

Supporting Information

Generating Standard Operating Procedures for the Manipulations of Hazardous Chemicals in Academic Laboratories

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SOP EXAMPLE FOR CHEMICAL PROCESS/REACTION: GRIGNARD REACTION

A structured SOP for a chemical process should include a description of the process, directions for reaction set-up, the general procedure, and identification of hazards, procedures for eliminating or minimizing risks, emergency response for “what-if” cases, and waste management procedures (Fig. 1).

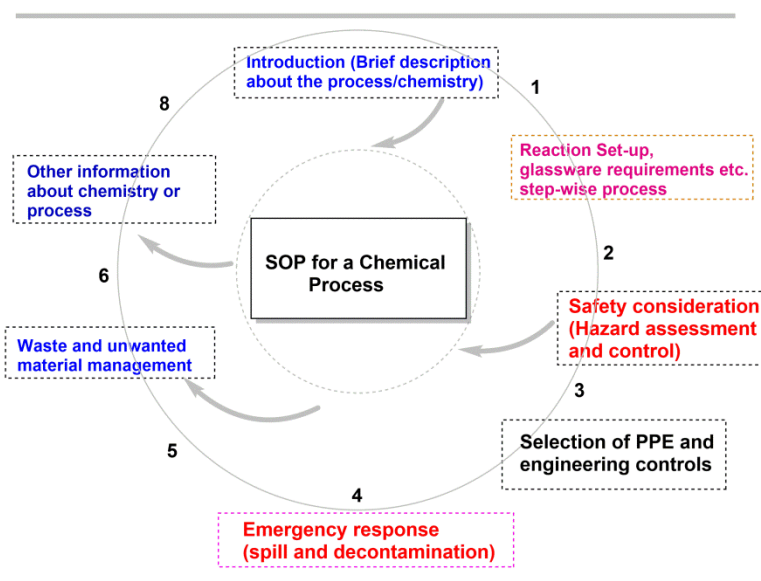


Figure 1: SOP Components for a Process SOP

The SOP would also define limitations on the quantities and types of materials to be used and would serve as a starting point for accessing significant changes to the experiment. It is imperative to consider the following before writing SOPs for chemical manipulations:

- A literature search (lessons learned database¹ from your institution as well as other institutions, ACS journals,² Synthesis Journal,³ and the Division of Chemical Health and Safety, DCHAS ⁴).
- Seek help from peers in your laboratory or from other groups in the department who are well versed in the experimental set-up and procedures.
- Review the experiment set-up, use of proper glassware set-up or a pressure vessel, heating, and cooling system.
- Review emergency plans using the RAMP (Fig. 2) method⁵⁻⁶.

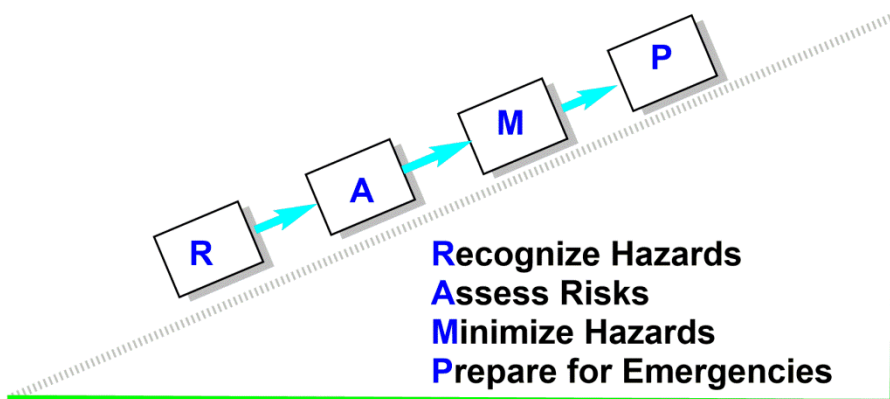


Figure 2: RAMP Method for Recognizing Hazards

Introduction/Objectives

A Grignard reagent (**GR**) is an alkyl- or aryl-magnesium halide.⁷ It is a nucleophile capable of forming carbon-carbon bonds with electrophiles (Figure 3). Grignard reagents are air- and moisture-sensitive; thus, handling these compounds requires the use of Schlenk line techniques or an inert atmosphere. Synthesis of a GR requires an alkyl- or aryl-halide and activated magnesium metal. Reactions are generally performed in ethereal solvents and are exothermic.⁸

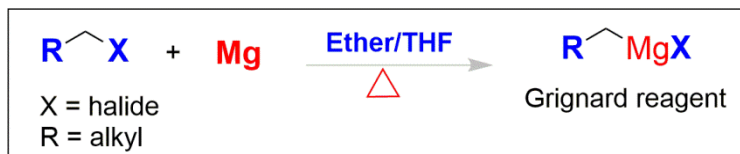


Figure 3: GR scheme

1. Reaction Setup

- Assemble glassware as shown in Figure 4. Select a vessel or a flask that is sufficient to hold the total volume of the solvent and substrate.

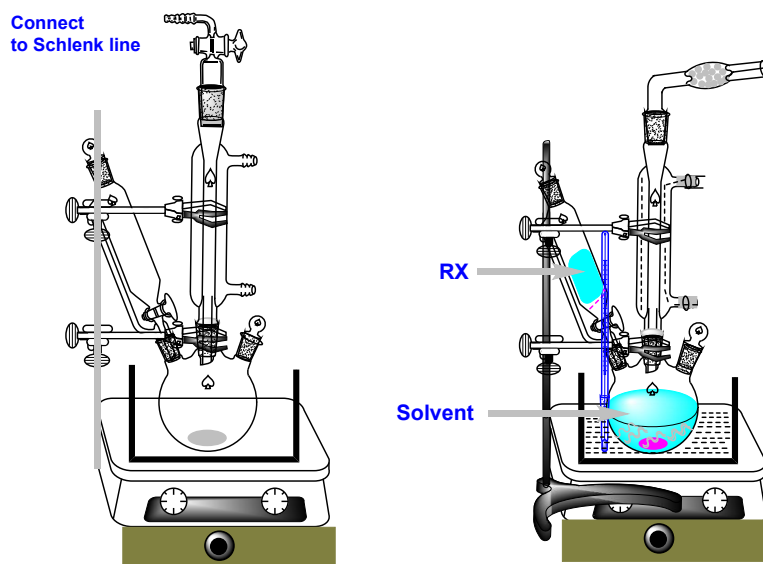


Figure 4: Reaction Set-up for a Grignard Reaction

Glassware Drying

- Glassware should be flame-dried or oven-dried and allowed to cool to room temperature under a vacuum or inside a glass desiccator.
- The large-size assembly can be dried using a Schlenk line vacuum and nitrogen gas by heating the reaction assembly (Fig. 5). After assembling the set-up, fill the vessel with nitrogen and leave it connected to nitrogen. The round bottom flask should be in an oil bath on a stirring hot plate. Attach a water line to a reflux condenser inlet of the reflux condenser; the outlet line should be secured to a drain.

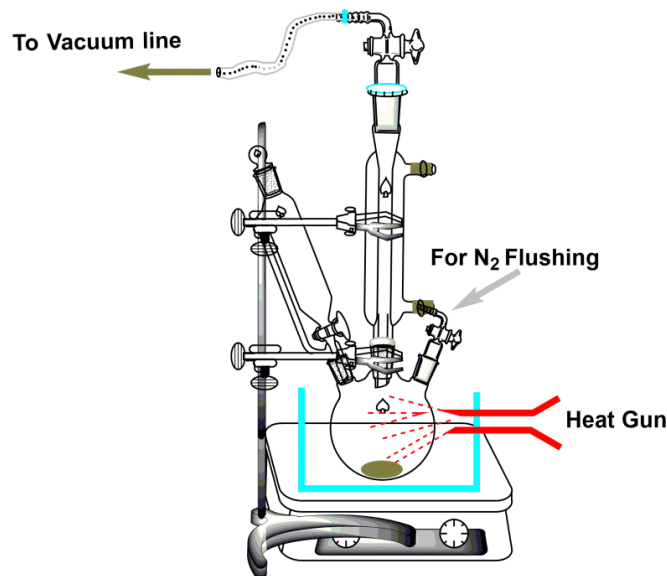


Figure 5: Glassware Drying Using a Heat Gun and Vacuum

- Required glassware includes a 3-neck round bottom flask equipped with a reflux condenser with a Schlenk line adapter, a pressure-equalizing dropping funnel, a stir magnet, a freshly prepared calcium chloride tube, and a stopper.
- Securely clamp the round-bottom flask and the reflux condenser to a ring stand or monkey bars.

2. General Use/Procedure

- Remove the stopper, add magnesium to the reaction vessel, and replace the stopper after the addition. **Note:** The reaction vessel should be under an inert atmosphere now and for the remainder of the reaction.
- Add dry solvent (diethyl ether or THF) to the reaction vessel. **Best Practice:** The solvent can be added through the dropping funnel which permits leak testing and checking the flow rate of the funnel.

- Activate the magnesium (Fig. 6). Typically, this is done by adding a catalytic amount of iodine (a few crystals) or a few drops 1,2-dibromoethane (remove the stopper and add through the neck of the flask, maintain the inert atmosphere).

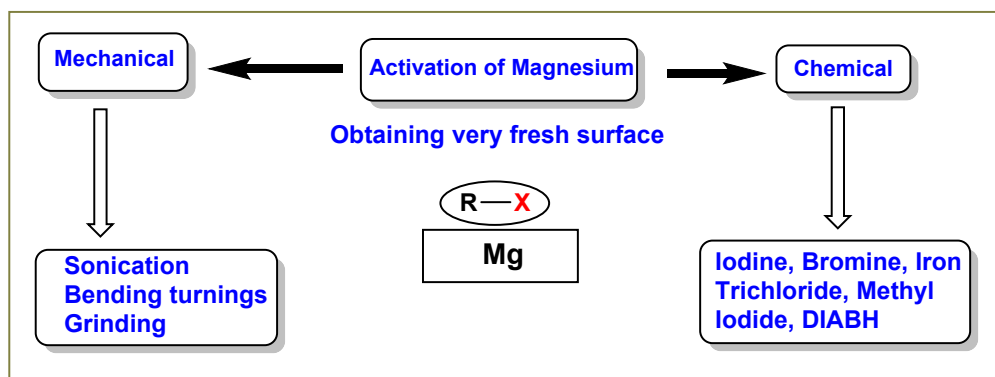


Figure 6. Activation of Magnesium Metal for GR Reaction

- Shut the stopcock of the dropping funnel that was used to add the solution of substrate (halide) to the flask, and add substrate to the same funnel as a solution in the same solvent. Open the stopcock of the dropping funnel and slowly begin to add the substrate to the activated magnesium.
- If the reaction is too vigorous, adjust the stopcock to slow the addition of substrate.
- Some Grignard reactions may need to be heated to drive the reaction to completion. Gently heat the oil bath to provide the needed heat.
- Reaction progress can be monitored by consumption of magnesium or by titrating aliquots.
- Once the reaction is complete, the Grignard reagent can be used for a reaction. Prepare a solution of the starting material under an inert atmosphere; add/or transfer the Grignard reagent to the starting material from the 3-necked flask using a filter cannula to separate unreacted Mg. Stir the material at ambient temperature until the all starting material is consumed. Once the reaction is complete, neutralize the remaining Grignard

reagent by slow addition of a saturated solution of ammonium chloride. This should be done at 0°C.

Safety Considerations

The major safety concern for Grignard reactions is fire. The reaction is exothermic and the magnesium, alkyl magnesium reagents and the solvent used are flammable.

Perform a thorough literature search about halide reactivity and your specific reagent before starting the reaction (some halides can produce explosive materials with Mg). Always perform the Grignard reaction in a properly functional fume hood. Use a flask for the Grignard reaction which is large enough to contain runaway vigorous reactions should they occur.

Best Practice The use of tetrahydrofuran (THF) with a large enough reflux condenser is recommended to prevent evaporation of the solvent. Halide (R-X) addition must be slow and controlled. Fast addition can cause a runaway reaction and product decomposition (Fig. 7).

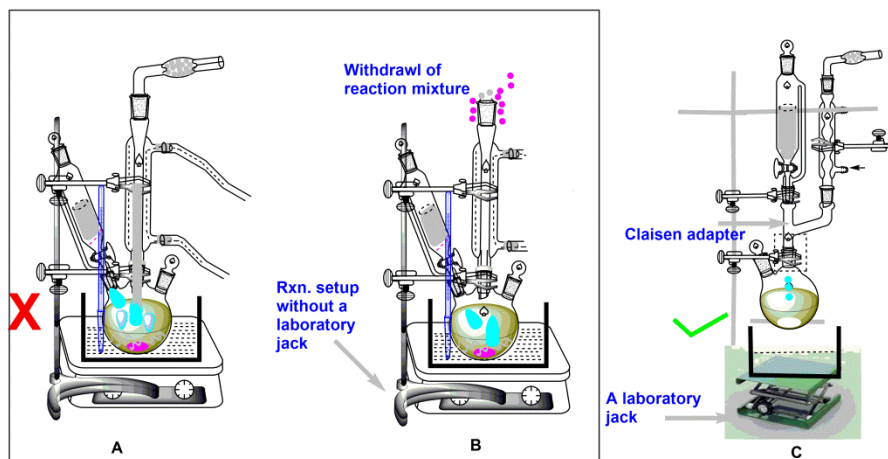


Figure 7. Use of a Laboratory Jack for the Grignard Reaction in Order to Control an Exotherm

If a reaction becomes too vigorous, turn off any heat, stop adding substrate, and make sure the reaction vessel is vented via a Schlenk line or an oil bubbler. Use of a laboratory jack can facilitate cooling by removing the flask from the oil bath, but do not try to cool the reaction

vessel too quickly as that may cause the glassware to fail. Monitor the reaction prudently and do not leave the reaction unattended.

3. Hazards and Controls

3a. Hazard Identification (What-if analysis)

GRs are flammable, corrosive and some are pyrophoric. GRs comprise considerable risk potential due to a large amount of heat released during the initiation of the exothermic reactions (Table 1) and the high reactivity of the Grignard reagents (200-380 kJ heat released per mole of Mg reacted). Fine magnesium powder is flammable and liberates flammable gas on contact with water. Several GRs are fast and exothermic in nature, carrying a risk of runaway if inadequately controlled.

3b. Hazard Analysis (Probability and Risk Matrix)

A hazard analysis should be conducted after recognizing the major hazards associated with the reaction. This analysis would include the reactivity of precursors, any cross-reactions, and the probability of a runaway reaction due to reagent instability, low ratio of solvent and Mg, poor heat transfer, and other circumstances (Fig. 8).

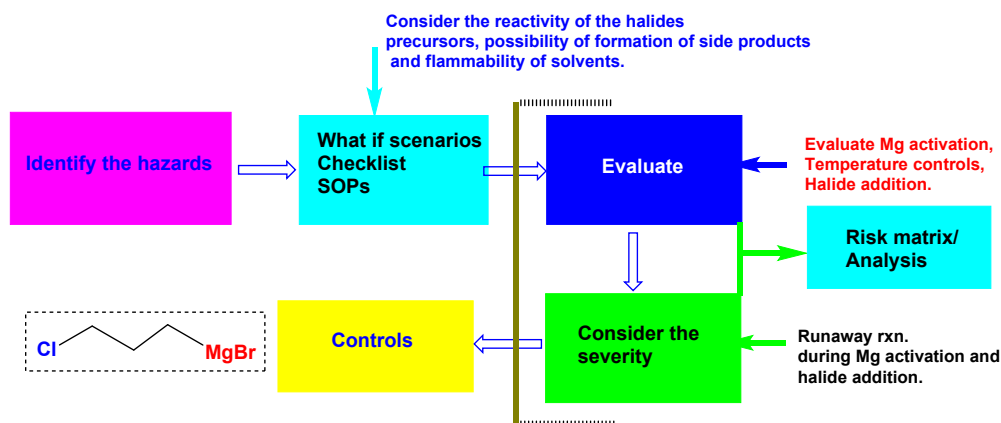


Figure 8. GR-hazard Assessment and Hazard Mitigations

Table 1: What-if Analysis Hazard Assessment⁹ for the Grignard Reaction

| | | |
|---|--|---|
| Division: Chemistry/Biochemistry | Description of Operation: Grignard Reaction | By: Tilak Chandra Date: 09/09/2020 |
|---|--|---|

| What if? | Answer | Result | Consequences | Recommendations |
|---|--|---|--|--|
| Glassware is not Moisture-free (improper drying) | Deactivation of Mg turnings, sudden initiation of rxn. | Difficult to initiate the reaction, and poor rxn. control | Loss of halide, chemical spill and a fire | Assembled glassware should be flame-dried under vacuum or being dried in an oven and allowed to cool to room temperature under vacuum before assembling. |
| Uncontrolled heating | High reflux rate | Sudden rxn. initiation, uncontrolled rxn. | Loss of halide and product | Use an effective and controlled heating system such as oil bath, sand bath and a lab jack. |
| Reaction flask size is too small to hold the complete rxn. volume in the event of sudden initiation | Discharge of rxn. content from vessel | Chemical spill | Fire and chemical exposures | Use a slightly larger size flask even for a small-scale reaction in order to contain the contents during the initiation step. All GR should be carried out inside a properly functional chemical fume hood. Use a glass containment dish beneath the reaction flask. |
| Mg turnings are not activated (dry) | Difficult to initiate rxn. | Use of excess activating reagent | Incomplete rxn., product loss, use of excess solvent, low yields | Use freshly activated Mg turning for the rxn. |
| Fast addition of halide to Mg turning | Excess heat is produced and uncontrolled rxn. | Difficult to control the rxn. temp. and possibility of discharge and a fire | Loss of halide and a fire | Halide (R-X) addition must be slow and controlled because fast addition will cause product decomposition and runaway rxn. Use a lab jack to remove oil bath. |

3c. Hazard Control

PPE: Safety glasses/goggles, gloves (nitriles/Nomex). Nitrile gloves are good for dexterity purpose but are combustible. Cotton or Nomex (preferred) laboratory coat.

Engineering Controls: Fume hood or blast shield (for vertical blast shield fume hood).

Administrative controls: Do not work alone if you are performing the Grignard reaction for the first time or while manipulating a large-scale GR.

3c. Emergency Response

Spills: For small spills, cover with sand or soda ash. For bigger spills **call 911** and notify others in the area.

Contact on clothing and/or skin: Remove clothing and rinse body thoroughly in emergency shower for at least 15 minutes. Seek medical attention.

Splashed into eyes: Immediately rinse the eyes and the inner surface of the eyelids with water from the emergency eyewash station for 15 minutes. Seek medical attention.

Fire: Use approved **class D** extinguishers or smother with dry sand.

4. Waste/Unwanted Material Disposal

Any unreacted Mg should be washed with water and placed in a “Recovered Magnesium” container. The aqueous solutions must be neutralized between pH 5.5-11 before disposing of the solution down the drain. The organic layers from the product should be collected in a halogenated or non-halogenated waste carboy.

***Note:** The information provided in this SI is the author’s opinion and does not represent the opinion of organizations where I worked or am working with. I elucidated my arguments from experience. This manuscript serves only as a guideline and is in no way intended to serve as the sole training source for a procedure, method or task. All references or mention of commercial products, trade names, trademarks, manufacturers, distributors or otherwise, are meant to be examples and do not represent endorsement of a particular product or service.*

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