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Grignard Reaction

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Overview

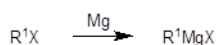
Source: Vy M. Dong and Faben Cruz, Department of Chemistry, University of California, Irvine, CA

This experiment will demonstrate how to properly carry out a Grignard reaction. The formation of an organometallic reagent will be demonstrated by synthesizing a Grignard reagent with magnesium and an alkyl halide. To demonstrate a common use of a Grignard reagent, a nucleophilic attack onto a carbonyl will be performed to generate a secondary alcohol by forming a new C-C bond.

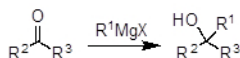
Principles

The Grignard reaction is a method for forming carbon-carbon bonds between alkyl/aryl halides and carbonyls like aldehydes, ketones, or esters. This Nobel-Prize-winning chemistry consists of two steps: Grignard reagent formation and subsequent Grignard addition onto a carbonyl to construct a new carbon-carbon bond. A Grignard reagent is an organometallic compound, specifically an organomagnesium compound. The synthesis of a Grignard reagent requires an alkyl or aryl halide (chlorides, bromides, or iodides) and magnesium. In this step, the electrophilic (an electrophile is electron deficient and accepts electrons) alkyl halide is transformed into a nucleophilic (a nucleophile is electron rich and donates electrons) carbanion-like compound. The second step of the Grignard reaction entails a nucleophilic addition of the Grignard reagent onto a carbonyl. After this step, a new carbon-carbon bond is formed and the carbonyl is transformed into an alcohol. It is important to perform both steps under moisture-free conditions otherwise the Grignard reagent used will react with water, and no desired Grignard or C-C bond formation results. The Grignard reaction is an important and widely used tool that allows synthetic chemists to take any alkyl or aryl halide and transform it into an organomagnesium compound, which can be used to construct carbon-carbon bonds.

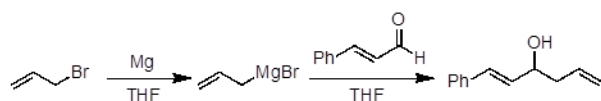
Grignard Formation



Grignard Addition



Procedure



1. Grignard Reagent Formation

1. Flame-dry a round bottom flask equipped with a magnetic stir bar.
2. Add magnesium (Mg, 1.1 equiv.) to the round bottom flask.
3. Add a small amount of iodine (I_2 , a few crystals). Addition of iodine is to help remove any MgO on the surface of the Mg. Removing MgO allows for Mg and the aryl/alkyl halide to come in contact and react. Sonication or addition of methyl iodide or 1,2-dibromoethane can also help with initiation.
4. Cool the reaction mixture to 0 °C with an ice-water bath.
5. Slowly add a THF (1 M) solution of allyl bromide (1 equiv.) to the round bottom flask with magnesium.
6. After adding the solution of allyl bromide, stir the reaction mixture for 3 h at room temperature.

2. Nucleophilic Addition

1. In a separate flame-dried round bottom flask, add *trans*-cinnamaldehyde (0.85 equiv.) and THF (0.5 M with respect to *trans*-cinnamaldehyde) and cool to 0 °C.
2. Slowly add the THF solution of the Grignard reagent (allyl-magnesium bromide) to the *trans*-cinnamaldehyde solution.
3. After the addition, warm the reaction mixture to room temperature by removing the ice-water bath and stir for 4 h.
 1. Monitor the reaction progress via TLC by looking for the disappearance of *trans*-cinnamaldehyde.
4. After reaction completion, cool the mixture to 0 °C with an ice-water bath.
5. Slowly quench the reaction with a saturated aqueous solution of ammonium chloride (NH_4Cl).
6. Transfer the mixture into a separatory funnel and extract the aqueous layer with ethyl acetate 3x.
7. Combine the organic layers and wash with water and brine (a saturated aqueous solution of NaCl).

8. Dry the organic layer with anhydrous MgSO_4 , filter, and evaporate the solvent via rotatory evaporation.
9. Purify the crude residue via flash column chromatography.

Results

The purified product should have the following ^1H NMR spectrum: ^1H NMR δ 7.23-7.39 (m, 5H), 6.60 (d, J = 16.0 Hz, 1H), 6.23 (dd, J = 6.4 Hz, 1H), 5.84 (m, 1H), 5.14-5.20 (m, 2H), 4.35 (q, J = 6.4 Hz, 1H), 2.37-2.43 (m, 2H), 1.9 (br s, 1H).

Applications and Summary

This experiment has demonstrated how to synthesize a Grignard reagent from an aryl/alkyl halide and how to use the Grignard reagent to perform a nucleophilic addition onto a carbonyl compound to construct a new carbon-carbon bond.

The Grignard reaction is widely applied in the synthetic chemistry world, and is used in university research labs, national laboratories, and pharmaceutical companies. Simple Grignard reagents are commercially available, but often times unique and specialized Grignard reagents are required. The Grignard reaction allows synthetic chemists to access the necessary compounds from aryl or alkyl halides. In addition to performing nucleophilic additions onto carbonyls, Grignard reagents can be used as nucleophiles in combination with a large variety of other electrophilic compounds. An example of a specialized Grignard reagent can be found in the synthesis of phorboxazole A, a natural product that exhibits potent anti-bacterial, anti-fungal, and anti-proliferative properties.

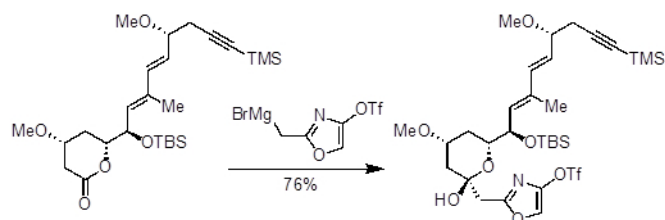


Figure 1. Phorboxazole A

Another way to generate Grignard reagents is via magnesium-halogen exchange. This method uses a premade Grignard reagent instead of using magnesium to generate the desired Grignard. The most commonly used Grignard reagents for magnesium-halogen exchange are *i*-PrMgCl and *i*-PrMgBr, both of which are commercially available. Magnesium-halogen exchange has been shown to exhibit broad functional group tolerance¹. As a result, this method has proven to be a useful way to generate highly functionalized Grignard reagents. Alkyl/aryl halides with functional groups that typically react with Grignard reagents can be used to make Grignard reagents via magnesium-halogen exchange. Esters, nitriles, and alkyl chlorides remain intact during magnesium-halogen exchange. In addition, iodides can selectively undergo magnesium-halogen exchange in the presence of bromides.

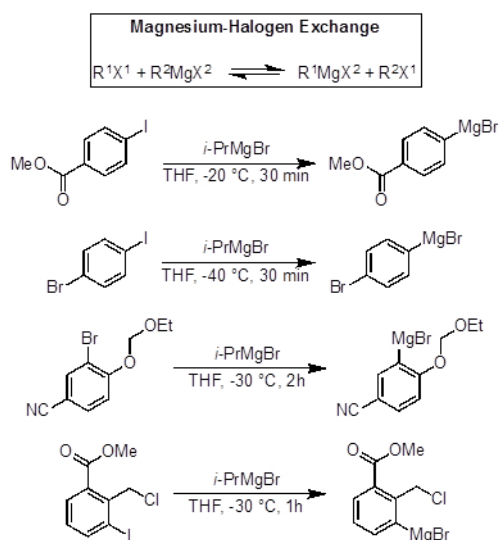


Figure 2. Magnesium-Halogen Exchange

Grignard reagents typically act as nucleophiles and add onto carbonyl compounds, but side reactions can occur depending on the nature of the Grignard and carbonyl used. A common side reaction is a Wurtz coupling, where the Grignard reagent couples to itself to form a dimer. Sterically bulky Grignards or carbonyls can make the nucleophilic addition challenging. Potential outcomes with sterically bulky substrates are the absence of an addition or reduction of the carbonyl via β -hydride transfer. The presence of enolizable protons in the carbonyl can also make nucleophilic addition challenging due to competitive carbonyl enolization. A common way to suppress these side reactions and promote

nucleophilic addition is to use lanthanide salts, especially CeCl_3 , as additives. Lanthanide salts are oxophilic (attracted to oxygen), and therefore they coordinate to the carbonyl oxygen and increase the electrophilicity of the carbonyl. It is expected that addition of cyclopentyl MgCl into cyclohexenone would give the tertiary alcohol, but instead the carbonyl is reduced to give the secondary alcohol. This side reaction can be suppressed in favor of the desired Grignard addition by adding LaCl_3 .

Lanthanide Salt Promoted Grignard Addition

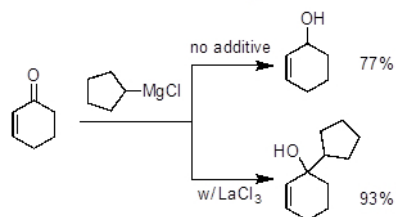


Figure 3. Lanthanide Salt Promoted Grignard Addition

References

1. *Angew. Chem. Int. Ed.*, **2003**, 42, 4302.