Reactions of (Hydroxymethyl)ferrocene. Esters[1a]

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Very little has been reported in the literature on the synthesis of esters of (hydroxymethyl)ferrocene. Nesmeyanov has described the preparation of ferrocenylmethyl acetate by decomposition of (ferrocenylmethyl)trimethylammonium iodide in the presence of sodium acetate or acetic acid.[2] Good yields of the same acetate have been reported from (dimethylaminomethyl)ferrocene and acetic anhydride.[2] Ferrocenylmethyl benzoate has been prepared by the reaction of (hydroxymethyl)ferrocene and benzoyl chloride in the presence of pyridine,[3] and also by heating (dimethylaminomethyl)ferrocene with methyl benzoate.[2] The reaction of (hydroxymethyl)ferrocene with ferrocenoyl chloride has given the corresponding ester in the presence of pyridine.[4] Evidently, therefore, the only previously acceptable preparations of these compounds have involved decomposition of the quaternary ammonium salts of (dimethylaminomethyl)ferrocene and reaction of acid halides with (hydroxymethyl)ferrocene. Presumably the reason, at least in our experience, is that direct esterification using strong acid catalysis yields significant amounts of ferricenium ion as a decomposition product.

We can now report preparation of esters of (hydroxymethyl)ferrocene directly from the alcohol and the free carboxylic acid *without added catalysts*. Presumably the organic acid alone suffices as a catalyst because of the unusually facile formation of the ferrocenylmethyl carbonium ion.[5] The reaction is accomplished quite simply by heating the (hydroxymethyl)ferrocene with an excess of the carboxylic acid on the steam bath for short periods. Products are obtained in yields up to 70%. Ferrocenylmethyl esters of straight chain aliphatic carboxylic acids through heptanoic acid were prepared, and the benzoate was prepared in good yield by heating (hydroxymethyl)ferrocene with benzoic acid in the absence of solvent or added catalyst.

Nesmeyanov reported formation of ethers by heating (hydroxymethyl)ferrocene in alcohols with acetic acid.[6] We have found that ether formation is not preferred when (hydroxymethyl)ferrocene is heated with an excess of 3-hydroxybutyric acid and that the hydroxy ester can be obtained in 57% yield. When this reaction was repeated using equal parts of water and 3-hydroxybutyric acid, ferrocenylmethyl 3-hydroxybutyrate again was obtained in good yields. In order to eliminate the possibility that the secondary hydroxyl group of 3-hydroxybutyric acid might be unreactive in ether formation, isopropyl alcohol was heated in aqueous solution with (hydroxymethyl)ferrocene, using a small amount of acetic acid. The product, ferrocenylmethyl isopropyl ether, was obtained in good yield. It thus appears that at least in the instance of 3-hydroxybutyric acid, ester formation is preferred over ether formation with or without an aqueous medium. Similar competition reactions are currently being investigated and will be reported later.

Experimental Section

Melting points were determined on a Buchi apparatus and are corrected with the excepetion of products which were liquids at room temperature. Because of a pronounced tendency toward supercooling, the latter compounds were crystallized at low temperatures, and a heating curve was used to obtain the melting point. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer. Moist extracts were dried over anhydrous magnesium sulfate, and solvent was then removed at 20 mm using a rotary flash evaporator.

Ferrocenylmethyl Acetate.—A solution of (hydroxymethyl)ferrocene (4.0 g, 0.0158 mol, from Research Organic Chemicals Co.) in glacial acetic acid (60 ml) was heated on the steam bath for 40 min, cooled, and filtered. Water (300 ml) was added to the filtrate, and the solid which precipitated was recovered and washed with sodium bicarbonate solution, then water. There resulted 3.27 g (69%) of yellow solid, mp 68–72°.

Chromatography on alumin (Alcoa F-20) with hexane afforded pure ferrocenylmethyl acetate, mp 75–77° (lit.[2] mp 74–76°), in 32% yield. The infrared spectrum was as reported.[2]

Anal. Calcd for $C_{13}H_{14}O_2Fe$: C, 60.50; H, 5.47. Found: C, 60.75; H, 5.56.

Ferrocenylmethyl Butyrate.—A solution of (hydroxymethyl)ferrocene (2.5 g, 0.0115 mol) in butyric acid (15 ml) was heated on a steam bath for 1 hr. The reaction mixture was cooled and poured into water. The oil which separated was taken up in ether, and the ether extracts were washed with aqueous sodium carbonate and then with water. The ethereal solution was dried and evaporated, and the residue was chromatographed on F-20 alumina with hexane. The yield of ferrocenylmethyl butyrate, mp 35–36°, was 2.5 g (72%).

Anal. Calcd for $C_{15}H_{18}O_2Fe$: C, 62.96; H, 6.34. Found: C, 63.31; H, 6.43.

Other esters made in a similar manner were propionate, mp 55–57°, 35% yield; valerate, mp 7–8°, $n^{20}\mathrm{D}$ 1.5535, 56% yield; caproate, mp −5 to −3°, $n^{20}\mathrm{D}$ 1.5560, 48% yield; heptanoate, mp 12–14°, $n^{20}\mathrm{D}$ 1.5522, 53% yield.

Ferrocenylmethyl Benzoate.—Benzoic acid (1.0 g, 0.0082 mol) was heated with (hydroxylmethyl)ferrocene (1.0 g, 0.0046 mol) on a steam bath for 45 min. The cooled reaction mixture was dissolved in ether. The ethereal solution was washed with aqueous sodium carbonate and water, dried, and evaporated affording 1.2 g (82%) of ferrocenylmethyl benzoate, mp 130–131° (lit.[3] mp 130–132°). The infrared spectrum agreed with the structural assignment.

Ferrocenylmethyl 3-hydroxybutyrate was made in essentially the same manner; the yield from (hydroxymethyl)ferrocene (2.5 g, 0.0115 mol) and 3-hydroxybutyric acid (15 ml) was 2.0 g (57%) of ferrocenylmethyl 3-hydroxybutyrate as viscous oil.

Anal. Calcd for $C_{15}H_{18}O_3Fe$; C, 59.63; H, 6.00. Found: C, 59.94; H, 6.40.

The infrared spectrum confirmed the structural assignment.

Similar reaction of (hydroxymethyl)ferrocene and 3-hydroxybutyric acid using a 1:1 (molar) mixture of the hydroxy acid and water at reflux for 3.5 hr gave ferrocenylmethyl 3-hydroxybutyrate in 67% yield.

Ferrocenylmethyl Isopropyl Ether.—A solution of (hydroxymethyl)ferrocene (5.0 g, 0.023 mol) in isopropyl alcohol (45 ml), acetic acid (0.2 ml), and water (35 ml) was heated at the reflux temperature for 24 hr. The product obtained by ether extraction was chromatographed on F-20 alumina using hexane to yield ferrocenylmethyl isopropyl ether, 4.0 g (67%), mp 33–34°.

Anal. Calcd for $C_{14}H_{18}OFe$: C, 65.14; H, 7.03. Found: C, 64.93; H, 6.88.

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Registry No.—Ferrocenylmethyl acetate 12300-24-2; ferrocenylmethyl butyrate, 12300-27-5; ferrocenylmethyl propionate, 12300-25-3; ferrocenylmethyl valerate, 12300-29-7; ferrocenylmethyl caproate, 12300-30-0; ferrocenylmethyl heptanoate, 12300-32-2; ferrocenyl methyl benzoate, 12300-31-1; ferrocenylmethyl 3-hydroxybutyrate, 12300-28-6; ferrocenylmethyl isopropyl ether, 12300-26-4.

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Conformational Analysis. XI.[1,2] 2-Carbomethoxy-7-oxabicyclo[2.2.1]heptane and 2-Carbomethoxy-7-oxabicyclo[2.2.1]hept-5-ene

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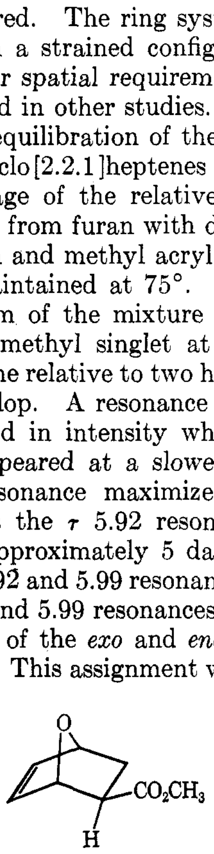
In recent years, the question of the effective size of lone-pair electrons relative to the bonded hydrogen atom has been of interest.[3] While there is some evidence that lone-pair electrons have larger spatial requirements than the bonded hydrogen atom,[4] there is considerable evidence to the contrary.[5] Recently Eliel[6] reported some important observations on the conformational preferences of alkyl groups in the 1,3-dioxane ring system. However, there is little data available with which to extrapolate to systems containing polar groups attached to a heterocycle such as 1,3-dioxane.[7]

The concept of effective steric size of lone-pair electrons is at best a nebulous one. Solvents may solvate one heterocyclic conformation more effectively than an alternate conformation. The problem then develops into one of separating differential steric requirements and solvent stabilization of conformations. A second problem resides in the variation of the nonbonded electron density of a heteroatom as a function of the hybridization of attached bonds. Incorporation of a heteroatom into rings of varying size should change the spatial requirements of the lone-pair electrons. Therefore, conclusions derived from a particular ring system may not be applicable to other heterocycles.

In order to study the possible effects of solvents and hybridization on the conformations of substituents attached to heterocycles, we have chosen the 7-oxabicyclo[2.2.1]heptene and 7-oxabicyclo[2.2.1]heptane ring systems. These rings eliminate the possibility of nonidealized conformations such as might exist in monocyclic compounds. Only the change in position of a substituent as a result of direct equilibration need be considered. The ring system also provides an oxygen atom in a strained configuration which could lead to lone-pair spatial requirements differing from those determined in other studies.

The equilibration of the isomeric 2-carbomethoxy-7-oxabicyclo[2.2.1]heptenes was accomplished by taking advantage of the relative instabilities of Diels–Alder adducts from furan with dienophiles.[8] Equal volumes of furan and methyl acrylate were sealed in nmr tubes and maintained at 75°. The τ 6 region of the nmr spectrum of the mixture was monitored. The three-proton methyl singlet at τ 5.90 gradually decreased with time relative to two high-field singlets which began to develop. A resonance at τ 5.99 appeared first and increased in intensity while a second resonance at τ 5.92 appeared at a slower rate. After 2 days the τ 5.99 resonance maximized and started to decrease, whereas the τ 5.92 resonance continued to increase. After approximately 5 days the relative intensities of the τ 5.92 and 5.99 resonances remained constant. The τ 5.92 and 5.99 resonances were assigned to the methyl singlets of the *exo* and *endo* adducts I and II, respectively. This assignment was based on the known thermal behavior of the Diels–Alder adducts of furan and established by chemical conversion into known derivatives. Mixtures of nonequilibrium composition were reduced by hydrogen over palladium on charcoal, and the isomeric saturated esters were separated from a 12-ft, 25% DEGS on Chromosorb W column. The individual esters were reduced by lithium aluminum hydride to the known saturated primary alcohols.[9]



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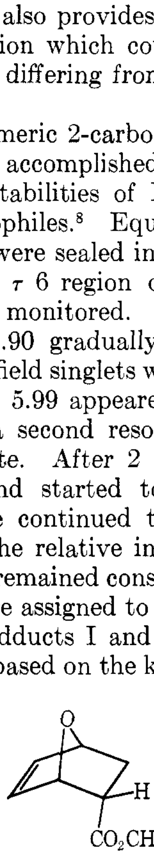

II

The equilibrium constant (*exo*/*endo*) was calculated to be 0.98 ± 0.06 at 75° from the integrated areas of the τ 5.92 and 5.99 resonances. The total yield of adduct was approximately 10% at the temperature examined. The reversibility of the equilibrium and the cleanness of the reaction were demonstrated by allowing equilibration to occur at 63° and then reequilibrating these samples at 75° and *vice versa*. At 63° a 14% yield of adduct results after 20 days. The equilibrium constant at 63° is 0.98 ± 0.06. Thus, while no apparent change in the value of the equilibrium constant is observed, the mole fraction of both adducts increases with decreasing temperature and *vice versa*.

A 10% solution by volume of the mixture of reacting diene and dienophile in dimethyl sulfoxide was studied

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