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THE DIRECT FORMATION OF CYCLOPROPANE TRICARBOXYLIC ESTERS FROM ACYCLIC α-HALOESTERS

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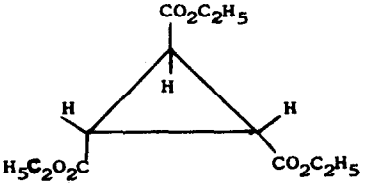
During the lithium-liquid ammonia reduction of an α,β-unsaturated ketone, the addition of various alkyl halides leads to the formation of α-alkylated ketones (1). We employed excess ethyl bromoacetate as the alkylating species, and the yield (65%) was considerably more than that expected. Vapor phase chromatography (VPC) (3% SE-30 on Chromosorb G ¼" x 6 ft. 200°C) showed a major product (~ 95%, R.T. 1'37") and a minor component (~ 5%, R.T. 3'30"). The mixture was separated by preparative VPC into the components A and B.

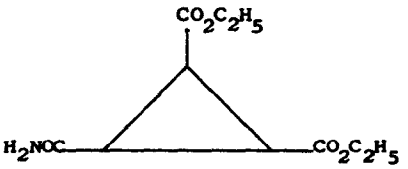
Product A showed infrared absorption at 3030 and 1725 cm^{-1}. The N.M.R. spectrum was composed of the following chemical shifts: 1.27 δ (9H; t, J = 7 cps.; CH_2-CH_3); 2.58 δ (3H; AB_2 m.) (2); 4.19 δ (6H; q., J = 7 cps.; CH_2-CH_3). A molecular ion was noted at m/e 258 in the mass spectrum.

These spectral data strongly suggested product A to be 1,2,3-trans-cyclopropane tricarboxylic acid triethylester (I).



Comfirmation of the structure came from acid hydrolysis of A to provide 1,2,3-trans-cyclopropane tricarboxylic acid m.p. 212-213 (3).

Infrared analysis of B showed various N-H absorptions along with ester and amide carbonyl bands. The N.M.R. spectrum contained ethylesters, cyclopropyl protons and an amide multiplet at 6.25 . Mass spectral analysis indicated a molecular ion at m/e 229. These data suggested structure II for B.

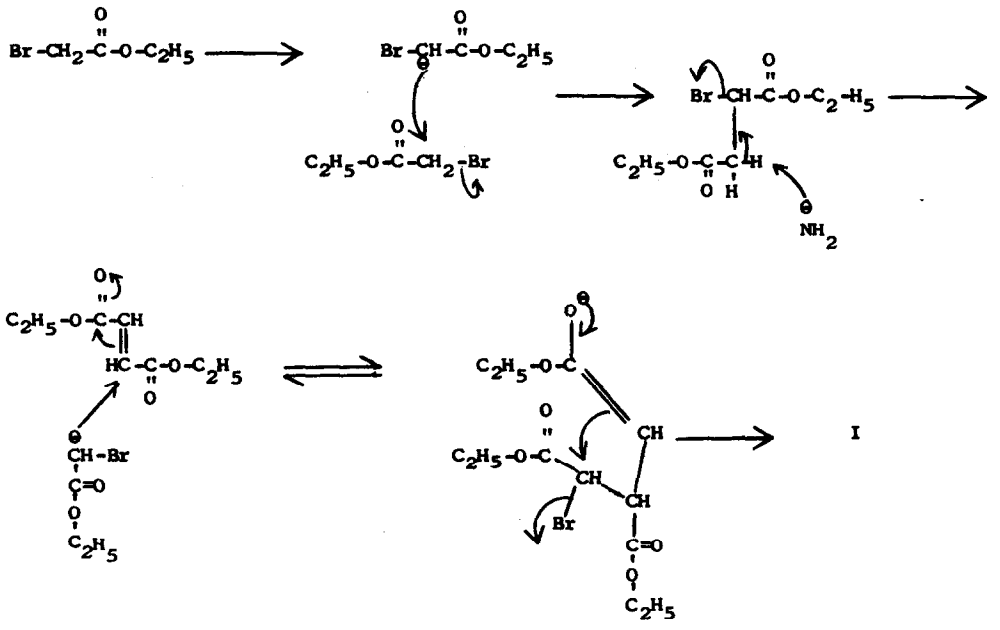


When the α,β-unsaturated ketone was omitted from the reaction mixture the yield of the cyclopropane products was not altered, thus eliminating any involvement of the α,β-unsaturated ketone in the formation of the products.

When sodium amide-liquid ammonia was used, instead of lithium-liquid ammonia, with ethyl bromoacetate, the yield dropped sharply. The only product isolated was the amide (II). This was not the case, however, when ethyl fumarate ethyl bromoacetate, and sodium amide were used. The yield of cyclopropane products was not altered (55-60%).

The formation of cyclopropane carboxylic acid esters from α-halo esters has been reported in reactions involving Michael addition of an anion of an α-halo ester to α,β-unsaturated esters (4-8). In the present case it would appear that a similar mechanism is involved, as outlined in Figure 1. Diethyl fumarate is formed by a nucleophilic attack of the anion of ethyl bromoacetate followed by elimination of hydrogen bromide. Michael addition of the bromoacetate anion to the fumarate and a subsequent nucleophilic cyclization lead to the product. A carbene would not be expected to be involved under these conditions, and indeed, inclusion of cyclohexene in the reaction mixture did not lead to other products. The formation of the amide appears to result from simple ammonolysis of the ester.

FIG. I



There seem to be two competing reactions that have a direct effect on the yield of cyclopropane products: the displacement of a halide by an amide ion, and the formation of an anion of the α-haloester. The latter reaction would be preferred when α-chloroesters are used, instead of α-bromoesters, due to the increased acidity of the α-proton. Thus, the incorporation of ethyl chloroacetate in equimolar concentrations with ethyl fumarate and sodium amide increased the yields of cyclopropane products up to 80%. When ethyl chloroacetate was subjected to lithium-liquid ammonia, the yield was extremely low, probably due to the failure of ethyl chloroacetate to form ethyl fumarate.

The use of liquid ammonia as a solvent appears to favor the formation of the α-anion, possibly because of the low temperature. When ethyl chloroacetate and ethyl fumarate were allowed to react in other solvent systems and various bases

(sodium ethoxide in ethanol, potassium t-butoxide in t-butanol, and sodium amide in toluene), the yields were not higher than 18% (8). The employment of such solvent systems seems to explain the failure of ethyl bromoacetate to undergo cyclization reactions similar to those of ethyl chloroacetate (6).

This method of synthesis of 1,2,3-trans-cyclopropane tricarboxylic acid esters appears to be the first such case in which the Michael olefin is formed in situ to undergo further addition reactions.

The scope and synthetic applications of the reaction are currently under investigation.

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