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POLYMETALLOPHILIC ORGANIC COMPOUNDS

III. COMPETITIVE INTRAMOLECULAR GRIGNARD COUPLING REACTIONS

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SUMMARY

Ring formation via an intramolecular Grignard coupling reaction of trihaloalkanes is presented. 2-Methyl-2-(chloromethyl)-1,5-dichloropentane was prepared and treated with two equivalents of magnesium in tetrahydrofuran, to study the possible ring formation through 1,5 and/or 1,3 coupling reactions. A 1,3 Grignard coupling reaction was shown to occur preferentially, and a cyclopropane derivative was formed. A 1,5 coupling reaction could not be realized under the prevailing reaction conditions. A diradical mechanism for the Grignard coupling reaction is proposed to account for the behavior of this compound and other similar polymetallophilic systems in their reaction with magnesium.

Many of the factors which contribute to the formation and the reaction of organomagnesium derivatives are not as yet clearly defined. For example, an alkyl halide forms a Grignard reagent as the primary product of reaction with magnesium; dihaloalkanes couple or are reduced preferentially[1]. 1,2-Dihaloalkanes react with magnesium to form olefins almost exclusively. 1,3-Dihaloalkanes, under identical conditions, form the strained, energy-rich cyclopropane derivatives while 1,4, 1,5 and 1,6-dihaloalkanes[1-12] exhibit a markedly decreasing tendency to cyclize despite the reduction in ring strain[13].

The Grignard reagent as it exists in solution appears to be ionic; however, recent evidence has led Walborsky[10,14] and others[11,12,15,16] to postulate the formation of a free-radical intermediate. Polymetallophilic compounds like the 2-alkyl-2-(chloromethyl)-1,3-dichloropropanes[17,18] which contain an additional chloromethyl group capable of forming a Grignard reagent after the intramolecular Grignard coupling reaction has taken place, first to form the strained (1-alkylcyclopropyl)-methylmagnesium chloride; however, as quickly as the Grignard reagent is formed, it isomerizes to relieve the strain, forming 3-alkyl-3-butenylmagnesium chlorides.

In view of the rather unique behavior of the different polymetallic compounds

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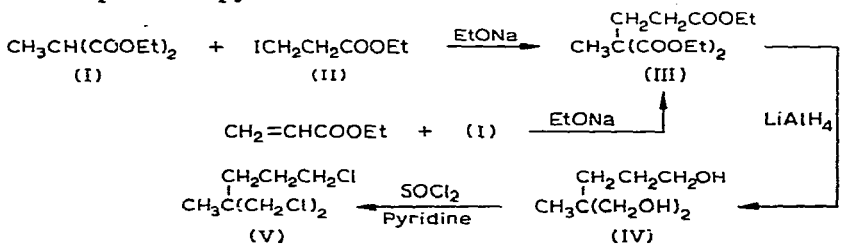
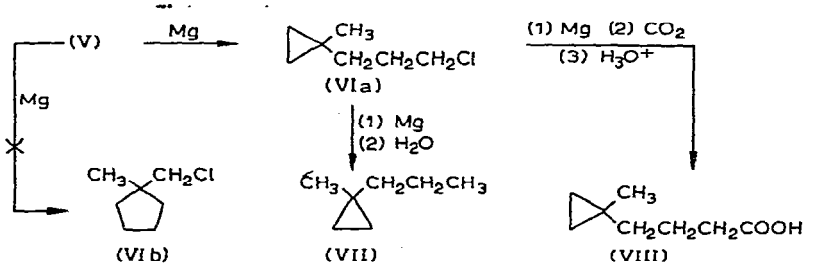
in their reaction with magnesium, it was felt pertinent to investigate situations where two types of intramolecular Grignard coupling reactions may compete to produce two types of ring systems from a particular trihaloalkane. The reaction of certain trichloroalkanes with magnesium was selected to study the competitive ring formation through a 1,3, 1,4 or 1,5-coupling reaction to form highly strained cyclopropane, strained cyclobutane or nearly strainless cyclopentane rings, respectively.

RESULTS AND DISCUSSION

The polymetallophilic system chosen as the basis for this study was 2-methyl-2-(chloromethyl)-1,5-dichloropentane (V) which was prepared according to the scheme shown below. The structure of compound V was confirmed both by elemental analysis and infrared spectroscopy.



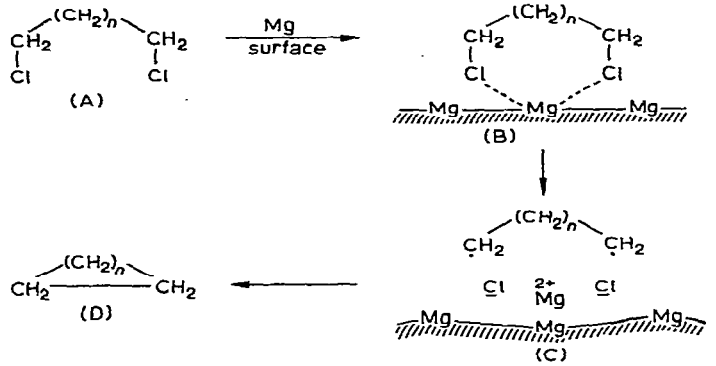
Compound V was allowed to react with two equivalents of magnesium under conventional Grignard conditions. Carboxylation of the Grignard product of V yielded a material which on gas-chromatographic analysis appeared to be a single substance. The compound was identified as 4-(1-methylcyclopropyl)-n-butyric acid (VIII) based upon its IR spectra, its NMR spectrum (two sharp singlets at τ 8.95 and 9.75 which are ascribed to the protons of the methyl group and the cyclopropane ring[19], respectively), its elemental analysis and molecular weight, and by comparative studies of the physical properties of VIII with isomeric acids[16]. Direct hydrolysis of the magnesium derivative of V also yielded a single product. The characteristic cyclopropane bands at 3080, 1020 and 860 cm^{-1} in the infrared spectrum indicated the presence of VII.



Data on the competitive intramolecular Grignard coupling reactions of V, 2-methyl-2-(chloromethyl)-1,4-dichlorobutane* and the dihaloalkanes previously

* Preliminary investigations in our laboratory on the competitive intramolecular Grignard coupling reactions of 2-methyl-2-(chloromethyl)-1,4-dichlorobutane revealed an 80% probability for 1,3 coupling compared with a 20% probability for 1,4 coupling[12].

reported[2-9], strongly suggest that 1,3 intramolecular coupling is favored over either 1,4 or 1,5 coupling. It would appear that the proximity of the reactive centers is essential to the mechanism of the reaction; likewise, since the coupling of ions of like charge is impossible, the participation of a diradical intermediate is distinctly possible. A mechanism similar to that proposed by Walborsky and Young[10] can be postulated to account for the observations on intramolecular Grignard coupling reactions.



When n = either 0 or 1, the dihalide is adsorbed on the surface of the magnesium to form a complex with a single magnesium atom since the quasi 5 or 6-membered ring is energetically favorable. As the complex is desorbed from the surface of the metal, $MgCl_2$ is formed leaving the reactive diradical (C). The lifetime of the diradical is too short to permit conformational changes, therefore, an intramolecular coupling reaction ensues to form either an olefin or a cyclopropane ring. Dimetallophilic compounds where n is greater than 1 would be forced into quasi 7-, 8-, or larger-membered rings; therefore, such compounds tend to complex at different sites along the surface of the metal giving rise to intermolecular coupling reactions. As the ring size increases, the ratio of cyclic to linear coupling should decrease sharply.

EXPERIMENTAL

Preparation of ethyl β-iodopropionate (II). Ethyl β-iodopropionate was prepared by bubbling dry, iodine-free hydrogen iodide (prepared from 80 g of 55% aqueous HI, 102 g of I_2 and 30 g of red phosphorus[20]) into a cooled trap containing ethyl acrylate (100 g, 1.0 mole) in 150 ml of dry ether. After the required amount of HI (128 g, 1.0 mole) was absorbed by the ether solution, the reaction mixture was transferred into a stoppered ground-joint flask and was left in the refrigerator overnight. The mixture was removed and was washed successively with water, dilute sodium bicarbonate solution, water, and was dried over anhydrous sodium sulfate. The ether was distilled and the residue was fractionally distilled to produce a yellow liquid (56%) b.p. 91–93°/16 mm; n_D^{25} 1.4980–1.4986 (lit.[21] b.p. 116°/45 mm).

Preparation of triethyl butane-1,3,3-tricarboxylate (III). Triethyl butane-1,3,3-tricarboxylate was prepared by two independent procedures.

Method A: A mixture of dry ether (400 ml) and dry ethanol (10 ml) was added, slowly to avoid vigorous refluxing, to finely divided sodium metal (3.45 g, 0.15 mole) contained in a flame-dried three-neck flask equipped with an efficient condenser fitted with a drying tube, a sealed mechanical stirrer, and a dropping funnel. The

stirring was maintained throughout the addition. After the vigorous reaction had subsided, the mixture was stirred for an additional half hour before diethyl methylmalonate[22] was added, and when the subsequent reaction apparently had ceased, ethyl bromoacetate was added to the reaction mixture at a rate sufficient to maintain gentle reflux. The mixture was refluxed for an additional 4–5 hours after the addition was completed until the mixture was no longer alkaline. The mixture was cooled and was washed successively with dilute hydrochloric acid, dilute sodium bicarbonate solution, and water. The ether solution was dried over anhydrous sodium sulfate and the solvent was distilled. The product was distilled as a colorless liquid (63%), b.p. 138–140°/2.25 mm; n_D^{25} 1.4330–1.4335 (lit. b.p. 145°/3 mm). The IR spectrum of III was consistent with the assigned structure. (Found: C, 57.2. $C_{13}H_{22}O_6$ calcd.: C, 56.95%.)

Method B: Diethyl methylmalonate was treated with ethyl acrylate according to the procedure reported by Swan[23]. The product was distilled as a colorless liquid (68%), b.p. 143–145°/3 mm; n_D^{25} 1.4328–1.4330. The IR spectrum was identical to that obtained in procedure A.

Preparation of 2-methyl-2-(hydroxymethyl)-1,5-pentanediol (IV). One liter of an ether suspension of powdered lithium aluminum hydride (22.8 g, 0.6 mole) was stirred under reflux in an anhydrous system for 5–6 hours. The solution was cooled and a 30% ether solution of the triester III (82.2 g, 0.3 mole) was added slowly over a three-hour period[24]. The mixture was refluxed for an additional five hours and was allowed to stand overnight at room temperature. The triol was liberated by the dropwise addition of 135 ml of a 40% aqueous ethanol solution. The precipitated salts were separated by filtration, and the filtrate was condensed to remove solvent. The condensation residue was heated at 100° under reduced pressure (0.5 mm). The crude product was obtained as a viscous, pale-yellow liquid (80%) which hardened upon cooling. No further purification of the product was attempted.

Preparation of 2-methyl-2-(chloromethyl)-1,5-dichloropentane (V). Compound V was prepared by the reaction of 37 g (0.25 mole) of triol IV with 119 g (1.0 mole) of thionyl chloride in the presence of 79 g (1.0 mole) of pyridine under conditions similar to those employed in the preparation of pentaerythrityl tetrachloride[25]. The product, purified by distillation, was obtained as a light yellow liquid (40%) b.p. 110–112°/4 mm; n_D^{25} 1.4888–1.4890. The IR spectrum of V was consistent with the assigned structure and quite similar to the IR spectrum of the 2-alkyl-2-(chloromethyl)-1,3-dichloropropanes[17,18]. (Found: C, 41.0; Cl, 52.8. $C_7H_{13}Cl_3$ calcd.: C, 41.2; Cl, 52.33%.)

Preparation and subsequent carboxylation of the Grignard reagent of V. The Grignard reagent of V was prepared by the reaction of 12.4 g (0.061 mole) of the trichloride with 2.93 g (0.122 mole) of magnesium metal in 120 ml of dry tetrahydrofuran using conditions previously employed[17,18]. Likewise, both the carboxylation reaction and the product isolation were conducted in the conventional manner. The crude product was fractionally distilled to give a colorless liquid (68%), b.p. 100–101°/2 mm; n_D^{25} 1.4408–1.4410. Gas chromatographic analysis of the product on a carbowax column revealed that over 95% of the mixture was a single component. The IR spectrum of the acid suggested the presence of a cyclopropane ring evidenced by the characteristic bands at 3080 and 1020 cm^{-1} and the less dependable, but useful, band at 860 cm^{-1}. The NMR spectrum of the product exhibited a singlet at τ9.75, a

singlet at 8.95, a triplet at 8.65, a complex multiplet at 8.25, and a triplet at 7.65. The relative area under the peak of the methyl group singlet at τ 8.95 to the singlet at 9.75 attributed to the cyclopropane protons is in a ratio of 3/4. The spectral analysis, the cryoscopic molecular weight determination in benzene, and the carbon analysis have led us to conclude that compound VIII is 4-(1-methylcyclopropyl)butyric acid. (Found: C, 67.8; mol.wt., 288. $C_8H_{14}O_2$ calcd.: C, 67.6%; mol.wt. dimer, 284.) A Varian HR-60 was used to record the NMR spectra in CCl_4.

Hydrolysis of the Grignard reagent of V. A small amount of the Grignard reagent of V was prepared as described above and was hydrolyzed with aqueous tetrahydrofuran[18]. The volatile products in the hydrolyzate were analyzed by gas chromatography on a diisodecylphthalate column and only one peak, other than tetrahydrofuran, was observed. The product exhibited the characteristic IR absorption peaks for cyclopropane. The assignment of compound VII as 1-methyl-1-n-propylcyclopropane was supported further by comparison of the retention time of the product of the hydrolysis of the Grignard reagent of V with the retention-time study made previously[18] on the isomeric hydrocarbon, 2-ethyl-1-pentene.

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