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Hexamethyltetralin Preparations
Effect of Methyltrioctylammonium Chloride on Solvent/Olefin Interdependency

Walter C. FRANK* and Donna M. MILLER
Union Camp Technology Center, P.O. Box 3301 Princeton, N.J. 08540-3301, U.S.A.

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The use of quaternary ammonium salts as co-catalysts in the $AlCl_3$ catalyzed cyclialkylation of *p*-cymene, 2-chloro-2methylpropane, and 3, 3-dimethylbutene-1 is reported. The addition of co-catalyst, in solvents which normally give low yields of 1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene with 3,3-dimethylbutene-1, improves product yields, comparable with the best published 3,3-dimethylbutene-1 methodology. Addition of co-catalyst permits the use of more environmentally acceptable solvent systems than those in existing syntheses of the desired tetralin. The yield improvement is rationalized on the basis of improved reaction homogeneity, facile cleavage of Al_2Cl_6 by Cl^- ion, and increased effective solvent polarity, promoted by addition of the quaternary ammonium salt co-catalysts.

Addition of quat co-catalysts to 3,3-dimethylbutene-1 based cyclialkylation systems did not increase rate, catalyst homogeneity or yield relative to a control (dichloromethane solvent). This suggests that the chlorinated hydrocarbon solvents normally used in this technology provide functions similar to that of quats in 2,3-dimethylbutene-1 based technology. These functions include the abilities to enhance $AlCl_3$ solubility, increase the polarity of the reaction medium, and provide facile scission of Al_2Cl_6 to a more active catalytic species.

In reactions where 2,3-dimethylbutene-1 is substituted for 3,3-dimethylbutene-1, addition of co-catalyst improves reaction rate, catalyst homogeneity, and yield reproducibility in non-polar solvents when compared to the best published, 2,3-dimethylbutene-1 methodology.

Several commercial musk aroma chemicals have intermediates prepared by hydride-transfer based cyclialkylation reactions. Researchers have long sought to understand and improve these reaction pathways. Ipatieff, Pines, and Olberg1) identified the phenomenon of hydride abstraction in 3° benzylic systems under cationic conditions and noted that cyclialkylation by olefins occurred in the presence of strong acids to give indanes. Schlatter2) and Eisenbraun3) provided further insights. Wood and Heilweil4) exploited this concept in their elegant synthesis of the polyalkyltetralin based musk aroma compound Tonalid® (**V**) (Chart 1) utilizing neohexene(3,3-dimethylbutene-1), *p*-cymene, and *t*-butyl chloride to form the tetralin intermediate, 1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthlene (**IV**) in 60% yield (Scheme 1). Their reported yield was easily reproduced in our hands. Wood and Heilweil utilized *t*-butyl chloride in the presence of a Lewis acid catalyst to act as a hydride abstractor (**I**). This provided for the *in situ* formation of cymyl cation (**II**), which was subsequently alkylated by neohexene to give **III**, with concurrent cyclization to generate **IV**. In Wood's patented system, only a select number of chlorinated solvents, such as dichloromethane, 1,2-dichloroethane, and chloroform were very effective. Use of solvents like carbon tetrachloride, 1,1,1-trichloroethane, nitrobenzene, and hexane gave unsatisfactory yield of the tetralin based on alkylating olefin. Sato, et al.5) developed a similar route to the same tetralin using 2,3-dimethylbutene-

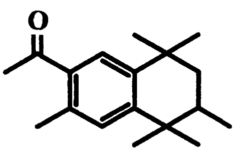

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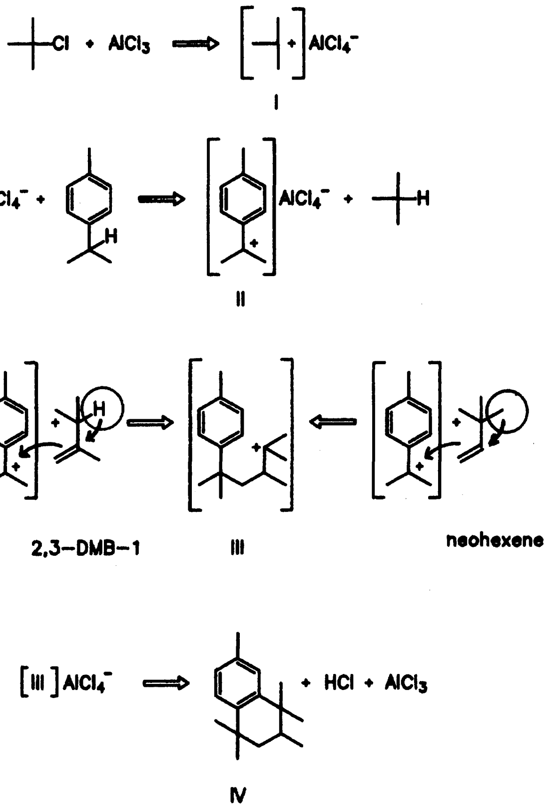
Chart 1.



Scheme 1. Reaction mechanism of HMT using neohexene or DMB-1.

1 (DMB-1) as the alkylating olefin (Scheme 1). Our confirmatory experiments provided as high as a 56% yield, but the reaction was prone to large fluctuations in yield. In Sato's invention, paraffin solvents were preferred, from the viewpoint of yield, safety, and process engineering. However, using the hydrocarbon solvent necessary for good alkylation yields with DMB-1, we found that the $AlCl_3$ catalyst was essentially insoluble during the initial moments of the reaction. Only slowly was the catalyst incorporated into the reaction solvent-(as indicated by the appearance of the red coloration of the liquid phase). Before the addition of reactants was 50% complete, both a red oil phase and a solid catalyst precipitate had developed. This chain of events was certain to cause complications in a large scale process. We sought to unify the seemingly disparate facts concerning olefin/solvent interdependency which surrounded these two reactions that generated the same musk intermediate (**IV**), and resolve the catalyst non-homogeneity difficulties.

Results and Discussion

It was apparent to us that the work of Chevier and Weiss,[6] concerning Friedel Crafts acylation, was applicable in the tetralin cyclialkylation chemistry of interest. Depending on the polarity of the solvent chosen, they demonstrated that a covalent or ionic complex could be interconverted by transposing the solvent used to recrystallize the complex. When extrapolated to the tetralin cyclialkylation system, this suggested that the cymyl cation might be more or less electrophilic depending on the solvent chosen. That is, solvent polarity would determine the extent of interaction between the cation and its counter ion. The stronger interaction caused by less polar solvents like cyclohexane would generate intermediates with less electrophilic character. These would require more nucleophilic olefins like DMB-1 to facilitate the cyclialkylation. Analogously, the argument could be made for neohexene in solvents like dichloromethane. Wilinski and Kurland[7] examined the interaction of quaternary ammonium salts with acyl halide-$AlCl_3$ complexes. Their work suggested to us that $AlCl_3$ could remain active as a Lewis acid in the presence of quats if sub-stoichiometric ratios of quat: $AlCl_3$ were used, although equimolar amounts would fully deactivate the catalyst. We theorized that the quat would be an effective co-catalyst for several reasons. First, quat would make the $AlCl_3$ dissolve more rapidly in the solvent, especially in those systems where solubility was limited. This would remove reaction inconsistencies caused by the normally slow transfer of $AlCl_3$ from the solid to liquid phase in previously described technologies, and make the reaction more reproducible. Second, Cl^- counter ion could assist in the break-up of the Al_2Cl_6 dimer to generate an active monomeric species. Third, quat would increase the polarity of hydrocarbon solvents and allow use of commercially available neohexene in non-polar solvents. Table 1 shows the results of our experiments with quat co-catalysts compared to known technologies. Note that for a given solvent, a change in olefin nucleophilicity causes the yield of HMT to fall off dramatically (compare examples 1 and 3, or 4 and 5). However, when Adogen® 464(commercial form of methyltrioctylammonium chloride) is added as a co-catalyst, neohexene provides excellent yields in non-polar solvents (compare examples 3 and 6). Clearly, addition of quat has a beneficial impact on the use of neohexene in hydrocarbon solvents to manufacture HMT. This same impact was not seen in the more polar solvents tested (compare examples 4 and 7). Furthermore, the quat/$AlCl_3$ molar ratio is important (Table 2). Low quat levels give rise to reduced yield, presumably through inefficient catalyst solvation. High levels also give lower yields, most reasonably due to interaction with $AlCl_3$ causing extensive catalyst deactivation. It appears that quat addition must alter the location of the cymyl cation along the reaction coordinate (and hence, its electrophilicity). With the improved electrophilicity of the cation, neohexene can then be substituted for DMB-1 without negative yield impact. Isomerization of neohexene to DMB-1 under conditions employing quats is not a major factor in these increased yields. Under these acidic conditions, 2,3-dimethylbutene-2 is the major product of isomerization in the absence of cymyl cation.

Table 1. Interdependency of Solvent and C_6 Olefin on HMT Yield

Example	Solvent	Procedure	Olefin	Yield [e]
1	Cyclohexane	a)	DMB-1	56.5%
2	Dichloromethane	a)	DMB-1	30.0%
3	Cyclohexane	a)	Neohexene	38.1%
4	1,2-Dichloroethane	b)	Neohexene	60.6%
5	1,2-Dichloroethane	b)	DMB-1	23.8%
6	Cyclohexane	c)	Neohexene	57.1%
7	1,2-Dichloroethane	d)	Neohexene	58.5%

a) Sato[4] Standard conditions. 20°C, 3 h reaction time. b) Wood and Heilweil[3] Standard conditions. −8°C, 5 h reaction time. c) Standard Quat conditions[8] in non-polar solvent. 0°C, 2 h reaction time. See Experimental Section. d) Standard Quat conditions in polar solvent. −8°C, 5 h reaction time. See Experimental Section. e) All yields are calculated based on weight % internal standard method of GC analysis. However, the product in Example 7 was isolated by distillation in 55% overall yield, reflecting a 94% distillation recovery.

Under conditions described by Sato, et al.,[5] solid $AlCl_3$ was only slowly transformed into a "red oil" phase, with minimal color development, and apparent limited solubility, in the reaction solvent. As addition of reactants continued, solubility of the red oil in the solvent increased until a point where an $AlCl_3$ complex reprecipitated. This "red oil" color was also noted by Olah,[9] and forms almost instantaneously in our system as the reagents are added to the quat-solubilized

Table 2. Effect of MTOAC/$AlCl_3$ Ratio on HMT Yield [a]

MTOAC [b]/$AlCl_3$ (mol)	HMT yield(%) [c]
>0.75	No reaction
0.5	60.6
0.36	63.5
0.25	55.6
0.15	35.5
0.0	38.4

a) All reactions were carried out at 0°C using cyclohexane (19.1 g), *p*-cymene (25.1 g), neohexene (7.0 g), *t*-butyl chloride (9.6 g) and $AlCl_3$ (0.96 g). Required amounts of MTOAC were calculated based on the $AlCl_3$. A general procedure can be found in the experimental section. b) MTOAC=Methyltrioctylammonium chloride. c) Yields are molar yields based on the weight % internal standard method of GC analysis.

Table 3. Catalyst Solubilization and Kinetics Studies

Example	Solvent	Olefin	Catalyst	Yield
1 [a]	Cyclohexane	DMB-1	$AlCl_3$/MTOAC	47.5%
2 [a]	Cyclohexane	DMB-1	$AlCl_3$	31.5%
3 [b]	Dichloroethane	Neohexene	$AlCl_3$	53.3%
4 [b]	Dichloroethane	Neohexene	$AlCl_3$/MTOAC	47.0%

a) Sato[5] Conditions, except organics added at twice the normal rate (90 min instead of the usual 3 h addition).
b) Wood and Heilweil[4] Cnditions, w/and w/o Quat.

catalyst. The two phase nature of the Sato reaction is virtually non-existent in the quat modified reaction.

While employing the general reaction condition of Sato,[5] addition of methyltrioctylammonium chloride (MTOAC) gave rise to a much greater degree of reproducibility and complete disappearance of the solid catalyst precipitation problem, but little, if any, improvement in yield. Although other quat/$AlCl_3$ molar ratios were tested, those close to 0.5 proved very effective and were used throughout this work, except where noted.

Assuming that the Sato reaction was optimized, we chose to stress the reaction by doubling the rate of addition for the mixture of reagents. Here the impact was quite obvious. Yields were higher in the presence of quat, in spite of the lowered amount of effective catalyst[10] (Table 3). More importantly, the rate of cyclialkylation was dramatically faster in quat assisted reactions. The results are depicted in Fig. 1. In these experiments, we made the assumption that the selectivity on *p*-cymene was high[11] and, thus, that the rate was proportional to the moles of **IV** formed divided by the sum of the moles of **IV** plus *p*-cymene. A horizontal line would indicate that reaction was essentially instantaneous upon addition. A negative slope would indicate a buildup of reagents due to a less reactive catalyst. At these increased reagent addition rates, it is the standard catalyst that fails to maintain the reaction rate necessary to prevent buildup of reagents.

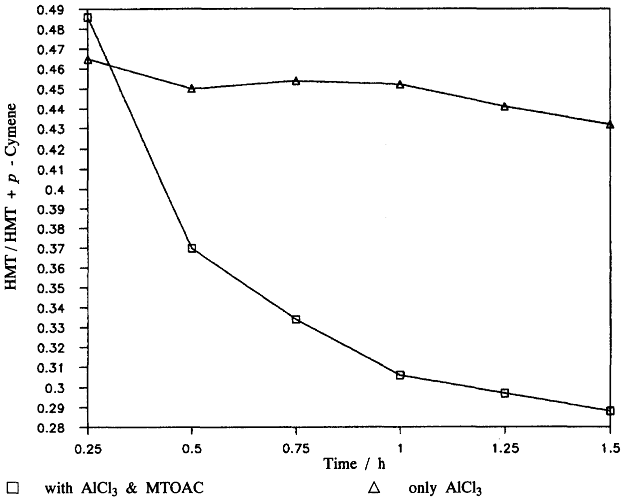


Fig. 1. Rate enhancement in cyclohexane.

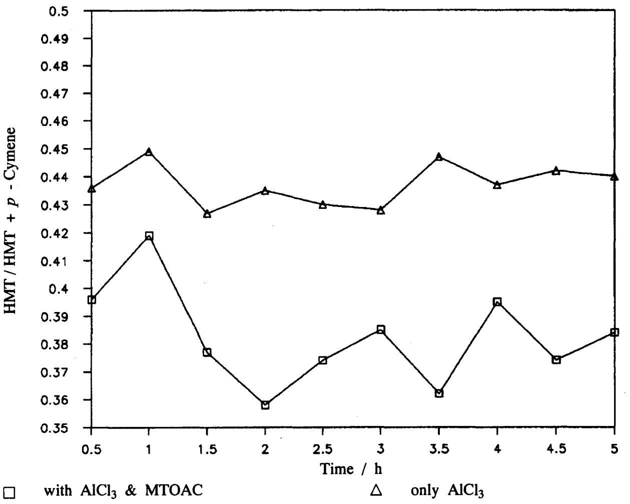


Fig. 2. Effect of added quat in Dichloroethane.

We then returned our attention to the neohexene based cyclialkylation of Wood and Heilweil.[4] Following their procedure which utilizes select chlorinated hydrocarbon solvents, we saw a decreased yield of **IV**, but no apparent change in reaction rate when quat was added (see Fig. 2). This suggests that, even in the quat added case, there is sufficient active catalyst to perform the reaction instantaneously upon reagent addition. It emphasis that, under these conditions, solvent polarity is a more critical factor in determining reaction selectivity. At no time during the Wood-Heilweil type reaction (w/wo quat) was catalyst non-homogeneity as issue.

It would seem that chlorinated hydrocarbons used in the Wood-Heilweil process, and quaternary ammonium salts used in hydrocarbon based cyclialkylation technology perform similar functions. These probably include enhancement of catalyst solubility, Al_2Cl_6 scission to a monomeric species by Cl^- (or the chlorinated solvent), and increased solvent polarity relative to hydrocarbon media. These findings help to clarify the role that solvent plays in olefin selection for HMT preparations, and unites two seemingly incongruous technologies. They also demonstrate the impact of ammonium salts on $AlCl_3$ solubility in non-polar solvents and the related issues of rate, yield, and reproducibility. Further studies are planned in order to fully understand the catalyst's nature and reactivity in cyclialkylation systems.

Experimental

General Methods. Each reaction flask was equipped with condenser, mechanical stirrer, addition funnel, and thermocouple/temperature controller connected to an automatic laboratory jack. The reaction was cooled automatically using a dry ice/isopropanol bath. Neohexene was provided by Phillips Petroleum Company of Bartlesville, OK. Pure methyltrioctyl ammonium chloride, purchased from Fluka, was used as the quaternary ammonium salt co-catalyst in the rate studies (Examples III and IV). However, other commercially available quats, such as Aliquat® 336 or Adogen® 464 were used effectively in other reactions provided that slight increases in $AlCl_3$ loading were utilized. All other materials were purchased from Aldrich Chemical Company, Milwaukee, WI. and used without further purification. Results were analyzed on both polar (Carbowax) and non-polar (DB-1) capillary gas chromatography columns using a weight percent internal standard method of analysis (tridecane). Structure confirmation was achieved by comparison with published data.[4,5] The ^{1}H NMR spectrum was measured at 60 MHz on a Varian T-60 spectrophotometer using TMS as internal reference. The electron impact (70 eV) MS was obtained utilizing a Finnegan MAT 8430 with 1000 resolution at a scan rate of 2 sec/decade. Representative experiments for the reaction using DMB-1 and neohexene in both polar and non-polar solvents follow.

Preparation of 1,1,3,4,4,6-Hexamethyl-1,2,3,4-tetrahydronaphthalene (IV) in Dichloroethane with Neohexene. Anhydrous aluminum chloride (0.50 g, 3.7 mmol), Adogen® 464 (0.83 g), and 1,2-dichloroethane (7.51 g) were charged into a 50 mL three-necked round bottom flask. The mixture was cooled to about −8°C. An addition funnel was charged with *p*-cymene (15.20 g, 111.3 mmol), *t*-butyl chloride (5.23 g, 49.1 mmol), and neohexene (4.07 g, 48.4 mmol), and the funnel mixture was added over a period of about 1.75 h, maintaining a reaction temperature of about −6 to −8°C. This temperature was held constant for an additional three hours with stirring. The reaction was then quenched with ice water (10 mL). The resultant product was washed with 5% aqueous HCL, 10% aqueous Na_2CO_3, and water. All aqueous washes were back extracted with ether. The organic layers were combined, dried over anhydrous K_2CO_3 and evaporated to yield a crude product (17.84 g) containing 34.3 weight % HMT (58.5% molar yield based on neohexene charged). Distillation of the crude material (93°C, 1.6 mbar) gave 5.87 g of HMT (98% purity): ^{1}H NMR ($CDCl_3$) δ=7.3—6.8 (m, 3H), 2.23 (s, 3H), 1.85—1.30 (m, 4H), 1.26 (s, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 1.02 (s, 3H), 0.95 (d, J=10 Hz, 3H); MS m/z 216.0 (M^+, 34), 201 (100), 159 (52), 145 (26).

Preparation of IV in Cyclohexane with Neohexene Adogen® 464 (1.515 g) and cyclohexane (19.10 g) were charged into a 100 mL four-necked round bottom flask. The mixture was cooled to about 16°C. Anhydrous aluminum chloride (1.43 g, 10.7 mmol) was then added and the mixture was stirred for about 0.5 h while maintaining the flask at about 16°C. Next, a mixture of *p*-cymene (25.14 g, 187.6 mmol) and *t*-butyl chloride (8.40 g, 78.8 mmol) was added to the flask. Immediately thereafter, neohexene (7.41 g, 88.1 mmol) was added over a period of 1.5 h (via syringe pump), while the flask temperature was adjusted to and maintained at about 0°C. After stirring an additional 0.5 h, the reaction was then quenched with water (10 mL) and the resultant product was treated as previously described, to yield a crude product (30.00 g) containing 36.22 weight % HMT (57.1% molar yield based on neohexene charged).

Preparation of IV in Cyclohexane A 500 mL three-necked round bottom flask was charged with cyclohexane (76.0 g), anhydrous aluminum chloride (7.21 g, 54 mmol), and methyltrioctylammonium chloride (10.93 g, 27 mmol), and stirred for 0.25 h at 20°C. A mixture of *p*-cymene (99.47 g, 742 mmol), 97% purity 2,3-dimethylbutene-1 (30.21 g, 359 mmol), and *t*-butyl chloride (37.67 g, 407 mmol) was prepared and added to the flask over a period of 1.5 h. Samples were taken and analyzed every 0.25 h. Immediately upon completion of the addition, the reaction was quenched with water (75 mL) and a sample was taken and analyzed. The remaining product was washed with, in order, 5% aqueous hydrochloric acid, 10% aqueous sodium carbonate, and a 50% brine solution. Each aqueous wash was individually extracted with ethyl ether, and the ether layers combined with the organic phase. The organics were dried over anhydrous K_2CO_3 and evaporated to give a crude product (134.47 g) containing 29.6 weight % HMT (47.5% molar yield based on 2,3-dimethylbutene-1 charged).

Preparation of IV in 1,2-Dichloroethane 500 mL three-necked round bottom flask was charged with 1,2-dichloroethane (40.40 g), anhydrous $AlCl_3$ (3.84 g, 28.8 mmol) and methyltrioctylammonium chloride (5.83 g, 14.4 mmol) at −8°C until a gold-colored homogeneous solution was attained (ca. 5 min). A mixture of *p*-cymene (126.57 g, 408 mmol), neohexene (35.32 g, 420 mmol) and *t*-butyl chloride (42.38 g, 458 mmol) was added to the flask over a period of two hours. The reaction was stirred an additional three hours at −8 to −4°C. Samples were taken every 0.5 h. The reaction was quenched with water (75 mL), then worked up as in the previous example to give a crude product (134.0 g) containing 31.3 weight % HMT (47.0% molar yield based on the neohexene charged.

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10) The authors make the assumption that part of the $AlCl_3$ reacts with Q^+CL^- to form a species inactive as a catalyst in cyclialkylations. This is further supported by the fact that increased molar loadings of Q^+CL^- cause a decrease in the yield until a point of total reaction suppression is reached.

11) Weight percent capillary GC data on a large number of similar reactions gave consistent *p*-cymene selectivities.