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INTERNAL LEWIS ACID CATALYZED RING-EXPANSION REACTIONS OF CYCLOPROPYLALKANOYL CHLORIDES

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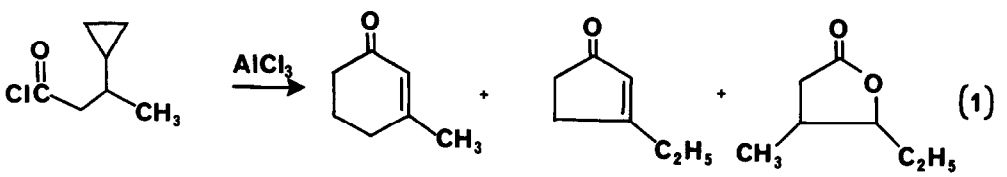
Lewis acid catalyzed cyclization reactions of alkenoyl chlorides and arylakanoyl chlorides have long been of synthetic interest and mechanistic importance.[2] Preferred formation of 5- and 6-membered rings occurs in these reactions, although 7-membered ring compounds have also been prepared.[3] The cyclopropane ring, owing to its unusual nucleophilicity and inherent strain energy, should also be susceptible to intramolecular acylation. The sensitivity of this ring system to electrophilic reagents, the observed cyclopropane participation in solvolytic reactions of cyclopropylethyl derivatives leading to 5-membered ring compounds,[4] as well as the occurrence of intermolecular acylations of cyclopropane and substituted cyclopropanes,[5] suggest the potential for Lewis acid catalyzed ring expansion reactions of cyclopropylalkanoyl chlorides. We wish to report that intramolecular acylation of the cyclopropane ring does occur to yield, depending on the substrate, 5-, 6- and 7-membered ring ketones.

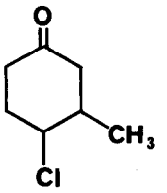
The reaction of 3-cyclopropylbutanoyl chloride with a 2-fold excess of anhydrous aluminum chloride in dry chloroform yields four identifiable products (eq 1): 3-methylcyclohex-2-enone (I, 34%), 3-ethylcyclopent-2-enone (II, 50%) and the *cis*- and *trans*- isomers of lactone III (4%). In a representative procedure the acid chloride (4.0 mmol) was added dropwise to the Lewis acid

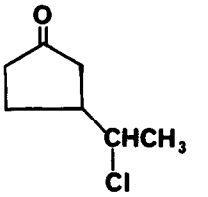


I II III

(8.0 mmol) in 50 ml of the anhydrous solvent constantly stirred at 0°. After complete addition, during which the reaction temperature was kept below 10°, the solution was allowed to warm to room temperature. Complete reaction occurred within 30 min. I and II were identified after quenching and workup by comparison of the isolated compounds with authentic samples. Lactone III was identified by spectral and glpc comparisons with the identical product formed by the action of hydrogen chloride on 3-cyclopropylbutanoyl chloride followed by hydrolysis.

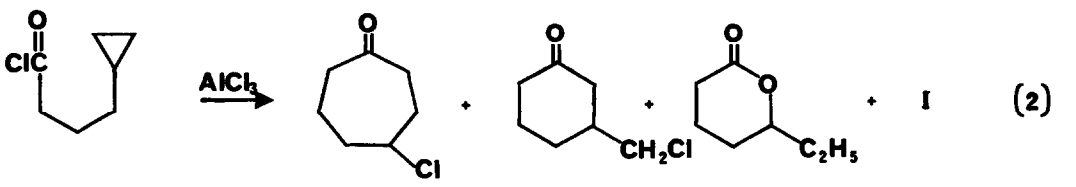
When 3-cyclopropylbutanoyl chloride was treated with aluminum chloride in nitromethane according to the same procedure, two additional products, 4-chloro-3-methylcyclohexanone (IV, 33%) and 3-(1-chloroethyl)cyclopentanone (V, 11%), were identified along with I (23%), II (15%), and III (4%). The chloroketones were identified by proton nmr, ir and mass spectral analyses. With stannic chloride employed as the catalyst only III (*trans*/*cis* = 10)[6] was isolated from the reaction

IV 

V 

in chloroform.[7] In nitromethane, however, the yield of III from the stannic chloride catalyzed reaction was 33%, and I (17%), II (9%), IV (10%) and V (14%) were also observed. No reaction occurred when 3-cyclopropylbutanoyl chloride was treated with boron trifluoride etherate in chloroform.

4-Cyclopropylbutanoyl chloride was converted by anhydrous aluminum chloride in dry chloroform (eq 2) to 4-chlorocycloheptanone (VI, 60%), 3-chloromethylcyclohexanone (VII, 12%), lactone VIII[8] (4%), I (5%) and two unidentified products that were formed in low yield (< 5% combined). Similarly, in nitromethane 4-cyclopropylbutanoyl chloride afforded VI (36%), VII (6%), VIII (28%) and I (15%). Structural determinations were made through comparison with authentic samples or from



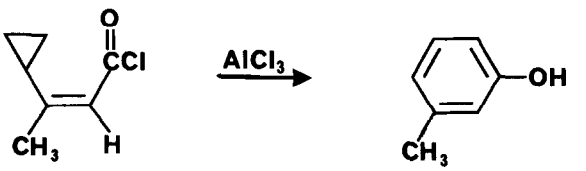
(2)

VI VII VIII

the characteristic spectra of samples isolated by glpc methods. Reaction times were less than 30 min. when 2 equivalents of aluminum chloride was used. Both VI and VII were stable over periods of 1 hr under the reaction conditions employed.

The cyclopropane ring, as the reported results demonstrate, is highly susceptible to ring expansion by intramolecular acylation. Product yields in these reactions are high and are comparable to those from Lewis acid catalyzed olefinic cyclizations.[2,3] However, isomeric cyclic products result from cyclopropane ring expansion reactions. The formation of VII from 4-cyclopropylbutanoyl chloride (% VII/% VI = 0.2), for example, contrasts with the corresponding olefinic cyclization of 6-heptenoyl chloride[3] from which this same compound was not observed. Structural rearrangement is the dominant process in aluminum chloride catalyzed internal acylations of 3-cyclopropylbutanoyl chloride in chloroform. Since the ring expansion reaction is considerably more energetic than comparable olefinic cyclizations, cyclopropane ring opening to carbeniun ion intermediates that are more susceptible to ring contraction might be expected. However, these results can also be interpreted by invoking protonated cyclopropane intermediates[5,9] from which the observed products could be formed directly.

The facility of the cyclopropane ring expansion reaction is also demonstrated by the conversion of (*Z*)-3-cyclopropyl-2-butenoyl chloride to *m*-cresol (eq 3). Treatment of this acid chloride (7 mmol) with an equivalent amount of aluminum chloride in anhydrous chloroform gave, after quenching,



workup and product distillation, isomerically pure *m*-cresol in 52% yield. No other reaction products were observed prior to distillation. The corresponding (*E*)-isomer did not undergo acylation under the same reaction conditions; only (*E*)-3-cyclopropyl-2-butenoic acid was isolated after quenching and workup. Considering the relative ease of preparation of 3-cyclopropyl-2-alkenoyl chlorides from readily available cyclopropyl alkyl (or aryl) ketones,[10] this procedure may be synthetically advantageous for the production of otherwise difficult to prepare *m*-substituted phenols.

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6. The same *trans/cis* ratio was observed in $AlCl_3$-catalyzed reactions and from the hydrogen chloride-hydrolysis reaction of 3-cyclopropylbutanoyl chloride yielding III.

7. Lactone III was similarly observed as the sole product when anhydrous zinc chloride was used in nitromethane.

8. Presumably formed from the acid chloride by hydrochlorination-hydrolysis through a process similar to that for the formation of III.

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