Journal of Pharmaceutics and Drug Research
JPDR, 3(1): 233-237
www.scitcentral.com

ISSN: 2640-6152

Mini Review: Open Access

Reactions of Grignard Reagents with Carbonyl Compound: Unexpected Observations

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Received July 09, 2019; Accepted July 19, 2019; Published January 06, 2020

ABSTRACT

Treatment of the ketones **1, 5, 7** with Grignard reagents yielded the products **4**, **6**, **8**, respectively. The ester **9** with Grignard reagent followed by alkaline hydrolysis afforded lactones **10** and **11**, respectively. The lactones **14** and **17** on being treated with Grignard reagent furnished the diketone **15** and the chloroketone **18** respectively. The epoxide **19** with Grignard reagent produced diol **21** whereas the epoxide **22** suffered ring contraction yielding the aldehyde **23**.

Keywords: Methylmagnesium bromide, Methylmagnesium iodide, Phenylmagnesium chloride, t-Butyl magnesium bromide, Epoxides, Lactones

INTRODUCTION

The reactions of Grignard reagents with carbonyl compounds are well documented [1,2]. The resulting products have been utilized for the synthesis of many natural products and many bioactive organic compounds. Though there are many Grignard reagents in this this micro review only the reaction of methyl magnesium bromide (MeMgBr) and methyl magnesium iodide (MeMgI) with carbonyl compounds have been discussed. The reaction of phenyl magnesium bromide (PhMgBr) and t-butyl magnesum bromide (t-BuMgBr) have been discussed briefly. The Grignard reagents are represented as R-Mg-X, where R is alkyl, alkenyl, alknyl aryl or t-butyl group and X is Cl, Br or I. For an alkyl halide, the ease of formation of Grignard reagent is of the RI>RBr>RCl. The reaction is performed under anhydrous conditions. In case the reaction is sluggish, a small amount of iodine is added to start the reaction. The workup of the Grignard reagents (MeMgI, MeMgI) is usually done by adding an aqueous solution of HCl or H_2SO_4. When the products cannot tolerate acids, however a large volume of saturated aqueous ammonium chloride solution is added to dissolve all magnesium salts. The formation of the product depends on: (a) the nature of the functional groups present in the organic compound; (b) the kind of Grignard reagents used; and, (c) reaction condition. It has been observed that the Grignard reagents with some ketones, esters, epoxides, lactones have afforded unexpected product instead of expected normal product.

With ketone

(i) It is known that ketone with the Grignard reagents yield alcohol which on dehydration affords alkene. An interesting observation was recorded as result of the reaction of cyclopropyl ketone **1** with methyl magnesium bromide [3]. The resulting product **2** was treated with aqueous hydrogen bromide. The expected alcohol **3** was not obtained because the ring cleavage occurred by Br^- anion affording **4 (Scheme 1)**.

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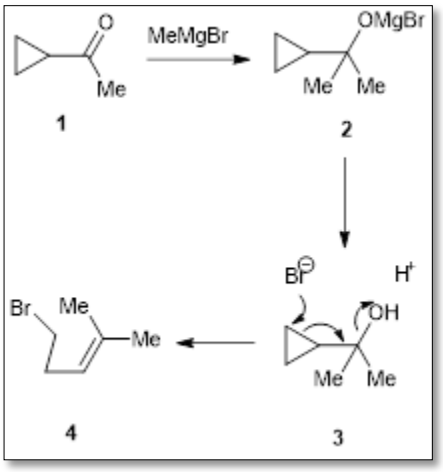
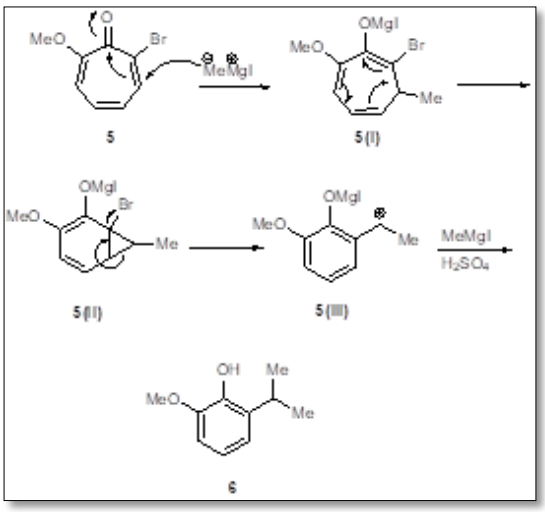
Citation: Banerjee AK, Arrieche D, Bedoya L, Vera WJ & Cabrera EV. (2020) Reactions of Grignard Reagents with Carbonyl Compound: Unexpected Observations. J Pharm Drug Res, 3(1): 233-237.



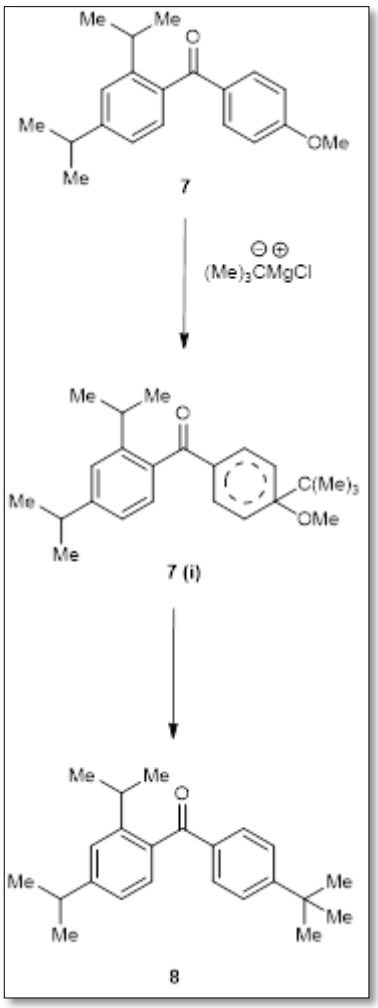
Scheme 1. Reaction of cyclopropyl ketone **1** with methyl magnesium bromide.

The reaction is an example of the ready rearrangement of cyclopropyl-carbinyl derivative to allyl carbonyl product [4]. The halide can react with Grignard reagent and used to repeat the process. In this way a chain of isopropenoids units can be built up. (ii) The rearrangement of 2-bromo-7-methoxytropolone **5** was observed when treated with methyl magnesium iodide and diluted sulfuric acid [5]. The normal product was not obtained. The resulting product was identified as 2-hydroxy-3-isopropylanisole **6 (Scheme 2)**. The intermediate **5(i)** is formed from a nucleophilic attack by the methylmagnesium iodide on the carbonyl carbon of the tropolone ring and this was followed by ring contraction yielding the intermediate **5(ii)**. The elimination of the halogen atom yields the anion **5(iii)** which reacts with another molecule of methylmagnesium iodide to afford the isopropylanisole **6.** The formation of **6** is an interesting example [6] of the rearrangement of the troponoid occurring by means of nucleophilic reagents.



Scheme 2. rearrangement of 2-bromo-7-methoxytropolone **5**.

iii) The reaction of the ketone [7] **7** with t-butyl magnesium chloride afforded an interesting product which was assigned to the structure **8**. The formation of **8** shows that due to steric hindrance the bulky Grignard reagent failed to attack the carbonyl group. The formation of **8** has been explained in **Scheme 3.** The Grignard reagent tert-butyl magnesium chloride group attacks the 4-methoxy group and forms the intermediate **7 (i)** which is finally converted (as shown in **Scheme 3**) into the compound **8**.

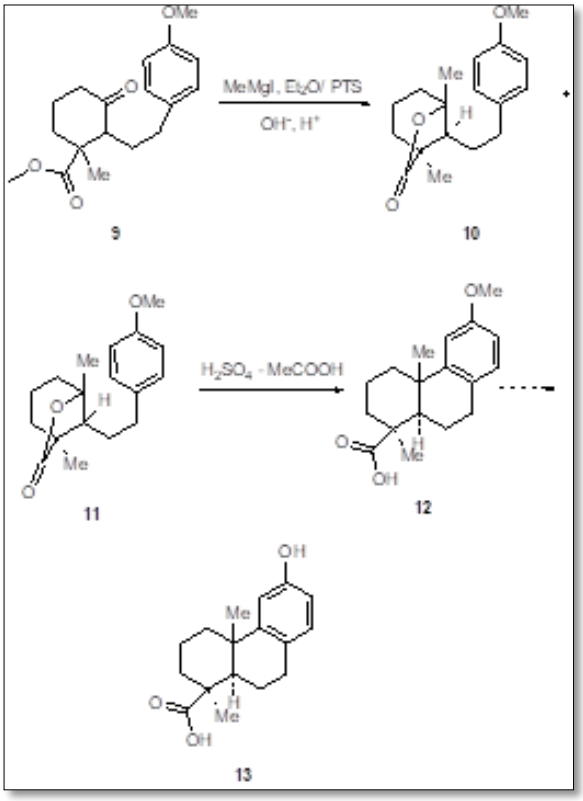


Scheme 3. Reaction of tert-butyl magnesium chloride group with the 4-methoxy group.

With ester

The reaction of the Grignard reagent with the ketoester **9** is very interesting [8]. The ketoester **9** on being treated with excess methylmagnesium iodide followed by heating with p-toluene sulfonic acid yielded a dense material which on partial alkaline hydrolysis and acidification with hydrochloric acid yielded a mixture of lactones **10** and **11.** The mixture of lactones on cyclization with sulfuric acid and acetic acid afforded 12-methoxypodocarpic acid **12.** The

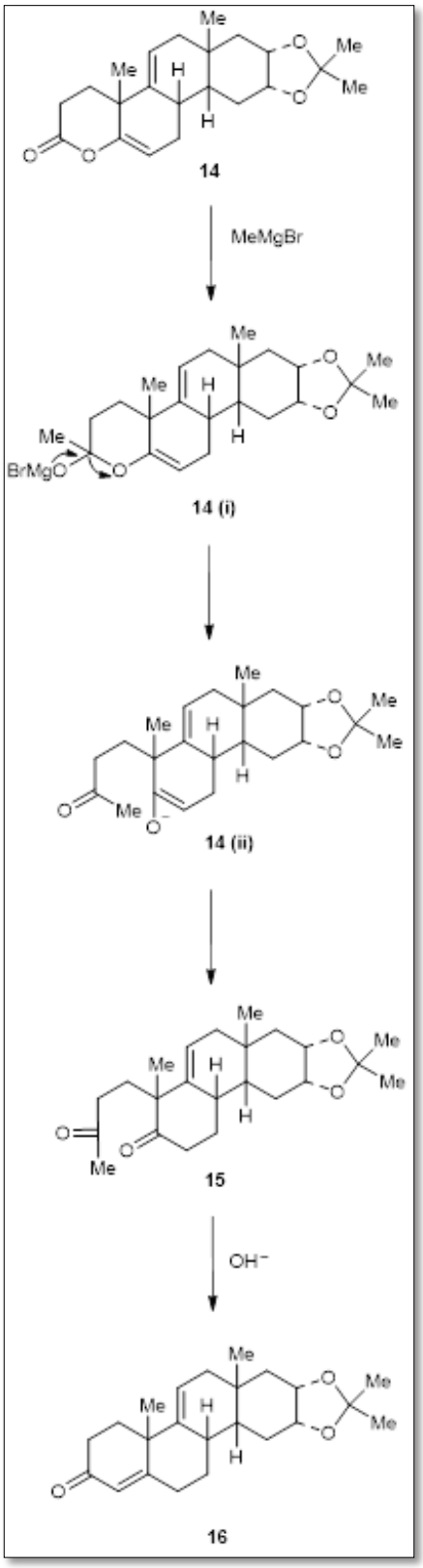
conversion of the acid **12** to (±) podocarpic acid **13** has already been reported [9] **(Scheme 4)**.



Scheme 4. Conversion of the acid **12** to (±) podocarpic acid **13**.

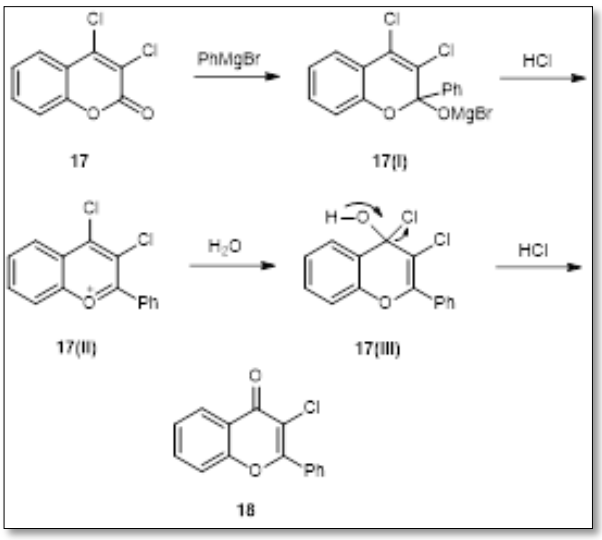
With lactones

Woodward et al. [10] observed that the enol lactone **14** can be easily converted to the diketone **15** by methylmagnesium iodide **(Scheme 5)**. The intermediate **14(i)** is formed by the reaction of the Grignard reagent with the lactone **14**. The ring cleavage occurred yielding the intermediate enolate anion **14(ii)** and finally to ketone **15** whose conversion to α, β-unsaturated ketone **16** was effected with base. It can be observed that a new method for the synthesis of an unsaturated ketone was developed by the reaction of the lactone with the Grignard reagent.



Scheme 5. Conversion of enol lactone **14** into the diketone **15** by methylmagnesium iodide.

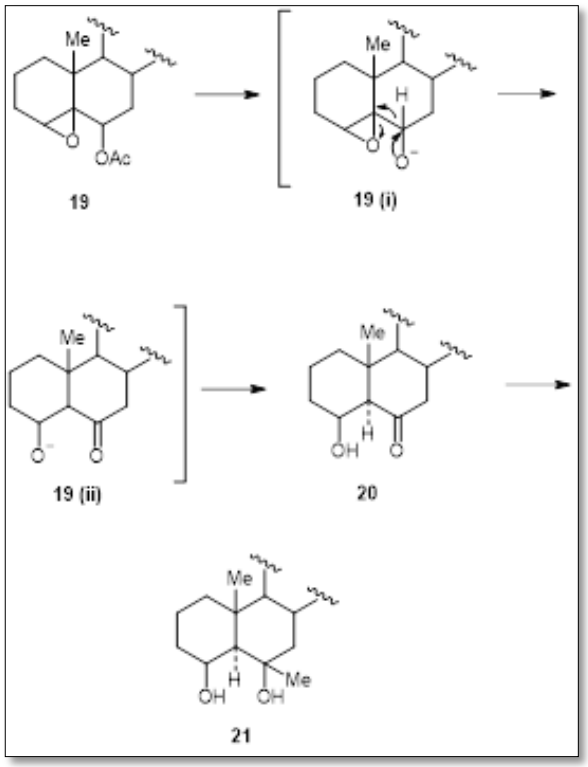
A very different result was obtained when the lactone **17** was treated with phenyl magnesium bromide [11]. The product obtained was identified as 3-chloroflavone **18 (Scheme 6)**. The mechanism of the transformation is described in **Scheme 6**. Phenyl magnesium bromide attacks the lactone **17** and resulting intermediate **17(i)** with HCl probably forms the intermediate **17(ii)** which is attacked by water at position **4** to form the intermediate **17(iii)** and finally the chloroflavone **18**.



Scheme 6. Treatment of lactone **17** with phenyl magnesium bromide.

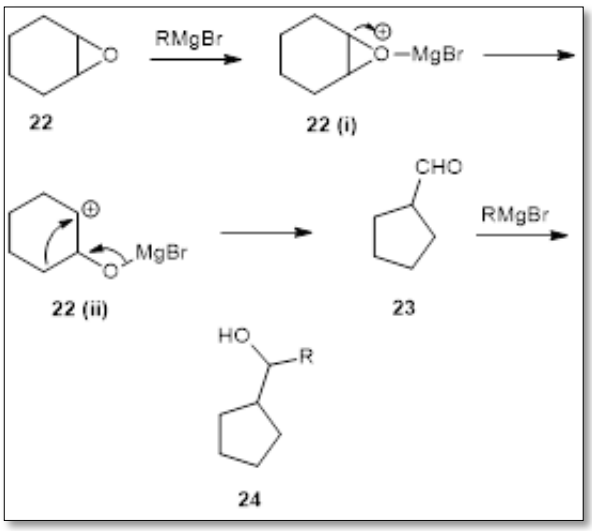
With epoxide

The epoxides can easily be cleaved by the Grignard reagents to yield alcohols. The known tendency for oxiranes to undergo rearrangement during Grignard reactions has been recorded [12]. Many steroidal epoxides have been cleaved by Grignard reagents to obtain alcohols. It is worthwhile to cite the work of Bull [13]. The epoxide **19** with methyl magnesium iodide afforded the β-alcohol **21 (Scheme 7)**. It can be observed that the proton attached to the acetate-bearing carbon atom cleaved the epoxide yielding the intermediates **19(i)** and **19(ii)** and finally afforded the β-ketol **20** which then underwent alkylation by the Grignard reagent to produce the diol **21**.



Scheme 7. Treatment of epoxide **19** with methyl magnesium iodide.

It has been observed that the some epoxides undergo cleavage along with contraction of rings [14]. Thus the epoxide **22** on treatment with Grignard reagent yielded the aldehyde **23** through the intermediate **22(i)** and **22(ii).** Further the reaction of the aldehyde **23** with Grignard reagent yielded the alcohol **24 (Scheme 8)**.



Scheme 8. Reaction of the aldehyde **23** with Grignard reagent.

The above mentioned examples convinced us that the formation of the final product by the Grignard reagent depends on the presence of functional group present in organic molecule. If the organic molecule contains more than one functional group then it is very difficult to expect normal product. Many examples can be cited which exhibit the formation of many unexpected products during the reaction of the Grignard reagent with organic compounds. In this short review due to the space limitation it is not possible to illustrate many examples.

ACKNOWLEDGEMENT

Dedicated with affections to the memory of Prof. Anselme JP, editor of the Journal, Organic Preparations and Procedures Internationals.

The authors gratefully acknowledge the collaborations of Mr. José Gregorio and Mr. Luis Mujica for literature references.

CONFLICTS OF INTEREST

The authors declare that there are not conflicts of interest.

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