

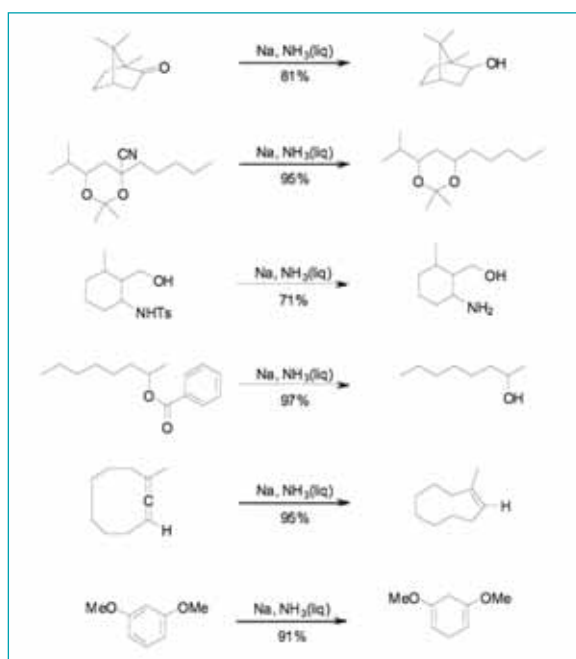


Making chemical reductions safer

Dissolving metal reductions are classic organic synthesis reactions but the hazards associated with such reactions present many safety problems. **Paul Vogt**, of SiGNa Chemistry, reveals a safer, alternative technology

Sodium metal is a powerful one-electron reductant, and solutions of sodium in ammonia, in which a metal cation and solvated electron are formed, have been used to reduce a large variety of functional groups.¹ Reductions using sodium or other alkali metals as the electron source represent some of the most important synthetic transformations in organic chemistry. The dissolving metal reductions that have been studied using sodium metal include, but are not limited to, ketone reductions,² decyanation,³ detosylation,⁴ ester reduction,⁵ allene reduction⁶ and Birch reductions⁷ (Scheme 1).

Dissolving metal reductions have also been used in the preparation of pharmaceutically relevant compounds, specifically vitamins and steroids. Some of the APIs that have been made by this methodology are; Allystrenol, Tibolone, Spironolactone, Medrogestone, Lynestrenol, and Epicillin.⁸

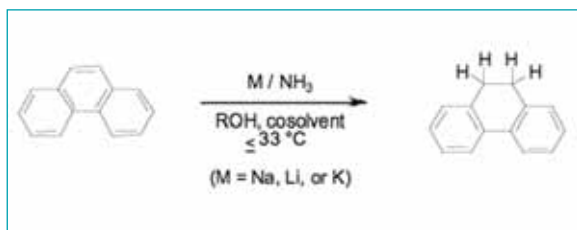


Scheme 1: Examples of sodium dissolving metal reductions

Despite their great utility, dissolving metal reductions have several less desirable attributes that limit their use, particularly on a large scale. Primary concerns centre on safety considerations associated with the toxicity of liquid ammonia, the hazard of cryogenic temperatures and the dangers associated with the handling of metallic alkali metals.⁹

Ammonia is a colourless gas that is strongly alkaline, highly corrosive and irritating to the skin, eyes and respiratory system.¹⁰ Ammonia has a characteristic pungent odour and is detectable by the average person at levels as low as 5 parts per million (ppm). The current recommended exposure limit for ammonia is 25 ppm, 8h time-weighted average. At 400 ppm, people experience immediate throat irritation, at 700 ppm immediate irritation to the eyes occurs, and exposure to levels greater than 1,700 ppm causes repeated coughing and can be fatal.¹¹

The boiling point of ammonia is -33°C. Thus, very cold temperatures are required when ammonia is used as the reaction solvent. If the temperature rises during the reaction or if cooling fails, there is a risk of over-pressurising the reaction vessel and a subsequent accidental release of ammonia. It is essential to eliminate all leaks, install suitable alarms, and provide excellent



Scheme 2: The Birch reduction

Example 1: Birch reductions using stabilised alkali metals

Of all dissolving metal reductions, the Birch reduction is arguably the most studied. The Birch reduction¹ is an alternative to hydrogenation that yields cyclohexadienes, and is one of only a few methods that can readily convert aromatic synthons into alicyclic structures. Consequently, it has the potential for widespread use in the synthesis of drugs and complex natural products. The full scope and limitations of this method were primarily expanded through the efforts of A. J. Birch, hence it now bears his name (Scheme 2).¹²

SiGNa has developed a safer and far more convenient modification of the classic Birch reduction that avoids the use of liquid ammonia and cryogenic temperatures. SiGNa's modification utilises Stage I sodium in silica gel, Na-SG(I), which is a more convenient and safer form of metallic sodium than either lump sodium or sodium sand.

SiGNa materials can be weighed out in open air without loss of reactivity and allow for a safer quench and post-reaction work-up procedure. The reduction of phenanthrene is one of many examples of a Birch reduction using stabilised alkali metals in the reaction (Scheme 3).

In a typical procedure, phenanthrene and Na-SG(I) are charged into a reactor and stirred under an inert atmosphere.

Scheme 3: Reduction of phenanthrene

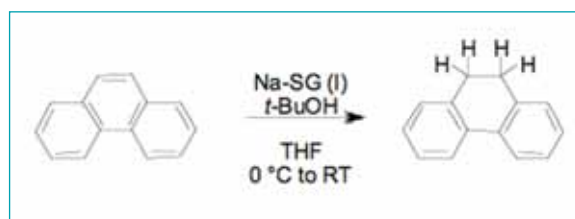


Table 1: Products and yields obtained from Birch reactions using NA-SG(1)

THF is added, and the slurry is cooled to 0°C. The proton source, tert-butanol, is added in one portion and the reaction is allowed to warm to room temperature. The desired product is

Starting Material	Product	Yield
		89%
		87%
		68%
		85%
		94%
		91%

ventilation near the equipment handling ammonia.

Hazards associated with the use of cryogenic gases/liquids include: asphyxiation, which occurs when the air necessary for the support of life is displaced; frostbite; freezing burns; and destruction of tissue. The dispensing areas need to be well ventilated, since cryogenic gases can make materials like plastic and rubber become brittle and fracture under stress, and can build up tremendous pressures in a closed system.

Sodium reacts vigorously with water and forms hydrogen, which is highly flammable. Sufficient heat is released when sodium metal reacts with water, causing the hydrogen to ignite and the sodium metal to melt. In this scenario, it is possible for liquid sodium in contact with water to react in a "fire-cracker" fashion, suddenly ejecting small droplets of molten sodium into the surroundings. Sodium can cause serious permanent damage if it gets into the eyes, since it reacts with the liquid present to generate concentrated sodium hydroxide, which is very destructive to living tissue.

stabilised alkali metals

Recently, SiGNa Chemistry has developed a technology for encapsulating alkali metals into nano-structured porous oxides, such as silica gel and alumina. Encapsulation reduces the dangers associated with the handling of alkali metals while retaining the reducing power of the metal. Sodium and sodium-potassium alloys in silica gel (generally M-SG; Na-SG, Na₂K-SG, and K₂Na-SG) are free-flowing, non-pyrophoric solids that are easy to handle in the lab, pilot plant, and commercial manufacturing facility. They are easy to produce with a loading of up to 40 wt% alkali metal.

The powders can be utilised in both batch and continuous processes at ambient temperatures and pressures and do not require the use of liquid ammonia. The by-products and waste-streams associated with these materials are non-toxic and environmentally safe (sodium silicate). A number of synthetic applications have been found for alkali metals in silica gel, validating their use in safer, sustainable syntheses. Three examples given below demonstrate the benefits of using stabilised alkali metals over traditional methods.

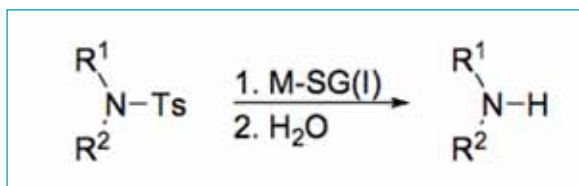


The powders can be utilised in both batch and continuous processes

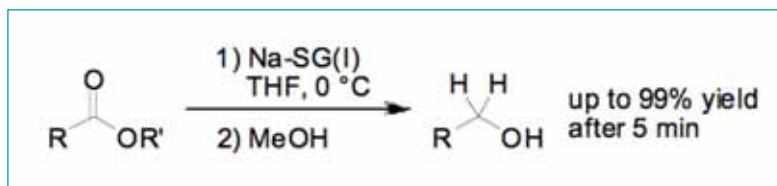
isolated in 60% yield after an aqueous work-up. Note that a Birch reduction using SiGNa materials proceeds without the need for liquid ammonia, cryogenic temperatures or pyrophoric reagents. This method has been used to produce a variety of structurally diverse Birch products as shown in Table 1, again without the use of ammonia, cryogenic temperatures, or sodium metal.

Example 2: Cleavage of toluenesulfonamides using stabilised alkali metals

SiGNa also has reported a novel method to cleave toluenesulfonamides to amines using stabilised alkali metals



Scheme 4: Cleavage of toluenesulfonamides using M-SG(I)



Scheme 5: Ester reduction using Na-SG(I)

Starting Material	Product	Yield
		96%
		81%
		83%
		79%
		85%
		99%

Starting Material	Product	Yield
		96%
		95%
		92%
		99%
		95%

(Scheme 4). Specifically, we have used M-SG (Stage I) where M is Na or Na2K.¹³

As described below, treatment with M-SG is a mild and general solution process to desulfonate protected amines. Various sulfonamide substrates were investigated to explore the scope of M-SG desulfonations (Table 2). The reactions were conducted in ethereal solvents, typically in THF with 2.5 - 5 equivalents of Na2K-SG(I) at room temperature over 8 hours and subsequently quenched with water. Detosylation with Na2K-SG(I) tolerates phenyl and ether moieties and is successful for both cyclic and acyclic amines.

Example 3: Ester reduction using stabilized alkali metals

Recently, SiGNa has developed a procedure for ester reduction using Stage I sodium in silica gel, Na-SG(I), as a far

safer alternative to the classic procedure using sodium metal in ethanol (Scheme 5).¹⁴

Table 2: (top) The results of some M-SG desulfonations
Table 3: (above) Primary alcohols are obtained in ester reductions using Na-SG(I)

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Before the advent of widely available hydride reagents, reduction of esters to primary alcohols was generally performed with alkali metals in ethanol (Bouveault-Blanc reduction).¹⁵ Because of the hazards associated with alkali metal handling and the vigorous reaction conditions, this procedure has become much less useful. Classic procedures for ester reduction using sodium metal involve rapid mixing of the ester, sodium metal, and alcoholic solvent at elevated temperatures, which can cause excessive foaming and even fires.

SiGNa has developed an improved procedure for ester reduction using Na-SG(I) in place of lump sodium or sodium sand to reduce a variety of aliphatic ester substrates. In a typical procedure, the ester is added to a slurry of Na-SG(I) in THF at 0°C, followed by the slow addition of methanol. Within minutes after the addition of methanol, the reaction is complete and excellent yields of primary alcohols are obtained after an aqueous workup (Table 3).

As described, SiGNa's sodium and sodium-potassium alloys in silica gel (Na-SG, Na2K-SG, and K2Na-SG) are strong reducing agents that eliminate many hazards and toxic processes associated with pure alkali metals by:

- 1) Reducing the storage and handling requirements associated with using alkali metals, liquid ammonia, and cryogenic conditions;
- 2) Reducing the risk of supply chain interruption, allowing for large scale manufacturing; and
- 3) Creating a safe, green, and easily disposable waste stream. ■

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