POLYMETALLOPHILIC ORGANIC COMPOUNDS

I. A GRIGNARD REARRANGEMENT

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Although much work has been done in characterizing the products of reaction of metals with monoalkyl and monoaryl halides, surprisingly little has been done systematically to investigate compounds containing more than one metallophilic* group. The potential of such compounds as a means of preparing organic intermediates and intriguing new macromolecules will be explored in this laboratory and reported in this series of papers.

The reaction of metals with monometallophilic compounds to produce organometallic reagents, and with dimetallophilic compounds to effect ring closure is common knowledge. Metal reactions with compounds with a metallophilicity greater than two have received little attention[1] despite the fact that a number of different rearrangements have been observed[2]. This sequence of reactions may be illustrated by reference to the neopentyl system using zinc and magnesium:

$$(XCH_2)_mC(CH_2Y)_n \text{ where } X = H,\ Y = \text{halogen and } m + n = 4$$

Neopentyl chloride produces a normal Grignard reagent[3]. Treatment of 2,2-dimethyl-1,3-dibromopropane with zinc and alcohol gives 1,1-dimethylcyclopropane[4]. Reaction of 2-methyl-2-(bromomethyl)-1,3-dibromopropane under the same conditions produced rearranged products in addition to the expected dimethylcyclopropane[5]. Pentaerythrityl tetrachloride likewise exhibited rearrangements under these conditions while some spiropentane was isolated[6]. Indeed it has been shown that the rearrangement is facilitated by zinc ion[7].

Because Grignard reactions have been the most thoroughly investigated of organometallic chemistry it was decided to use magnesium in the initial phases of this study.

RESULTS AND DISCUSSION

Treatment of (I) with one mole of magnesium per halogen atom resulted in incomplete reaction as evidenced by the presence of unreacted magnesium. The mixture was poured over dry ice to produce 4-methyl-4-pentenoic acid (III). This product could only have formed as a result of a molecular rearrangement during the formation of the Grignard reagent or the subsequent carboxylation reaction.

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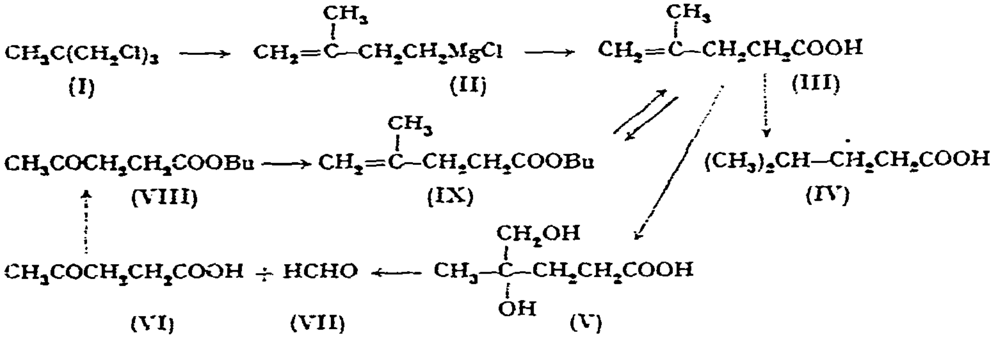
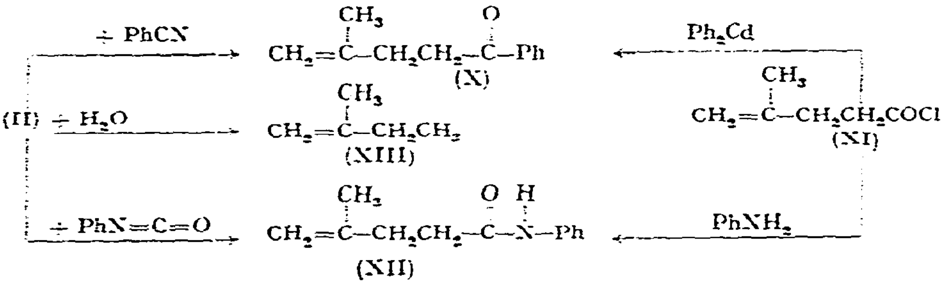
* The word metallophilic is employed to distinguish a group which is capable of reacting directly with a metal to produce an organometallic reagent from other functional groups which may also be present in the same molecule.

The structure of (III) was established, after elemental analysis and both cryoscopic and chemical determination of molecular weight had established the correct formula, by the reactions indicated:



Compound (III) which indicated the presence of unsaturation both from the absorption of bromine and infrared evidence was catalytically hydrogenated to 4-methylpentanoic acid (IV) which was identified by comparison of its infrared spectra with that of an authentic sample of (IV). Treatment of (III) with formic acid and hydrogen peroxide followed by hydrolysis gave (V) which was not isolated. Cleavage of (V) with lead tetraacetate gave a mixture of levulinic acid (VI) and formaldehyde (VII) which were confirmed by ascending paper chromatography of their 2,4-dinitrophenylhydrazones. Levulinic acid was esterified to (VIII) which was converted to (IX) by a Wittig reaction using methylenetriphenylphosphorane. Compound (IX) was also prepared by reaction of (III) with butanol.

With the structure of (III) firmly established[*] it became necessary to determine when the rearrangement had taken place. Titration of the Grignard (II) showed it to be *monofunctional*. Hydrolysis of (II) gave 2-methyl-1-butene (XIII). Treatment of (II) with benzonitrile produced the ketone (X) which was also prepared by treatment of (XI) (4-methyl-4-pentenoyl chloride) with diphenylcadmium. Further substantiation that rearrangment had occurred during the formation of the Grignard reagent was obtained by reacting (II) with phenyl isocyanate. The amide (XII) produced was identical with that obtained by treatment of (XI) with aniline.



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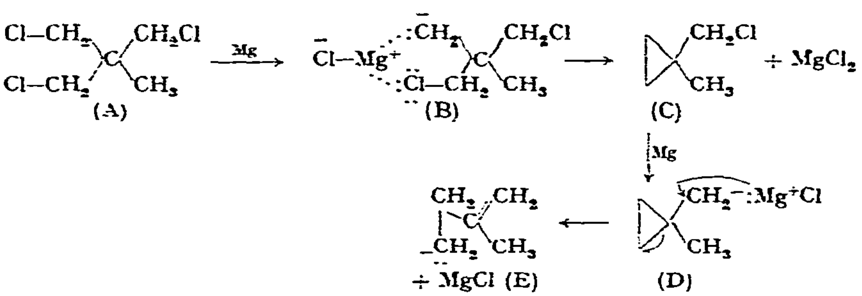
[*] Baumgarten[8] claimed to have prepared (III). Based on the marked resistance of (III) to lactonize under the conditions he reported and on the melting point of the anilide, it is most probable that he had formed 4-methyl-3-pentenoic acid and not (III).

A mechanism for the rearrangement of (I) to (II) is proposed below consistent with our observations and current knowledge regarding the nature of the Grignard reagent and rearrangements in the cyclopropylmethyl anion system[9–13].



The trichloro compound (A) reacts with 1 mole of magnesium to produce the Grignard reagent which forms the complex (B) because of the close proximity of the electronegative chlorine. A coupling reaction ensues forming the cyclopropane derivative (C) and magnesium chloride. Although (C) was not isolated precedence for the formation of the cyclopropane ring and other high energy ring compounds from organometallic intermediates has been well established. Reaction of (C) with more magnesium results in the formation of the cyclopropylmethyl Grignard reagent (D) which then undergoes a concerted electron readjustment (one possibility is indicated above) to form the lower energy compound (E).

Work is presently underway in this laboratory to isolate the cyclopropane intermediate and to study organometallic reactions with other polyhalides such as 2,2-bis(chloromethyl)-1-chlorobutane, pentaerythrityl tetrachloride and some α,ω-dihalides to support this mechanism and to determine the scope over which it may be applied.

EXPERIMENTAL

Preparation of 2-methyl-2-(chloromethyl)-1,3-dichloropropane (I)

2-Methyl-2-(chloromethyl)-1,3-dichloropropane was prepared from 2-methyl-2-(hydroxymethyl)-1,3-propanediol (m.p. 188–190°) by treatment with thionyl chloride and pyridine according to the procedure followed by Urry[14] to give (I) in 87% yield. Treatment with alcoholic silver nitrate verified the absence of tertiary or allylic chlorine. Compound (I) was identical to that obtained by Urry based on boiling point, refractive index and IR spectrum.

Preparation of 4-methyl-4-pentenoic acid and its butyl ester

4-Methyl-4-pentenoic acid (III) was prepared by slowly adding 35 g (0.2 mole) of (I) dissolved in tetrahydrofuran (THF) to 9.6 g of flame-dried magnesium under a nitrogen atmosphere. When the addition was complete the mixture was refluxed for two hours, cooled, and slowly poured over powdered dry ice in a beaker cooled in a dry ice-acetone bath. The product was mixed with water and acidified with dilute HCl. The mixture was extracted with ether and dried over sodium sulfate. After removal of the ethers the residue was distilled under reduced pressure to give 12.5 g (66 %) of a colorless liquid b.p. 62–63° (1 mm), (n_D^{25} 1.4363) which indicated the presence of unsaturation both from its IR spectrum and from its ability to decolorize bromine water. (Found: C, 63.56; mol. wt. cryoscopic in benzene, 220; neutral equiv., 114. $C_6H_{10}O_2$ calcd.: C, 63.52 %; mol. wt. dimer. 228; neutral equiv., 114.) No volatile products could be collected during the formation of the Grignard, and when (II) was hydrolyzed with water and titrated potentiometrically with 0.1 N hydrochloric acid the results indicated that this magnesium compound was monofunctional and formed in quantitative amounts. It would appear therefore that the low yield of acid resulted from the carbonation procedure.

Butyl 4-methyl-4-pentenoate (IX) was prepared (*a*) from (III) and *n*-butanol by a trap reflux procedure using benzene as the entrainer and *p*-toluenesulfonic acid as the catalyst. Compound (IX) was a colorless liquid b.p. 46° (0.6 mm); n_D^{25} 1.4331; mol. wt. (cryoscopic) found 164, calcd. 170.

(*b*) Reaction of 52.4 g (0.2 mole) of triphenylphosphine (m.p. 79°) with 30 g (0.21 mole) of methyl iodide using the Wittig[15] procedure produced trimethylphosphonium iodide (m.p. 173–175° from benzene–alcohol) in quantitative yield. The trimethylphosphonium iodide was converted to the ylide, methylenetriphenylphosphorane, by reaction with sodamide according to the procedure of Bestmann[16]. The benzene solution of the ylide was mixed with (VIII) and the characteristic red color of the ylide disappeared when all of the ester had been added. The mixture was heated under reflux for two hours and allowed to stand overnight. The mixture was poured over water and extracted with ether. The ether extract was washed with dilute hydrochloric acid, water and dried over sodium sulfate. The ether was removed and the product distilled under reduced pressure to give (IX), b.p. 60–61° (1.6 mm), in 37 % yield. The identity of the product was established by comparison of its refractive index and IR spectrum with (IX) prepared by method (*a*). Saponification of (IX) gave (III).

Reduction of 4-methyl-4-pentenoic acid

4-Methylpentanoic acid (IV) was prepared by the catalytic hydrogenation of (III) in ethanol using Adam's catalyst[17]. The infrared spectrum of the compound was identical to that of an authentic sample of (IV). Preparation of the anilide of (IV) gave the correct melting point (110°) and no depression was observed when mixed with an authentic sample.

Preparation of 4-methyl-4-pentenanilide (XII)

4-Methyl-4-pentenanilide was prepared (*a*) by the addition of 0.1 mole of (II) to a cooled THF solution of 11.9 g of phenyl isocyanate. Fourteen grams of an oily product separated which was extracted with boiling water and after recrystallization from water gave colorless needles, m.p. 79–81°.

(*b*) Reaction of (XI) with aniline produced a crystalline derivative which had the same melting point as (XIIa) and produced no depression when mixed with it.

Oxidative degradation of (III)

The monoformate of (III) was prepared with formic acid and 30 % hydrogen peroxide[18]. The ester was hydrolyzed with base and the glycol (V) cleaved with lead tetraacetate in glacial acetic acid[19]. The degradation products were isolated as their 2,4-dinitrophenylhydrazones.

The 2,4-dinitrophenylhydrazones were subjected to ascending paper chromatography using isooctane–methanol and two spots were produced which indicated that the degradation products were (VI) and (VII). Fractional crystallization of the mixed phenylhydrazones gave a single product which showed no depression in melting point when mixed with an authentic sample of the 2,4-dinitrophenylhydrazone of (VI).

Preparation of 4-methyl-4-pentenophenone (X)

4-Methyl-4-pentenophenone was prepared (*a*) by reacting 0.2 moles of (II) with 20.6 g (0.2 mole) of benzonitrile in THF[20]. The ketone was isolated in 27 % yield by distillation under reduced pressure, b.p. 98–99° (2.2 mm); n_D^{25} 1.5267. Two derivatives of (X) were prepared: the 2,4-dinitrophenylhydrazone from ethanol–benzene, m.p. 178–179°, and the semicarbazone from 50 % aqueous ethanol, m.p. 128–130°.

(*b*) Treatment of (III) with thionyl chloride produced 4-methyl-4-pentenoyl chloride (XI), b.p. 153–155°. Reaction of 26.5 (0.2 mole) of (XI) with 0.22 mole of freshly prepared diphenylcadmium gave (X) when isolated by distillation under reduced pressure. The infrared spectra of the 2,4-dinitrophenylhydrazones of (Xa) and (Xb) were identical and the mixture produced no depression in melting point.

Preparation of the olefin

2-Methyl-1-butene (XIII) was prepared by hydrolysis of a cooled solution of (II) with wet THF. The low boiling fraction was removed by distillation. Fractional distillation showed it to boil 31–32° at atmospheric pressure. The refractive index (n_D^{25} 1.3771) and IR spectrum established it to be (XIII).

SUMMARY

In an attempt to study polymetallophilic organic compounds for use in the synthesis of chemical intermediates and new macromolecular systems, 2-methyl-2-(chloromethyl)-1,3-dichloropropane was reacted with magnesium. The reaction consumed two moles of magnesium per mole of compound and was shown to have produced 3-methyl-3-butenylmagnesium chloride which resulted from a skeletal rearrangement during the formation of the Grignard reagent. Carbonation of the Grignard reagent produced 4-methyl-4-pentenoic acid. The organomagnesium compound was also reacted with phenyl isocyanate to produce the corresponding anilide, with water to obtain 2-methyl-1-butene and with benzonitrile to form 4-methyl-4-pentenophenone. All of these compounds with the exception of the olefin have never been characterized and were therefore prepared by an independent method. A mechanism for the rearrangement is proposed.

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