FEATURE

Hazards associated with laboratory scale hydrogenations

We report hazards associated with laboratory scale hydrogenations and the best practices for handling catalyst and hydrogen with three case studies. Fire, runaway reactions and explosions are commonly associated with hydrogenations due to the involvement of pyrophoric catalysts, hydrogen, flammable solvents and pressure. Laboratory hydrogenation methods as well as procedures to minimize hazards associated with catalyst and hydrogen are presented.

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INTRODUCTION

Catalytic hydrogenations are extremely useful for chemical transformations on small and large industrial scales. Various functional groups (C=O, NO_2, C=C, etc.) are reduced using hydrogen over suitable catalysts such as Pd, Pt, Rh, Ni, and Ru at ambient and/or elevated pressure.[1–6] The nature of the catalyst, purity of substrates, temperature, pressure, contaminants in the substrate, instability of intermediates, and solvents affect hydrogenation processes. The major safety concern for any hydrogenation reaction is fire and explosion due to the pyrophoric[7,8a,b] nature of the catalyst, reagent, substrate, intermediate instability, and use of the flammable solvents, hydrogen and pressure (Figure 1). The primary hazard associated with any form of hydrogen is inadvertently producing a flammable mixture, leading to a fire or detonation when exposed to air, oxygen, or sparks. Thus applying a systematic approach of risk analysis is critical for small as well as large-scale laboratory hydrogenations.

Catalytic hydrogenation of nitro compounds (Figure 2) is an economical route[2,9–12] for generating pharmaceutical intermediates at laboratory and industrial scales. Such reductions via hydrogenation are a well-defined class of reactions with high hazard potential.[13] Substrate impurities, the wrong choice of catalyst, contaminated hydrogen (carbon dioxide, carbon monoxide and hydrocarbons) and low concentration of catalyst are major contributing factors for the runaway reactions during hydrogenation of the nitro groups.

The reduction of nitro compounds requires higher temperatures and use of alcoholic/flammable solvents. Evaluation of operating procedures for the apparatus and a thorough inspection of reaction vessels are critical before manipulating any high pressure experiment.

A proper hazard assessment such as a literature search about substrate/intermediate reactivity, catalysts and solvent effects should be conducted for preventing runaway reactions associated to large scale and high pressure hydrogenations. Large scale reaction success also depends on the hands on experience of researchers. Standard operating procedures (SOPs) developed by a subject matter expert for the hydrogenations should be used for training new students and researchers. Proper handling of catalysts is critical due to high reactivity before and after introducing hydrogen. Existence of any impurity or colored impurity in substrate can inhibit the catalyst activity resulting in partial reduction of the substrate and occasionally in a run-away reaction. Substrates should be completely purified prior to subjecting them to hydrogenations. Hydrogenation reactions are largely exothermic in nature and can eventually increase overall pressure inside the vessel.

LABORATORY HYDROGENATIONS AND HAZARDS

The primary hazard associated with any form of hydrogen is inadvertently producing a flammable mixture, leading to a fire or detonation (Figure 1). Use of hydrogen, pyrophoric catalyst, flammable solvents and generation of in situ unstable intermediates are the main safety concerns during laboratory hydrogenations. Laboratory scale hydrogenations are mostly carried out using a round bottom flask (ambient pressure), balloon method, suitable pressure vessels, shakers[14,15] (Figure 3), or using a continuous-flow hydrogenation (H-cube). Understanding properties of hydrogen, catalysts, their manipulations and hands-on experience[16,17] is critical for a successful hydrogenation at both small and large scales. Polar solvents (water) and low flammable solvents are preferred over non-polar and flammable solvents to prevent flash fires during catalyst addition and during spent catalyst isolation. If used properly, water generally

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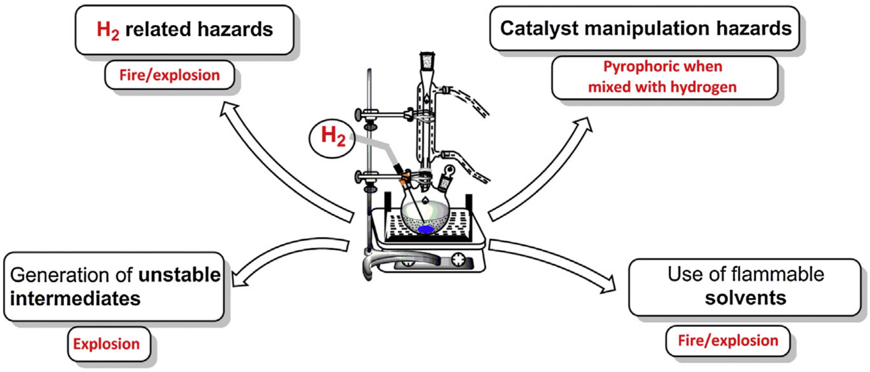

Figure 1. Hydrogenation hazards.

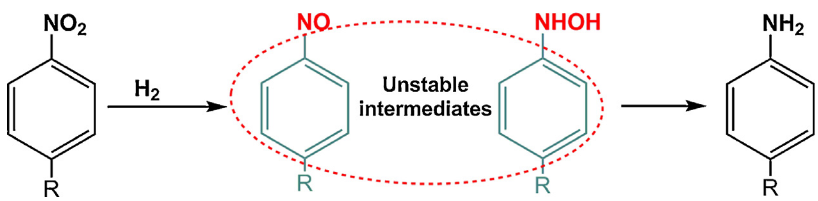

Figure 2. Formation of unstable intermediates during catalytic hydrogenations of nitro compounds.

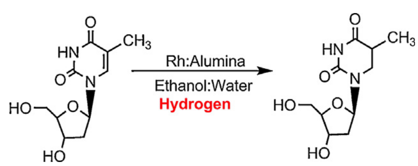

Figure 3. Ambient pressure hydrogenation of thymidine.

keeps the catalyst wet during transfer and filtration. For any hydrogenation reaction, flask and other glassware should be crack free, intact and free of contamination. A properly functional chemical fume hood or designated area for hydrogenation should be used to avoid the accumulation of hydrogen inside the lab. Use of open heating systems, such as oil baths and heating mantles should be circumvented to prevent flash fires. Uses of a water bath, sand bath or heating blocks are safer options.

Ambient Pressure Hydrogenation

Ambient pressure hydrogenations[18,19] (Figures 3, 4a and 5) are frequently used in laboratories and generally safer to manipulate at smaller and larger scales in a properly functional chemical fume hood using a suitable glass assembly (condenser, round bottom flask, cannula, septum and rubber tubing). An ambient pressure hydrogenation set-up is shown in Figures 4a and 6.

Although hazards associated with the catalyst, hydrogen and solvents still persist during ambient pressure hydrogenations, explosions associated with pressure are unlikely. In this method a round bottom flask is equipped with a condenser and a bubbler (needle) for hydrogen supply; the same needle is used for nitrogen purging. Hydrogen is directly bubbled from a cylinder (equipped with low flow regulator) by placing a Tygon tube and a cannula into the reaction mixture, comprising a catalyst and a substrate.

Loss of the solvent from the reaction is prevented using a cold-water condenser (Figure 4a). This is critical for elevated temperature reactions. Solvent and catalyst loss should be monitored while purging the reaction mixture. Solvents such as methanol and ethanol will escape from the reaction mixture due to hydrogen purging. There is always a possibility of an explosion from the catalyst that was converted into dry powder adsorbed with hydrogen. During transfer, a dry catalyst will disperse into air and around the flask if nitrogen flow is not regulated. Aqueous solvents (water and water: alcohol mixtures) are preferred over organic solvents for hydrogen bubbling due to their high boiling point and low flammability.

A cold condenser is required to avoid a quick evaporation of the solvents from the reaction. A blanket of inert gas can also be supplied, using a funnel, over the beaker containing the solvent and catalyst being transferred to the reaction vessel (Figure 5).

Hazards

Ambient pressure hydrogenations are the safest among all hydrogenations if conducted using a proper SOP and reaction set-up inside a chemical fume hood. Hazards related to pressure are generally eliminated when hydrogen gas is bubbled through a reaction mixture at ambient pressure. Also, ambient pressure hydrogenations are easy to monitor using TLC, GC and HPLC, and reaction aliquots which are withdrawn easily without dis-assembling the reaction set-up. Although hazards associated with the catalyst and hydrogen are still present, uncontrolled reactions are less likely. Analyzing planned reactions to identify hazards[16] and determining appropriate controls are critical for all hydrogenation reactions in laboratory. The "What if strategy"[20] (Table 1) developed by the American Chemical Society's Committee on Chemical Safety's can be employed to understand hazards associated with laboratory hydrogenation at various steps. Table 1 highlights some of the safety issues associated with ambient pressure hydrogenations; however various factors such as reaction scale, catalyst nature, substrate and solvent should be taken into consideration during a hazard assessment.