FRIEDEL-CRAFTS ACYLATION OF 1-METHYLCYCLO-HEXENE

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The acylation of alkenes by means of acyl halides or anhydrides under the influence of Lewis acid catalysts, is a general reaction.[1] Darzens, for example, using $AlCl_3$ added to a solution of acetyl chloride and cyclohexene in carbon disulfide at 0°, obtained a compound presumed to be the saturated 2-chlorocyclohexyl methyl ketone,[2] which on treatment with base at elevated temperatures gave 1-acetylcyclohexene in 42% overall yield. This general method has been widely applied in the preparation of 1-acylcyclohexenes in yields of 40-50%.[3] The use of acid anhydrides rather than acyl halides with cyclohexene has been shown to lead directly to 1-acylcyclohexenes in 50-60% yields without the necessity of a dehydrohalogenation step. Stannic chloride is reported to be the most effective catalyst for these acylations,[4] requiring about one mole of catalyst per mole of acid anhydride to afford optimum yields.

We have attempted to apply these teachings to the acylation of 1-methylcyclohexene **1a** assuming that the carbonium ion mechanism[4] would be most readily accommodated by the tertiary structure of the transition state cation. The results obtained afford

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support for two conclusions of both theoretical and practical inter-
est. (i) The more stable carbonium ion formed in the transition
state of these acylation reactions, permits the use of far less than
molar quantities of Lewis acid catalysts; as little as one mole per-
cent of stannic chloride is actually required to produce optimum
yields. (ii) The olefinic product, whether acetyl chloride or acetic
anhydride is used as the source of acylating agent, consists of
almost entirely the β, γ unsaturated ketone, **3.**
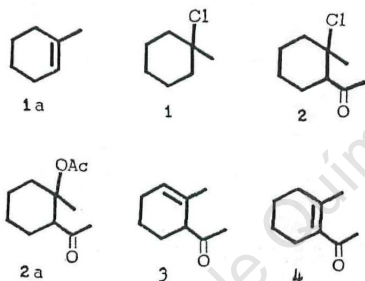
EXPERIMENTAL

The General Acylation Procedure: Into a 50 ml round bottom,
3 neck flask, equipped with magnetic stirring, reflux condenser,
micro dropping funnel and drying tube are charged

     8 g l-methylcyclohexene (ca. 0.08M)
    10 g acetic anhydride (ca. 0.1M)
or 7.7 g acetyl chloride (ca. 0.1M)

A cooling bath was then applied and, when the desired temper-
ature was attained, 0.35 g of stannic chloride (ca. 0.001M) was
added in small portions. The reaction which ensued was extremely
exothermic and care must be taken during addition to keep the
temperature within the predetermined limits. After the selected
reaction time and temperature was experienced, the flask contents
were poured into ice water, followed by addition of excess dilute
NH_4OH and shaking for 15 minutes to destroy all the stannic chloride

complex and any unreacted anhydride or acetyl chloride. The oily product was extracted from this mixture with four 25-ml portions of pentane and the combined pentane extracts were washed once with dilute H_2SO_4 and twice with water, and finally dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum at 25° and the crude residue was examined in several aternative ways as described below.

Fractional Distillation of the Products:

Acylation Condition	Reagent	Weight of Distillate[c]	Residue	% Yield Products
High Temp[a]	Ac_2O	5.2	0.35	46
High Temp	AcCl	4.1	1.3	28
Low Temp[b]	Ac_2O	5.0	0.7	43.5
Low Temp	AcCl	3.7	0.7	22

[a]Reaction at 60° for ½ hr.
[b]Reaction at 25° for 1 hr.
[c]Distilling in the range 39° → 65° at ca. 0.6 mm.

Column Chromatography of the Crude Reaction Mixtures: A 75 cm column, 25 mm. I. D. was packed with 400 g of neutral alumina which was further neutralized by passage of 1 g chlorobutane in dilute pentane solution. (This treatment was repeated after a total of 11 g crude product had been processed on the column.) The crude reaction product sample was introduced in pentane solution and was eluted (first) with pentane and then with pentane-ether mixtures successively enriched with ether as the elution proceeded. Fractions of 50 ml were collected and the pure fractions (as determined by tlc sampling) were analyzed by nmr. All fractions were monitored by IR.

Gas-liquid phase chromatography analysis of distillation product: The most appropriate column for effecting separation of the components of the reaction mixtures was 6 feet in length and packed with 5% silicone rubber on heliport. The distillate from the low

Chromatography Results :

Source of Crude : Reaction with Acetyl Chloride at 25°

Solvent Composition	Fractions (Inclusive)	Structures(s) Identified	Weight(g)	% of Crude
Pentane	1 → 3	1	4.6	40
Pentane	4 → 5	2	0.3	2
Pentane	6 → 8	2 + 3	0.6	5
90 Pentane 10 Ether	9 → 17	90% of 3 + 10% of 4	3.8	33
Up to 100% Ether	18 → 27	Some 3 with higher M.W. products	1.8	20

Source of Crude : Reaction with Ac_2O at 25°

Solvent Composition	Fractions (Inclusive)	Structures(s) Identified	Weight(g)	% of Crude
Pentane	1	1a	0.6	7.5
Pentane	2 → 3	1a + 2a	2.3	18
Pentane	4 → 7	3	1.1	20.5
Pentane 80 Ether 20	8 → 10	(87%) 3 + (13%) 4	1.4	12
Ether 100	11 → 15	Contains 3 along with higher M.W. products—not analyzed	4.2	41

temperature (25°) reaction with Ac_2O showed mainly one peak with minor impurities. A 2% peak corresponded to starting material (1a), a 93% peak consisted of the β,γ-unsaturated ketone 3. After isomerization with base (see next section), this peak was reduced to about 25% and nearly 70% of a new peak which proved to be the α,β-unsaturated ketone 4. Both peaks were collected and identified by IR and nmr data, which are discussed in a subsequent section of this report.

The distillate from the acetyl chloride runs at 25° was difficult to analyze by glpc. The results, moreover, were inconclusive because of the presence of the tertiary chloride 1 and the β chloroketone 2 (as confirmed in column chromatographic analysis of the crude).

Evidently dehydrochlorination in the heated entrance port of the glpc produced considerable tailing and base line unsteadiness, thus vitiating any quantitative significance of the results.

Isomerization, dehydrochlorination, deacetoxylation: Approximately 1 g of distilled product in a typical case was treated with roughly three equivalents of sodium ethoxide in 50 ml ethanol (calculated on the assumption of 100% yield of ketone 3) during overnight stirring at room temperature. After 14 hrs a sample was quenched, which after extraction with pentane and the usual work up procedure showed 46.5% of the α,β-unsaturated ketone 4. Three hours of subsequent refluxing of the residual sodium ethoxide solution increased the degree of isomerization to 70%. Identical results were obtained with products distilled from both the Ac$_2$O and AcCl reactions, but in the latter case a good deal of NaCl was formed and crystallized from the solution.

Infrared analysis: All spectra yere recorded with a Perkin Elmer model 137 using thin films of sample on sodium chloride plates. The spectra of the pure components isolated by either glpc or column chromatography discussed above are presented (as follows). Fig. 1, corresponding to fraction 5 from column chromatography, can be identified as pure 2-chloro-2-methylacetylcyclohexane 2. Fig. 2 is the isomerized product collected as a pure fraction from the gas chromatograph and identified as 2-methylacetylcyclohexene 4. Fig. 3 is the primary acetylation product separated by
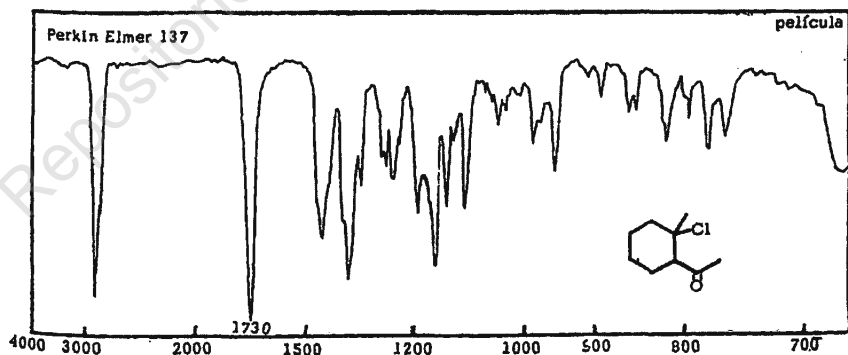

Figura 1

column chromatography and identified as the 2-methyl-3-acetylcyclo-hexene **3**.
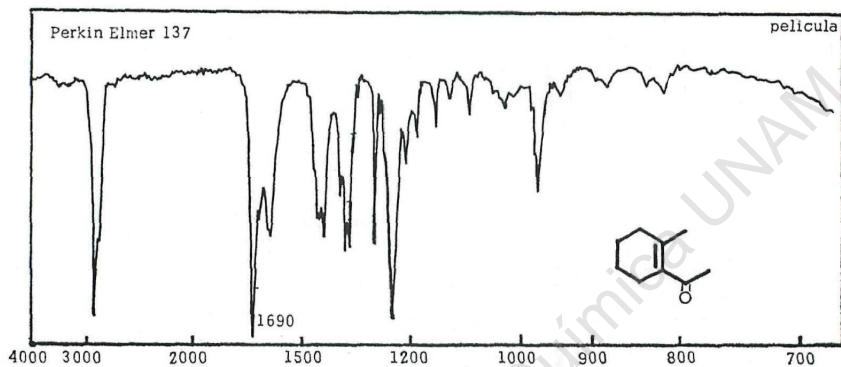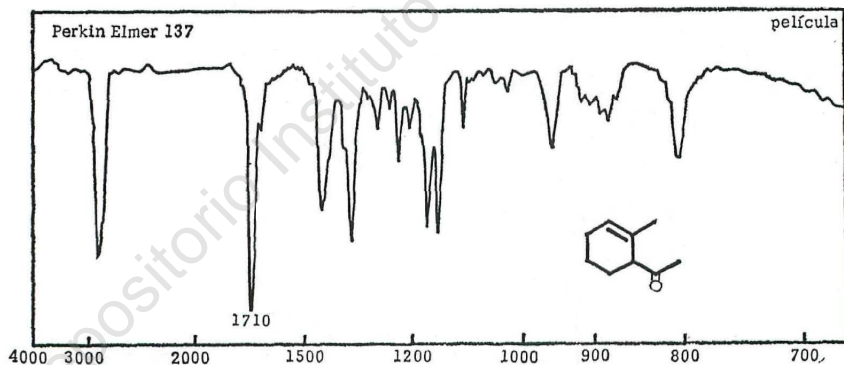

Figura 2

Figura 3

Nmr analysis: Fig. 4, the spectrum of the material **3,** analyzed by IR (above) as Fig. 3. Fig. 5, nmr of the material 4 analyzed by IR (above) as Fig. 2. Fig. 6, nmr of a sample of β-chloroketone **2** separated by column chromatography.
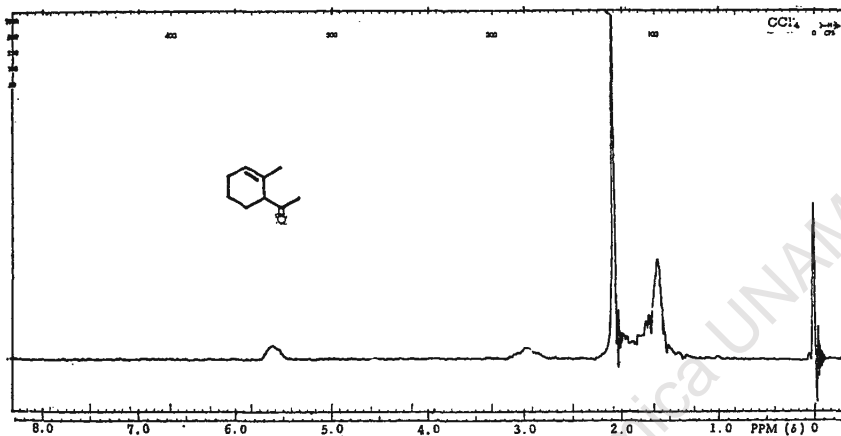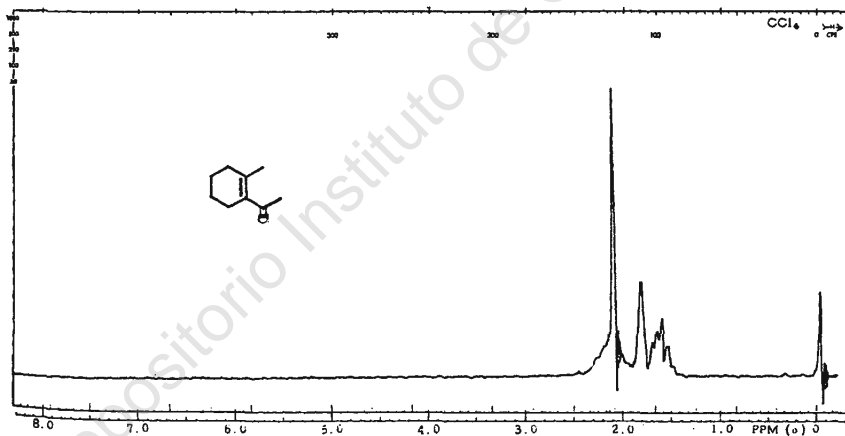
Figura 4

Figura 5

DISCUSSION

The reaction conditions devised to carry out the acylation of 1-methylcyclohexene, clearly lead to acceptable yields of product
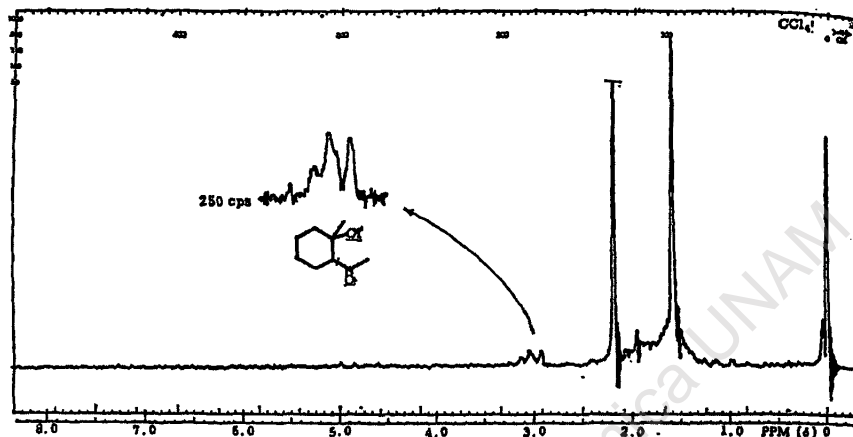
Figura 6

using acetic anhydride as the acetylating agent. The crude product of this reaction, as determined by column chromatography, appears to contain significant amounts of the saturated ketone 2a. An even larger amount of the chloroketone 2 is found in the crude product from the acetyl chloride reaction.

The distilled product from the acetic anhydride reaction, however, shows by glpc analysis almost *no* α,β product 4 and no saturated acetoxy product 2a. This is in contrast to the column chromatography analysis of the crude in both acetic anhydride and acetyl chloride reactions which show some formation of the α,β-unsaturated product 4.

The most consistent explanation of these results is that some isomerization of β,γ to α,β, is occurring on the activated alumina column but *not* in the glpc column. The (by-far) preponderant product in both instances, is the β,γ-unsaturated ketone 3. It is nearly the exclusive product to be identified upon distillation of the crude, presumably because any of the 2-acetoxy product 2a or the 2-chloro product 2 can undergo thermal elimination in the glpc column to the β,γ isomer 3 rather than the α,β isomer 4.

These results provide the clue to the origin of what is clearly the kinetically determined acylation product 3, in preference to

the equilibrium product 4. As sketched in the flow diagram below, the initially formed carbonium ion 5, resulting from axial attack by the acylium ion species (generated by the Lewis acid catalyst), may react with any axially-approaching nucleophile (—OAc or —Cl) to give a saturated product. However, when elimination occurs instead, apparently (only), a more axially dispossed hydrogen Ha can be abstracted. Even though the step of elimination of He from carbon bearing the CH$_3$CO- group would remove the most acidic proton, the preference for both axial elimination and axial addition appears to be overwhelming. It will be noted that exercise of this preference conforms to the rule that the entering group (CH$_3^+$CO addition) and the departing group (H$^+$ abstraction) have access to only one face of the cyclohexyl ring.

The fact that dehydrohalogenation of 2 and deacetoxylation of 2a result in the β,γ isomer is again to be interpreted as a consequence of the preference for (trans) diaxial elimination, as represented in the flow diagram. It is doubtful, however, that the latter reaction is an uncatalyzed thermal process, since the normal steric course of such reactions is said to require *cis* elimination of the elements of Hx.[5]
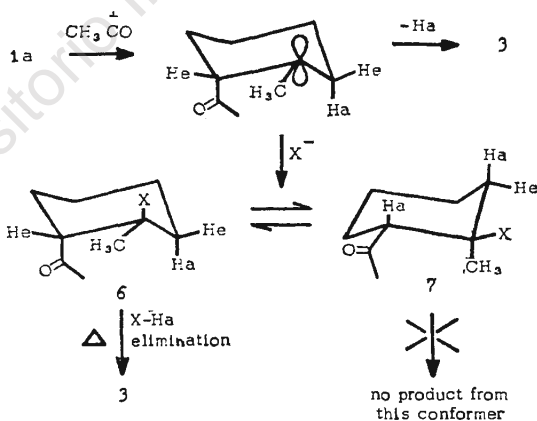
ABSTRACT

As little as one mole percent of Lewis acid catalyst is required to form acceptable yields of the acylation products of 1-methylcyclohexene. The predominant component of this product is identified as the β,γ unsaturated ketone, in contrast to cyclohexene acylation which is reported to form only the α,β unsaturated product. The significance of these results for the mechanism and steric course of the acylation of olefins is briefly discussed.

RESUMEN

La presencia de una mol por ciento de un ácido de Lewis funciona como catalizador para producir rendimientos aceptables de los productos de acilación del 1-metilciclohexeno. El producto predominante se identificó como la cetona β,γ-no saturada, en contraste con la acilación de ciclohexeno que, de acuerdo con lo descrito, forma solamente el producto α,β-no saturado. Se discute ligeramente el significado de estos resultados en función del mecanismo de acilación de olefinas así como su curso estérico.

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