Developing SOPs for Hazardous Chemical Manipulations

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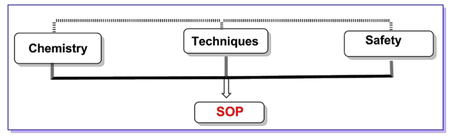
INTRODUCTION

Standard operating procedures (SOPs) are critical for high-risk chemical processes and manipulations involving pyrophoric, toxic or self-reactive chemicals and/or energetic materials. The SOP development process provides an opportunity to perform a hazard assessment, determine the reaction set-up (glassware assembly) requirements, identify unsafe conditions and determine the proper management plan for the unwanted materials. A well thought, step-wise documented SOP is useful for training new students and enhancing safety in the lab. Here we use Grignard reaction as an example for how to develop an effective SOP.

A well thought designed SOP should start from a clear objective and a brief description of the chemistry and manipulations. The following items should be included in a SOP involving a reaction or a chemical process.

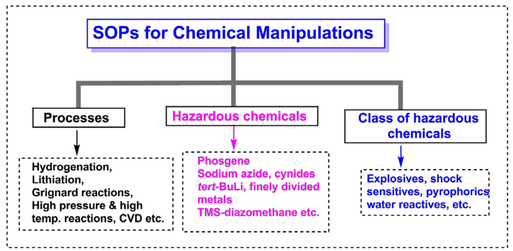
- Brief introduction about the rxn. and process
- Reaction set-up (assembly)
- Brief step-wise procedure
- Safety considerations
- Hazard identifications and controls
- Emergency planning and response
- Spill management and decontaminations
- Reagent storage and product handling
- Waste/unwanted material management

Components of SOPs



Mainly, three types of SOPs can be generated: chemical processes, hazardous chemicals and class of hazardous chemicals.

Categories of SOPs



Example SOP (Grignard Reaction)

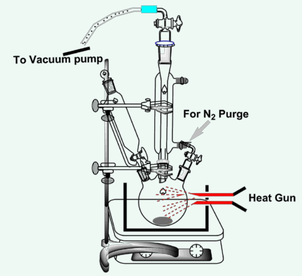
1. Introduction: A Grignard reagent (**GR**) is an alkyl- or aryl-magnesium halide. It is a nucleophile capable of forming carbon-carbon bonds with electrophiles. Grignard reagents are air- and moisture-sensitive. Handling these compounds requires the use of Schlenk line (SL) techniques. Synthesis of a Grignard reagent requires an alkyl- or aryl-halide and activated magnesium metal. Reactions are generally performed in ethereal solvents and are generally exothermic.

2. Reaction Set-up: Reaction glassware should consist of a 3-neck round bottom flask equipped with a reflux condenser with a Schlenk adapter attached, 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.

Best Practice: Glassware should be flame-dried under a vacuum or assembled after being dried in the oven and allowed to cool to room temperature under a vacuum.

Grignard Reaction Scheme

Large-size glass assembly drying for GR



3. General use/procedure

Remove stopper and add magnesium to the reaction vessel, replacing the stopper once complete.

Note: The reaction vessel should be under an inert atmosphere now and for the remainder of the reaction. Add dry solvent to the reaction vessel.

Best Practice

- The solvent can be added through the dropping funnel allowing for leak testing and checking the flow rate of the funnel.
- Activate the magnesium using appropriate methods.
- Slowly add the substrate to the activated magnesium by opening the stopcock of the dropping funnel. If the reaction is too vigorous, slow the addition of substrate.

Hazard Assessment (What if Analysis)

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 uncontrolled rxn.	Loss of halide, chemical spill and fire	Glassware should be flame-dried under vacuum or assembled after being dried in the oven and allowed to cool to room temperature under vacuum.
Uncontrolled heating	High reflux rate	Sudden rxn. initiation, uncontrolled rxn.	Loss of halide and product	Use an effective and controlled heating system.
Reaction flask size is not enough to hold the 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. Use a glass dish beneath the reaction flask.

4. Safety considerations

The major safety concern for Grignard reactions is fire due to an **uncontrolled reaction**. Magnesium, alkyl magnesium reagents and the solvent used for these reactions are flammable.

- Perform a thorough literature search about halide reactivity and reagent before starting the reaction (some halides can produce explosive materials with Mg).
- Use a right size flask for the GR in order to contain the runaway reaction/vigorous reaction.
- **Best Practice:** Use THF as a solvent and have an effective reflux condenser to prevent evaporation of the solvent. Halide (R-X) addition must be slow and controlled because fast addition will cause product decomposition and a runaway reaction.
- If a reaction becomes too vigorous, turn off any heat, stop adding substrate and make sure the reaction vessel is vented through an SL bubbler.
- Do not try to cool the reaction vessel quickly, as that may cause the glassware to fail.

KEY POINTS: GRIGNARD REACTIONS
Reaction nature: Heterogeneous
Physical Hazards: Exothermic, Runaway
Reaction Initiation: Difficult, delayed initiation
Formation of side products: Cross coupling
Difficult to monitor: Moisture sensitive

Hazards and Control

5a. Hazard identification

GRs are flammable, corrosive and some are pyrophoric. The major safety concern for Grignard reactions is fire due to an uncontrolled reaction. Magnesium, alkyl magnesium reagents and the solvent used for these reactions are flammable.

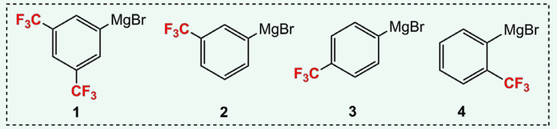
Reports from Literature: Explosion during Grignard Reaction/Manipulations

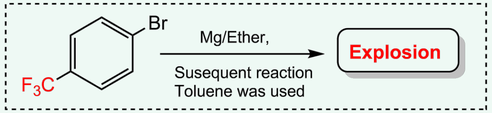
Note 1. It is well recognized that phenyl Grignard reagents containing CF_3 group in ortho, meta or para positions to chlorine or bromine can unexpectedly detonate on synthesis. It is important to emphasize the danger in making such Grignard reagent. Synthesis **of *p*-trifluoromethylphenylmagnesium** chloride on a commercial scale resulted in a violent explosion resulting in the destruction of a chemical plant and loss of life.

The following compounds exhibited significant exothermic activity under DTA Differential

Pfizer scientists reported a violent explosion of **3-(trifluoromethyl) phenyl magnesium** bromide resulting in extensive laboratory damage.

Unstable Grignard Reagents





Causes for Runaway Reactions During GR Preparation
1. Low ratio of solvent and Mg
2. Inadequate reaction stirring due to content viscosity
3. Poor heat transfer
4. Complex formation with solvent
5. Reagent instability

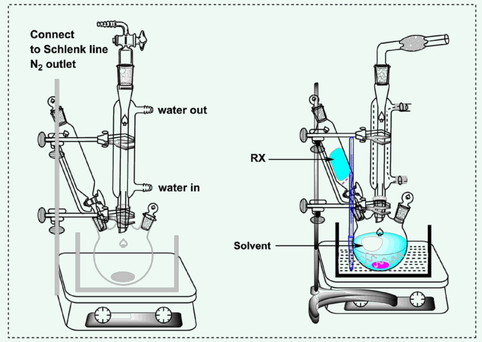
5b. Hazard control

PPE: Safety glasses/goggles, cotton lab coat, gloves (nitriles/Nomex). Nitrile gloves are good for dexterity purposes but are combustible.

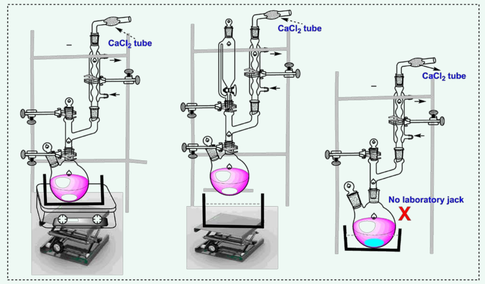
Engineering Controls: Chemical fume hood, blast shield when appropriate.

Administrative controls: If possible do not work alone when performing a large-scale reaction/or if you are performing a Grignard reaction for the first time.

Typical set-up for the Grignard Reaction



Heat Control (Use of a Laboratory Jack and Cold Condenser)



CONCLUSIONS

- SOPs shall be written by laboratory personnel having the **most experience** and knowledge and who are routinely involved in the **experimental process.**
- SOPs are useful tools when developing hazard assessments and training new students in the lab.
- Hazards identifications and their mitigations are critical for any SOP development process.

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