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Bouveault-Blanc reductions using stabilised alkali metals

Dr Paul Vogt and **Dr Brian Bodnar** of **Signa Chemistry** present an alternative method for ester reduction in flavours and fragrances

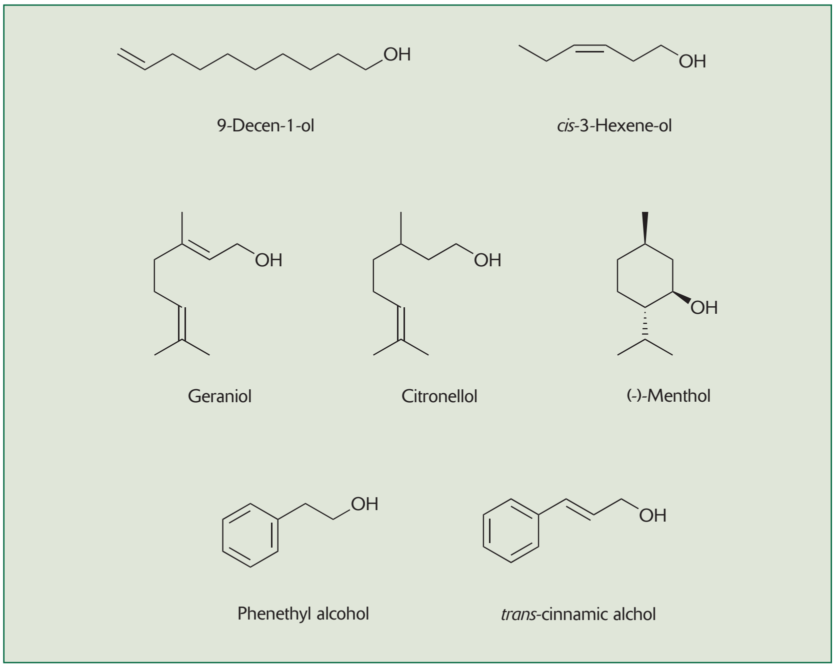
Molecules that contain an alcohol functional group play a large role in the preparation of products for the flavours and fragrances industry. Whilst saturated primary alcohols occur widely in nature and in aroma compositions, unsaturated primary alcohols, such as 9-decen-1-ol and *cis*-3-hexenol, are seen as more important and often add characteristic notes to fragrance compositions.

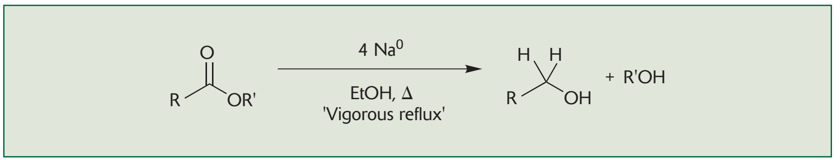
Terpene-derived alcohols, such as geraniol, citronellol and menthol, are widely used and occur in many essential oils. Aromatic alcohols occur in natural fragrances and flavours including phenethyl alcohol and *trans*-cinnamic alcohol (Figure 1).[1]

Although many alcohols used in the flavours and fragrances industry are found in nature and can be isolated from natural products via known techniques, such as extractions and distillations, much research has been performed on synthetic organic chemistry protocols to make compounds of this type. Of these protocols, the reduction of esters and other carbonyl moieties to the corresponding alcohols remains as a principal technique in industry.

Industrial reductions include catalytic hydrogenation over catalysts such as osmium-carbon, calcined catalysts based on the nitrates of copper and zinc, Ru-Sn-Al_2O_3 catalysts and $RuCl_2(PPh_3)_3$ as well as carbonyl reductions using a variety of enzymes and other biological systems.[2,3]

Another popular method involves hydride reductions using reagents such as $LiAlH_4$, Vitride and $NaBH_4$. For the selective reduction of α,β-unsaturated ketones to allylic alcohols, $NaBH_4$ treated with cerium chloride is often used.[2,4] These reagents are often troublesome to manipulate, have difficult work-up protocols and are expensive, especially when one considers the limited added value of products in the flavours and fragrances industry.





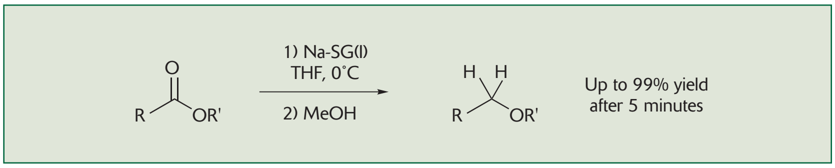


Figure 1 - (top) **Commonly used alcohols in the flavours & fragrances industry**

Figure 2 - (middle) **Classical Bouveault-Blanc reduction**

Figure 3 - (above) **Ester reduction with Na-SG(I)**

Bouveault-Blanc reduction

Before the advent of widely available hydride reagents, reduction of esters to primary alcohols was generally performed with alkali metals in ethanol, the Bouveault-Blanc reduction (Figure 2).[5,6] This was first described by Bouveault and Blanc in 1902.

These reductions are typically performed using one of two procedures. In the first, the substrate to be reduced is dissolved in alcohol and sodium metal is added rapidly to the solution.[7,8] The second begins with sodium in an inert solvent such as toluene, to which the substrate is added rapidly as a solution in alcohol. In both cases, it is important to mix the sodium and the alcohol as quickly as possible or the reaction will fail to achieve complete conversion of the ester substrate.[9,10]

The use of sodium metal alone has its associated hazards. Sodium reacts vigorously with water and alcohols to form 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.

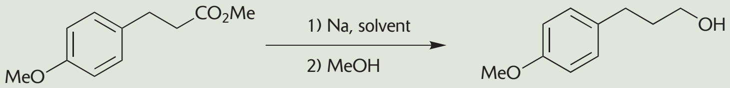
In spite of these associated hazards and the added risks of working with reactive mixtures of sodium metal and alcohol, the Bouveault-Blanc reduction can be employed successfully in large-scale continuous or batch processes.[6] However, caution must be taken as the reaction conditions may still result in excessive foaming and even fires.[7,10]

Stabilised alkali metals

Recently, a new technology has been developed for encapsulating alkali metals into nano-structured porous oxides, such as silica and alumina.[11,12] The resulting novel materials reduce the dangers associated with the handling of alkali metals while retaining the reducing power of the parent metal or alloy.

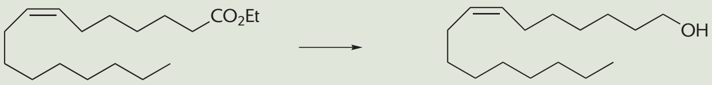
Sodium and sodium-potassium alloys in silica gel (generally M-SG; Na-SG, Na_2K-SG and K_2Na-SG) are free-flowing, non-pyrophoric solids that are easy to handle in the open air in the lab, pilot plant and commercial manufacturing facility. They are easy to produce with a loading of up to 40 wt% alkali metal. The powders can be used in both batch and continuous processes at ambient temperatures and pressures and, in dissolving metal reductions, do not require the use of liquid ammonia.

Table 2 - Comparison of classical Bouveault-Blanc reduction with Na-SG(I)



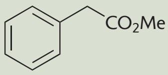
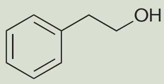
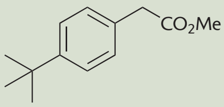
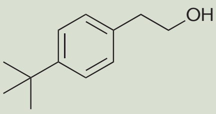
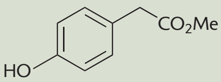
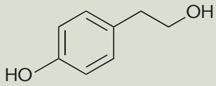
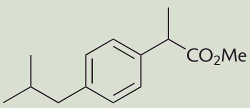
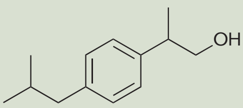
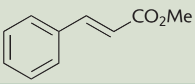
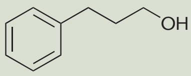
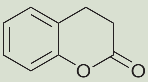
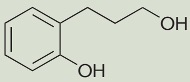
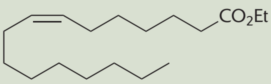
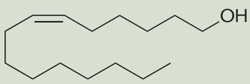
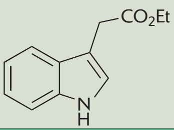
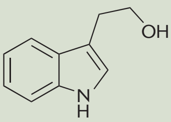
Entry	Na source	Solvent	Temp. (°C)	Yield
1	Na-SG(I)	THF	0	99%
2	Na-SG(I)	Toluene	60	29% conversion
3	Na^0	THF	0	61%
4	Na^0	Toluene	60	51% conversion

Table 3 - Ethyl oleate reduction: Comparison of known methods



Parameter	Na/EtOH	LAH	LAH sodiu,m	Na-SG
Yield (%)	50	92	92	99
Reagent safety	Sodium metal (-)	LAH powder (- -)	LAH solution (-)	Sodium Silica (+)
Temperature (˚C)	78	66	66	25
Isolation process	Incomplete reaction, product distillation	Precipitate, exotherm at quench	Precipitate, exotherm at quench	Quench separate from workup
Process volumes (l/kg)	36	26	26	11
Cost of goods ($/kg)	129	93	175	210
Cost of goods ($/kg) (if substrate at $1,000/kg)	2,422	1,331	1,413	1,368

Table 1 - Reduction of aliphatic ester using Na-SG(I)

Starting material	Product	Yield (%)
		89
		94
		93
		96
		95
		92
		99
		95

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 including desulphonation, desulphurisation, Birch reductions and phosphine reductive alkylations, validating their use in organic synthesis.[12-13]

Ester reduction using stabilised alkali metals

A procedure has been developed for the reduction of a variety of aliphatic ester substrates using Stage I sodium in silica gel, Na-SG(I), as a far safer alternative to the classic procedure that uses lump sodium or sodium sand (Figure 3).[14]

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. After the addition of methanol, the reaction is complete within minutes and excellent yields of primary alcohols are obtained after an aqueous work-up.

A variety of phenylacetate esters, other aliphatic esters, cinnamate esters, coumarins, fatty acid esters and heterocyclic esters were reduced in excellent yields (Table 1). The new method also allows for a variety of solvents to be used and expands the scope of the classical Bouveault-Blanc reduction parameters.

Also examined was a direct comparison of Na-SG(I) with sodium metal to determine if different reactivity resulted (Table 2). Under the improved Bouveault-Blanc conditions in THF at 0°C, the phenylacetate ester shown was reduced to yield the corresponding alcohol in good yield using Na-SG(I) (Entry 1). When Na-SG(I) was replaced with sodium metal; however, the ester was not fully consumed and the alcohol was obtained in only 61% yield (Entry 3).

The Bouveault-Blanc reaction is normally conducted in refluxing toluene/ethanol mixtures; however, higher temperatures resulted in incomplete reactions using both Na-SG(I) and sodium as a dispersion in toluene (Entries 2 & 4). Overall, the use of Na-SG(I) rather than sodium metal resulted in both cleaner and more complete reduction of the ester substrate.

Also investigated was a comparison between Na-SG(I), sodium metal and LAH on the reduction of ethyl oleate. Using Rondaxe's cost-of-goods software module, which can be used to model drug manufacturing processes and carry out cost analysis simulations, one can demonstrate that the Na-SG(I) process has clear cost advantages for valuable substrates (Table 3).

This study also showed that the new methodology, with milder and safer reaction conditions, higher yields and simpler work-ups has clear processing advantages over the comparable literature examples. It noted that the Na-SG(I) process has no expected capital investment requirements in a typical synthetic facility, whereas the comparable processes are expected to require some specialised equipment to safely handle the reagents and reaction conditions.

Conclusion

The need for alcohol functionality in products for the flavours and fragrance industry continues to be relevant. The classic Bouveault-Blanc reduction, although an inexpensive and viable methodology, has been largely avoided, due to the hazards associated with the use and handling of alkali metals as well as the often violent reaction conditions that are necessary for the transformation to be successful.

By substituting lump sodium metal or sodium sand with sodium in silica gel, Na-SG(I), aliphatic esters were reduced in excellent yield under mild reaction conditions and this has opened up the possibility of returning the Bouveault-Blanc reduction to a useful technique for industrial ester reduction applications.

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