed allylic cyanate **3** underwent rapid rearrangement to isocyanate **4**. In this paper we report what to our knowledge is the first study of the reaction of allylic and propargylic alcohols with cyanogen chloride. As detailed below, the methodology of Scheme I was found to be synthetically useful for the introduction of nitrogen at highly hindered positions.

Scheme I



Results and Discussion

Sequential treatment of a tetrahydrofuran (THF) solution of geraniol at 0 °C with *n*-butyllithium (1 equiv) and cyanogen chloride (1 equiv) and subsequent reaction for 3 h at room temperature afforded a mixture of linalyl isocyanate **6** and the dimeric carbamate **7**. Isocyanate **6** was isolated in 40% yield by direct distillation of the crude reaction mixture at reduced pressure, and it was characterized by reaction with pyrrolidine to afford the known[3] urea **8**. Carbamate **7** was isolated in 50%

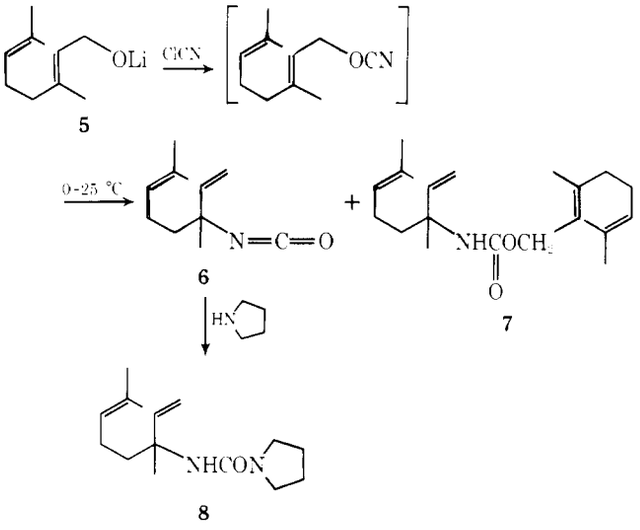


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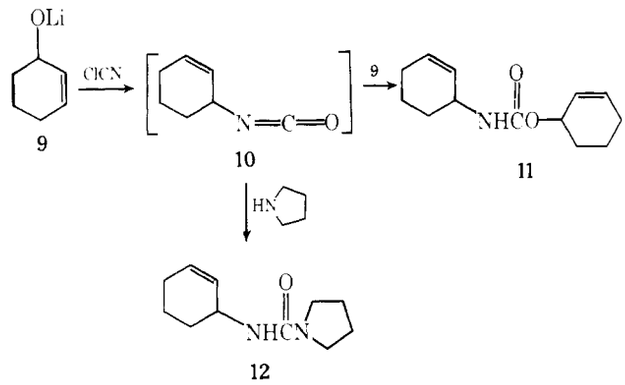
Table I. Reaction of the Lithium Salt of Geraniol (5) with Cyanogen Chloride in THF

CNCl, equiv	reaction conditions[a] time of addn, min	temp, °C	isolated yield of 6, %
1.0	15	0	40
1.5	15	0	48
10	15	0	68
10	15	−78	65
13	600[b]	25	34[c]

[a] A THF solution of cyanogen chloride was treated dropwise at the indicated temperature with a THF solution of **5**. All reactions were stirred at room temperature for 3 h after the addition was complete. [b] A syringe pump was used. [c] Isolated as urea **8**.

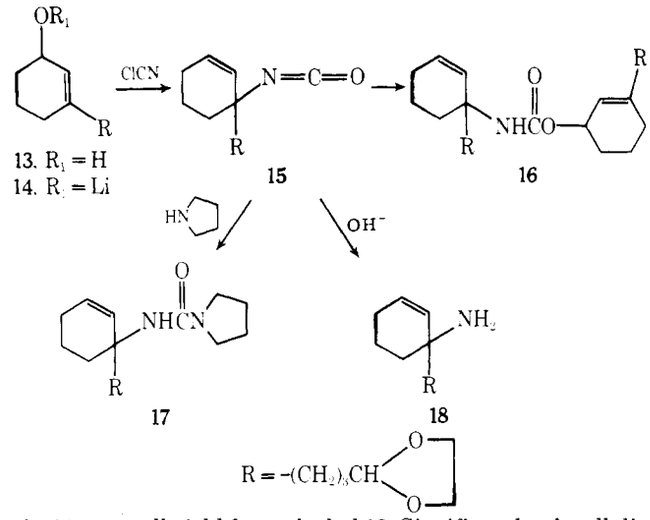
yield by a combination of chromatography and distillation. That **7** was likely formed from the reaction of isocyanate **6** with alkoxide **5** was confirmed by the quantitative conversion of **6** → **7** under identical conditions. A variety of experimental parameters (Table I) was examined in an attempt to optimize the formation of **6**. As expected, the yield of **6** was improved when excess cyanogen chloride was employed, although the increase was not dramatic (**6** formed in 68% yield) even when 10 equiv of cyanogen chloride was employed. The use of lower reaction temperatures and longer addition times had surprisingly little effect.

Similar treatment of the lithium salt of 2-cyclohexen-1-ol with 20 equiv of cyanogen chloride followed by product isolation after the addition of pyrrolidine afforded a mixture of carbamate **11** (51%) and the known[3] urea **12** (21%). The higher

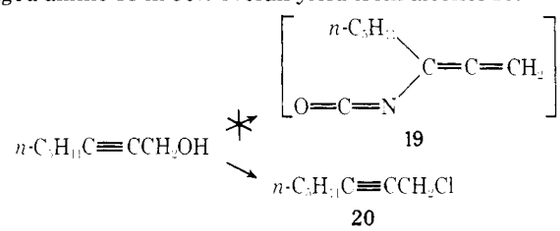


yield of carbamate produced in this case reflects the greater reactivity toward alkoxide of the less sterically hindered isocyanate **10**. The ability of unhindered isocyanates to compete with cyanogen bromide for an alkoxide anion has been noted previously.[13] The tertiary alcohol linalool was recovered unchanged from sequential treatment with *n*-butyllithium and cyanogen chloride.

We next examined the application of the allyl cyanate methodology for introducing nitrogen functionality at the hindered 3 position of a 3-substituted 2-cyclohexenyl system, e.g., **13** → **18**. The inability to accomplish conversions of this type in even moderate yield is the major limitation of the allylic trichloroacetimidate method[2] of transposing alcohol and amine functions. This appeared at the outset as a potentially attractive application of the allyl cyanate methodology since the rearranged isocyanate would be highly hindered, and the low temperature of the thermal rearrangement might reduce complications from competing elimination pathways.[2] In the event, treatment of the lithium salt of alcohol **13**[2c] with 20 equiv of cyanogen chloride afforded a mixture of the rearranged isocyanate **15** and the dimeric carbamate **16** in yields of ~50 and 14%, respectively. Isocyanate **15** was characterized by conversion to the crystalline urea **17**,[3] which was produced



in 44% overall yield from alcohol **13**. Significantly, the allylic urea with an unrearranged carbon skeleton, which was produced[3] to a minor extent in the rearrangement of the pyrrolidinecarboximidic ester of alcohol **13**, was *not* formed (<2%) in the cyanogen chloride reaction. The regiospecific conversion of **13** to acyl derivatives of the rearranged amine **18** in overall yields of greater than 50% represents a significant improvement over the existing methodology.[2,3] In a single experiment, the crude mixture of **15** and **16** was directly hydrolyzed with ethanolic potassium hydroxide to afford the allylically rearranged amine **18** in 36% overall yield from alcohol **13**.



In an attempt to generate allenyl isocyanate **19**, 2-octyn-1-ol was treated in a similar fashion with *n*-butyllithium (1 equiv) and cyanogen chloride (10 equiv). No isocyanate or allene products were detected, and the only product isolated (in 70% yield) was the propargylic chloride **20**. 1-Octanol was similarly converted to 1-chlorooctane in 81% yield. Although the formation of alkyl chlorides from the reaction of alkoxides and cyanogen chloride has apparently not been noted previously,[7,10,11] it is not surprising since alkyl cyanates are known to be converted to alkyl chlorides when treated with HCl[11a] and to alkyl iodides when treated with potassium iodide.[11b]

Conclusions

This study provides further support to the belief that the [3,3] sigmatropic rearrangement of allylic cyanates occurs at or below room temperature.[6] The low temperature allylic cyanate method for the 1,3 transposition of hydroxyl and amine functions (Scheme I) has been demonstrated, but its general synthetic application is seriously limited by the ability of the rearranged isocyanate to compete with cyanogen chloride for the starting alkoxide. The allylic trichloroacetimidate methodology[2] is clearly the method of choice for most functional group transpositions of this type. However, in cases where the starting allylic alcohol is particularly prone to elimination and the nitrogen is to be introduced at a highly hindered position, the allylic cyanate method would appear to be a useful addition to the synthetic repertoire.

Experimental Section[14]

Reaction of Geraniol with Cyanogen Chloride. Preparation of 3,7-Dimethyl-1,6-octadien-3-yl Isocyanate (6) and Carbamate 7. (*Caution! Because of the toxicity of cyanogen chloride, all oper-*

ations should be carried out in a well-ventilated hood.) A stirred solution of cyanogen chloride (5 mL, 0.1 mol) and 30 mL of anhydrous THF was treated dropwise at 0 °C over 15 min with a THF solution of alkoxide **5** [prepared from the reaction of 1.54 g (10 mmol) of geraniol with *n*-butyllithium (1.6 M in hexane) at 0 °C in 10 mL of THF using bipyridyl as an indicator]. The cooling bath was removed and the reaction mixture stirred for 3 h at room temperature. Excess cyanogen chloride and THF were removed at reduced pressure on a rotary evaporator, and the residue was dissolved in ethyl acetate and filtered through a short plug of silica gel. After concentration, the residue was distilled to afford 1.22 g (68%) of pure isocyanate **6**: bp 69–72 °C (2.5 mm); IR ν_{max} (film) 2260 (strong N=C=O), 1460 (C=C), 1380, 980, and 920 (CH=CH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.8–6.1 (m, four vinylic hydrogens), 1.62 (s, CH_3), 1.56 (s, CH_3), 1.38 (s, CH_3); ^{13}C NMR ($CDCl_3$) δ 142.2 (C2), 132.2 (C7), 123.4 (C6), 120.8 (N=C=O), 112.8 (C1), 62.2 (C3), 43.0 (C4), 29.2 (CH_3), 25.6 (CH_3), 23.2 (C5), 17.6 (CH_3); mass spectrum, *m/e* 179.130 ($C_{11}H_{17}NO$ requires *m/e* 179.131), 136, 121, 96.

Treatment of a hexane solution of the distillation residue with activated charcoal followed by bulb-to-bulb distillation (bath temperature 150 °C, 10^{-3} mm) afforded 422 mg (25%, >90% pure by ^1H NMR) of carbamate **7** as a colorless liquid: IR ν_{max} (film) 3350 (NH), 1720 (C=O), 1505, 1240, and 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.96 (dd, J = 10 and 18 Hz, CH = CH_2), 4.8–5.7 (m, five vinylic hydrogens), 4.7 (broad s, NH), 4.5 (d, J = 7 Hz, CH_2O), 1.65 (s, CH_3), 1.55 (s, CH_3), 1.36 (s, CH_3).

Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.61; H, 10.60; N, 4.20. Found: C, 75.57; H, 11.09; N, 4.51.

Preparation of Urea 8. A solution of 540 mg (3.0 mmol) of isocyanate **6**, 280 mg (4.0 mmol) of freshly distilled pyrrolidine, and 5 mL of THF was maintained at room temperature for 2 h and concentrated to afford a solid residue. This residue was dissolved in hexane, treated with activated charcoal, and crystallized to afford **8**, mp 48–50 °C (lit.[3] mp 37–38 °C), in essentially quantitative yield. This sample of **8** was identical (TLC, ^1H NMR, and IR) with a sample prepared from the thermal rearrangement of geranyl 1-pyrolidinecarboximidate.

Preparation of Carbamate 7 from the Reaction of Alkoxide 5 and Isocyanate 6. A solution of 720 mg (4.0 mmol) of **6** and 15 mL of THF was treated dropwise at 0 °C with a THF solution of **5** (10 mL of a 0.40 M solution) and then stirred for 3 h at room temperature. The solution was neutralized with acetic acid and concentrated, and the residue was purified by chromatography on silica gel (ethyl acetate) to afford 1.32 g (99%) of **7**, which was identical (TLC, ^1H NMR, and IR) with a sample prepared from geraniol.

Reaction of 2-Cyclohexen-1-ol with Cyanogen Chloride. Preparation of Carbamate 11 and Urea 12. A stirred solution of cyanogen chloride (10 mL, 0.19 mol) and 100 mL of anhydrous THF was treated dropwise at 0 °C over a period of 10 h with a 0.10 M THF solution of alkoxide **9** (100 mL, 10 mmol; prepared from 2-cyclohexen-1-ol as described for **5** and added with a syringe pump). After stirring for 12 h at room temperature, the reaction mixture was concentrated and the residue was dissolved in 50 mL of THF and treated dropwise with 10 mL of freshly distilled pyrrolidine. After stirring at room temperature for 1 day, the reaction mixture was concentrated and purified by chromatography on silica gel (5:1 hexane–ethyl acetate) to afford 400 mg (21%) of the known urea **12**, mp 91–93 °C (lit.[3] mp 92.5–93 °C; identical by mixture melting point, IR, and ^1H NMR), and 567 mg (51%) of carbamate **11**: mp 81–83 °C (after sublimation); IR ν_{max} (KBr) 3320 (NH), 1680 (C=O), 1520, 1240, 1055, and 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.2–6.1 (m, four vinylic hydrogens), 5.6 (m, CHOR), 5.0 (m, NH), 4.1 (m, CHNH).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.36; H, 8.71; N, 6.37.

Reaction of 3-(4-Ethylenedioxy-1-butyl)-2-cyclohexen-1-ol with Cyanogen Chloride. Isolation of Isocyanate 15, Carbamate 16, and Urea 17. In a similar fashion, cyanogen chloride (5 mL, 0.10 mol; in 30 mL of THF) was treated dropwise at 0 °C over 15 min with a 0.50 M THF solution of alkoxide **14** (10 mL, 5.0 mmol; prepared from 3-(4-ethylenedioxy-1-butyl)-2-cyclohexen-1-ol[2c] as described for **5**). After stirring for 4 h at 0 °C, the reaction mixture was concentrated, filtered through a short column of silica gel (ethyl acetate), and distilled (90–120 °C, 0.05 mm) to afford 795 mg of a ~70% pure sample of isocyanate **15**: IR ν_{max} 2250 cm^{-1} (strong). Purification of the distillation residue by chromatography on silica gel (1:1 hexane–ethyl acetate) afforded 172 mg (14%) of carbamate **16** as a viscous oil which was pure by TLC: IR ν_{max} (film) 3350 (NH), 1715 (C=O), 1515, 1235, 1140, and 945 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.81 (apparent s, CH=CH), 5.5 (broad s, =CH), 5.1 (broad s, NH), 4.82 (broadened t, J = 4 Hz, OCHO), 4.6 (broad s, CO_2CH), 3.6–4.0 (m, OCH_2CH_2O).

A 237-mg portion of the crude isocyanate sample described above was treated in THF for 12 h at room temperature with 1 mL of pyrrolidine. Concentration and purification of the residue by chromatography on silica gel (7:3 hexane–acetone) afforded 203 mg of the pure urea **17** (0.66 mmol, 44% overall from alcohol **13**), mp 74–75 °C (hexane) (lit.[3] mp 62–64 °C), which was identical (TLC, ^1H NMR, and IR) with an authentic sample.[3] An early chromatography fraction yielded 90 mg of a mixture[2c] of the 1- and 2-(4-ethylenedioxy-1-butyl)-1,3-cyclohexadienes (**21**). The known[3] urea with an unrearranged carbon skeleton, 3-(4-ethylenedioxy-1-butyl)-2-cyclohexene-1-yl-1-pyrrolidinecarboxamide, could not be detected (TLC and ^1H NMR) in the crude reaction mixture or in any of the chromatography fractions.

1-(4-Ethylenedioxy-1-butyl)-2-cyclohexen-1-ylamine (18). In an identical fashion, cyanogen chloride (100 mmol) was treated with alkoxide **14** (5.0 mmol) to afford a mixture of **15** and **16**. This mixture was heated at reflux for 36 h under a nitrogen atmosphere with 15 mL of ethanol and 7.5 mL of a 40% potassium hydroxide solution. The alkaline mixture was then acidified (pH ~6) with 50% acetic acid, extracted one time with 20 mL of ether, and basified, and the amine product was isolated by extraction with ether. Short-path distillation (85–90 °C, 0.02 mm) of the dried (Na_2SO_4) extract yielded 443 mg (42%) of amine **18** (85% pure, contaminated with diene **21**). A pure sample of amine **18** was obtained by extraction with cold 1% HCl, washing with ether, basification, and short-path distillation as a colorless liquid: IR ν_{max} ((film) 3350 and 3290 (NH), 2930, 1440, 1140, 1035, 940, and 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.4–5.7 (m, CH=CH), 4.81 (t, J = 4 Hz, OCHO), 3.5–4.0 (m, OCH_2CH_2O), 1.8 (s, NH_2); ^{13}C NMR ($CDCl_3$) δ 135.3 (CH=), 127.0 (CH=), 104.6 (OCHO), 64.8 (OCH_2), 50.5, 43.0, 36.4, 34.5, 25.2, 19.3, 18.3.

Preparation of 1-Chloro-2-octyne (20). A stirred solution of cyanogen chloride (4 mL, 80 mmol) and 20 mL of THF was treated dropwise at 0 °C over 15 min with a 0.5 M THF solution of lithium 2-octyne 1-oxide (8.0 mmol, prepared as described for **5**). After stirring at room temperature for 3 h, the reaction mixture was concentrated and bulb-to-bulb distilled (bath temperature 50–100 °C, 2 mm) to afford 807 mg (70%) of the known[15] chloride **20**: IR ν_{max} (film) 2930 (CH), 2230 (C≡C), 1468, 1262, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.13 (t, J = 2.5 Hz, CH_2Cl), 1.7–0.7 (m); ^{13}C NMR ($CDCl_3$) δ 87.7, 75.2, 31.23, 31.18, 28.4, 22.4, 19.0, 14.0. This sample of 1-chloro-2-octyne was identical (IR, ^1H NMR, and ^{13}C NMR) with an authentic sample which was prepared by the reaction of 2-octyn-1-ol with thionyl chloride.

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Registry No.—**5**, 67761-64-2; **6**, 67761-65-3; **7**, 67761-66-4; **8**, 60441-39-6; **9**, 67761-67-5; **11**, 67761-68-6; **12**, 60441-42-1; **14**, 67761-69-7; **15**, 67761-70-0; **16**, 67761-71-1; **17**, 60441-43-2; **18**, 67761-72-2; **20**, 51575-83-8; cyanogen chloride, 506-77-4; pyrrolidine, 123-75-1; lithium 2-octyne 1-oxide, 67761-73-3; geraniol, 106-24-1; 2-cyclohexen-1-ol, 822-67-3; 3-(4-ethylenedioxy-1-butyl)-2-cyclohexen-1-ol, 56460-82-3; 2-octyn-1-ol, 20739-58-6.

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Reactions of Long-Chain Chloro Alcohols or Unsaturated Alcohols with Benzene by Aluminum Chloride Catalyst

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A study was made of the reactions of 2-, 4-, and 5-chlorooctan-1-ols, 2-chlorohexan-1-ol, or 4- and 7-octen-1-ols with benzene in the presence of an excess of aluminum chloride catalyst. Isomeric x-phenylalkan-1-ols were obtained from both types of alcohols, but the isomer distributions differed considerably depending on the starting compounds. 2-Chloroalkan-1-ol yielded x-phenylalkan-1-ols (x is between 2 and the penultimate carbon number), but neither 2- nor 3-phenyloctan-1-ol was detected from the reactions of a mixture of 4- and 5-chlorooctan-1-ol or reactions of 4- and 7-octen-1-ol. Both the cation isomerization and phenyl migration toward the 2 or 3 position, close to the terminal substituent ($OAlCl_2$), were considered unlikely to occur. From the fact that the ratios of 6-/7-phenyl isomers in the product distributions were similar to those of 3-/2-phenyloctanes in the reaction product of octyl halide with benzene, the terminal functional group is presumed to hardly affect these remote positions.

Numerous reports have been published on Friedel–Crafts alkylation, and recently extensive studies have also been done on the reactions using long-chain alkylating agents which yield many isomeric products. These studies are well summarized in the preface of the report recently published by Roberts, McGuire, and Baker.[1] There are some reports on Friedel–Crafts reactions using long-chain compounds which contain functional groups,[2] such as carboxyl, carbonyl, and nitrile groups; however, little information is available for the reactions with alcohol derivatives except for lower halohydrin compounds.[3]

We have already reported that Friedel–Crafts reaction of 1,2-epoxyoctane with benzene in the presence of an equimolar amount of aluminum chloride catalyst produced 2-phenyloctan-1-ol as the main product,[4] and that the reaction catalyzed by an excess (1.5 mol) amount of aluminum chloride produced a mixture of phenyloctan-1-ol isomers.[5] This isomeric mixture is thought to be produced from 2-chlorooctan-1-ol which was formed by reaction of 1,2-epoxyoctane with the excess catalyst. Moreover, the isomer distribution of the products seemed to be affected by the terminal polar group. In this paper, we report results of Friedel–Crafts reactions of long-chain chloroalkan-1-ols or octen-1-ols with benzene in the presence of excess aluminum chloride, carried out in order to investigate how the isomer distribution is affected by the terminal polar group in long-chain alkylating agents.

Results and Discussion

In the reaction of an alcoholic compound with aluminum chloride catalyst, one molar amount of the catalyst is consumed by the hydroxy group.[3] In this work, then, the catalyst used was 1.5 times the molar quantity of the alcohol in each reaction.

Reaction of 2-Chlorooctan-1-ol. 2-Chlorooctan-1-ol (0.02 mol) was added to a suspension of aluminum chloride (0.03 mol) in benzene (0.4 mol). The mixture was allowed to react at 5 °C, and the isomer distribution of the reaction products after various reaction times was determined by gas chromatography (GC).

The secondary chloride was substituted by a phenyl group in preference to the terminal hydroxy group, which remained apparently unchanged. A mixture of isomeric x-phenyloctan-1-ols (x is between 2 and 7) was obtained in fairly high yield suggesting no major side reactions occurred under the conditions used to develop the data shown in Table IA.

It was found that a higher yield of 7-phenyloctan-1-ol was obtained than any of the other isomers, and that the total amount of 2- and 3-phenyloctan-1-ols was the lowest in product distribution. These latter two isomers were not separable from each other by GC even after being converted to their trimethylsilyl ethers. However, the content of 2-phenyl isomer was presumed to be less than that of 3-phenyl isomer from a consideration of the results of the reaction with 2-chlorohexan-1-ol, in which the 2-phenyl isomer was found to be produced in lesser amount than the 3-phenyl isomer.

Friedel–Crafts reactions of arenes with long-chain alkylating agents generally involve various reaction processes, such as isomerization of intermediate ions, ion attacks on the arene, or isomerization and transalkylation of the products. In this work, therefore, the following experiments were carried out to confirm the results shown in Table I. Although 3-phenylhexan-1-ol was added as a tracer with the catalyst (1:1.5) to a reaction of 2-chlorooctan-1-ol with benzene catalyzed by aluminum chloride, the tracer compound did not isomerize to other phenylhexan-1-ols after 4.5 h at 5 °C; however, 4- and 5-phenylhexan-1-ols were detected after an additional several hours at 40 °C. 2-Phenyloctan-1-ol did not isomerize after being treated with benzene for 5 h at 5 °C in the presence of 1.5 mol of the catalyst. As mentioned later, isomerization of the products, even if it occurred among 4- to 7-phenyl isomers, occurred only very slowly at this temperature. The starting chloro alcohol was not isomerized under these reaction con-

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