JOC Note

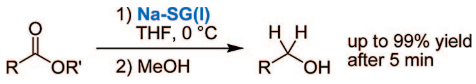
An Improved Bouveault−Blanc Ester Reduction with Stabilized Alkali Metals

Brian S. Bodnar* and Paul F. Vogt

Process Development Services, SiGNa Chemistry, Inc.,
1 Deer Park Drive, Suite C, Monmouth Junction,
New Jersey 08852

bsbodnar@signachem.com

Received December 19, 2008



Significantly improved Bouveault−Blanc conditions for ester reduction have been developed using sodium in silica gel (Na-SG), a free-flowing powder that can be easily handled in the open atmosphere. Primary alcohols were prepared in excellent yield from a variety of aliphatic esters under mild reaction conditions. The chemistry presented here is far safer than the classic Bouveault−Blanc reduction and is competitive with more modern hydride reduction methods.

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.[1] Because of hazards associated with alkali metal handling and the vigorous reaction conditions (typically refluxing toluene or xylene), this process has been largely replaced by the use of metal hydrides such as lithium aluminum hydride (LAH) or sodium borohydride. This paper describes an improvement upon the classic Bouveault−Blanc procedure that utilizes stabilized alkali metals to prepare primary alcohols from aliphatic esters in high yield (Figure 1). The mild reaction conditions, simple aqueous workup, and quick reaction times required make this updated method competitive with more modern methods of ester reduction.

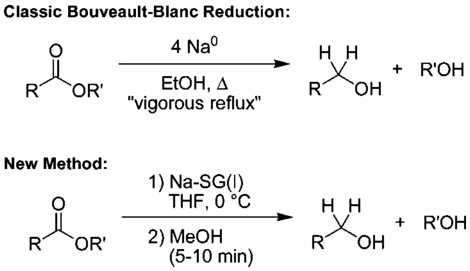


FIGURE 1. Improved Bouveault−Blanc procedure using Na-SG(I).

Classical Bouveault−Blanc reductions are typically performed using one of two procedures. In one method, the substrate to be reduced is dissolved in alcohol and sodium metal is added rapidly to the solution.[2] The second method begins with sodium in an inert solvent such as toluene, to which the substrate is added rapidly as a solution in alcohol.[3] In both cases, it is important to mix the sodium and the alcohol as fast as possible or the reaction fails to achieve complete conversion of the ester substrate.[3] While the Bouveault−Blanc reduction can be successfully employed in large-scale continuous or batch processes,[1d] the reaction conditions may result in excessive foaming and even fires.[2a,3b]

Recently, we have developed technology for encapsulating alkali metals into nanostructured porous oxides, which reduces the dangers associated with the handling of alkali metals while retaining the reducing power of the metal.[4] Sodium or sodium−potassium alloys in silica gel (Na-SG, Na_2K-SG, and K_2Na-SG) are free-flowing solids that have demonstrated applications in desulfurization,[4b] Birch reduction,[4b] and detosylation[4c] at room temperature. Herein, we present the use of Stage I sodium in silica gel [Na-SG(I)][5] in place of lump sodium or sodium sand to reduce aliphatic esters.

We found that by adding the substrate ester **1** to a mixture of Na-SG(I) in THF at 0 °C followed by the dropwise addition of methanol, primary alcohols **2** were formed in excellent yields (Table 1).

Similar to other Bouveault−Blanc reductions, the methanol could be replaced by a variety of alcohols, including ethanol and *tert*-amyl alcohol; however, the conditions described above were found to be optimal for most aliphatic ester substrates. In most cases, esters **1** were transformed to alcohols **2** completely after the addition of methanol was complete (5−10 min). Additionally, most alcohols **2** were obtained in high purity after a simple aqueous workup without the need for further purification.[6]

Carboxylic acids were not reduced under these conditions (Table 1, entry 1). Alkyl substitution was tolerated very well for phenylacetate esters **1** as substituents on the aromatic ring (Table 1, entries 3 and 4) and at the α-position (Table 1, entries 13−15). Other aromatic functional groups that were tolerated included -OH (Table 1, entry 5), -OR (Table 1, entry 6), and -NR_2 (Table 1, entry 7).

---

[1] (a) Chablay, E. *Compt. Rend* **1913**, *156*, 1020–1022. (b) Bouveault, L.; Blanc, G. *Bull. Soc. Chim. Fr.* **1904**, *31*, 666–672. (c) Bouveault, L.; Blanc, G. *Compt. Rend.* **1903**, *136*, 1676–1678. (d) Palfray, L.; Anglaret, P. *Compt. Rend.* **1947**, *224*, 404–406.

[2] (a) Adkins, H.; Gillespie, R. H. *Org. Synth.* **1949**, *29*, 80. (b) Reid, E. E.; Cockerille, F. O.; Meyer, J. D., Jr.; Cox, W. M.; Ruhoff, J. R. *Org. Synth.* **1935**, *15*, 51. (c) Manske, R. H. *Org. Synth.* **1934**, *14*, 20.

[3] (a) Shriner, R. L.; Ruby, P. R. *Org. Synth.* **1953**, *33*, 76. (b) Ford, S. G.; Marvel, C. S. *Org. Synth.* **1930**, *10*, 62.

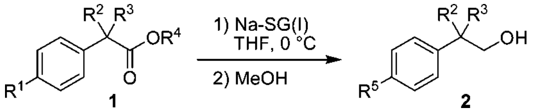
[4] (a) Shatnawi, M.; Paglia, G.; Dye, J. L.; Cram, K. C.; Lefenfeld, M.; Billinge, S. J. L. *J. Am. Chem. Soc.* **2007**, *129*, 1386–1392. (b) Dye, J. L.; Cram, K. D.; Urbin, S. A.; Redko, M. Y.; Jackson, J. E.; Lefenfeld, M. *J. Am. Chem. Soc.* **2005**, *127*, 9338–9339. (c) Nandi, P.; Redko, M. Y.; Petersen, K.; Dye, J. L.; Lefenfeld, M.; Vogt, P. F.; Jackson, J. E. *Org. Lett.* **2008**, *10*, 5441–5444.

[5] SiGNa Chemistry has developed three categories of alkali metals in silica gel (M-SG): Stage 0 materials are strongly reducing pyrophoric powders; stage I materials are nonpyrophoric, free-flowing, black powders that have applications in organic syntheses; stage II materials have the least reducing capability but react with water to form hydrogen. All three categories of M-SG are available commercially.

[6] Upon the addition of water, hydrogen gas is evolved and sodium silicates are formed. The sodium silicates remain dissolved in the aqueous layer during workup.

10.1021/jo802778z CCC: $40.75

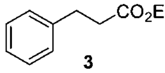
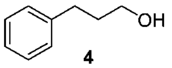
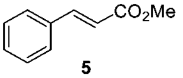
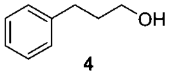
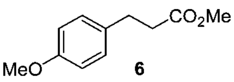
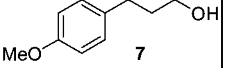
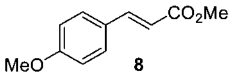
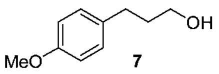
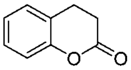
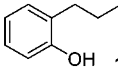
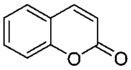
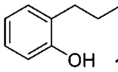
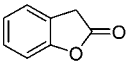
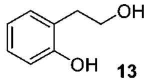
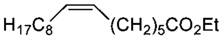
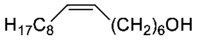
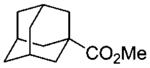
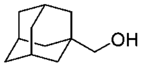
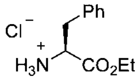
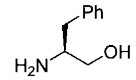
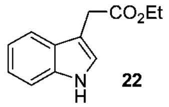
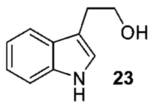
TABLE 1. Reduction of Phenylacetate Esters 1 to Phenethyl Alcohols 2 using Na-SG(I)



entry	1	R1	R^2/R3	R^4	2	R^5	yield (%)[a]
1	**1a**	H	H/H	H	**2a**	H	~5[b]
2	**1b**	H	H/H	Me	**2a**	H	89
3	**1c**	Me	H/H	Et	**2c**	Me	84
4	**1d**	tBu	H/H	Me	**2d**	tBu	94
5	**1e**	OH	H/H	Me	**2e**	OH	93
6	**1f**	OMe	H/H	Me	**2f**	OMe	94
7	**1g**	NH_2	H/H	Et	**2g**	NH_2	78
8	**1h**	NO_2	H/H	Et	**2g**	NH_2	36[c]
9	**1i**	CN	H/H	Me	*d*	*d*	*d*
10	**1j**	Cl	H/H	Me	**2a**	H	71[e]
11	**1k**	F	H/H	Me	**2k/2a**	F/H	79[f]
12	**1l**	CF_3	H/H	Me	**2c**	Me	64[g]
13	**1m**	iBu	(±)-Me	Me	**2m**	iBu	96
14	**1n**	H	$(CH_2)_2$	Me	**2n**	H	90
15	**1o**	H	$(CH_2)_4$	Me	**2o**	H	81
16	**1p**	H	(*S*)-OH	Et	*d*	*d*	*d*
17	**1q**	H	(*S*)-OMe	Me	*d*	*d*	*d*

[a] Isolated yield. [b] Starting material (**1a**) was recovered (~90% yield). [c] Complete reduction of the NO_2 group was observed. [d] Complex mixture of products obtained. [e] Complete reduction of the Cl group was observed. [f] **2k** and **2a** were recovered in a 2:1 ratio. [g] Complete reduction of the CF_3 group was observed.

TABLE 2. Reduction of Aliphatic Esters Using Na-SG(I)[a]

Entry	Ester substrate	Product	Yield[b]
1	 **3**	 **4**	99%
2	 **5**	 **4**	95%
3	 **6**	 **7**	99%
4	 **8**	 **7**	98%
5	 **9**	 **10**	92%
6	 **11**	 **10**	77%
7	 **12**	 **13**	96%
8	$CH_3(CH_2)_{10}CO_2Et$ **14**	$CH_3(CH)_{11}OH$ **15**	99%[c]
9	 **16**	 **17**	99%[d]
10	 **18**	 **19**	97%
11	 **20**	 **21**	27%[e]
12	 **22**	 **23**	95%

[a] Conditions: (i) Na-SG(I), THF, 0 °C; (ii) MeOH. [b] Isolated yield. [c] 65–75% yield[3b] using classic conditions. [d] 84% yield[2b] using classic conditions. No olefin isomerization was observed. [e] Yield after recrystallization obtained in 98% ee. Crude mixture obtained in 59% ee.

Several aromatic functional groups were found to be reactive under these conditions. Nitro groups were reduced cleanly to anilines (Table 1, entry 8), indicating the potential use of Na-SG(I) in place of hydrogenation and other methods for the reduction of nitroaromatic groups. Trifluoromethyl groups were reduced to methyl groups (Table 1, entry 12). Aromatic halogens were either fully, as with the chlorine-substituted ester **1j** (Table 1, entry 10), or partially reduced, as with the fluorine-substituted ester **1k** (Table 1, entry 11). Aromatic nitriles yielded complex mixtures (Table 1, entry 9). Esters containing α-hydroxy or α-alkoxy groups such as mandelates **1p** or **1q** yielded complex mixtures (entries 16 and 17), which has also been observed under classic Bouveault–Blanc conditions.[7]

Our study was expanded to include a variety of other aliphatic esters (Table 2). The scope of the Bouveault–Blanc reduction using Na-SG(I) predictably mirrored that of classic Bouveault–Blanc reductions using sodium metal. Cinnamate esters **5** and **8** provided 3-aryl-1-propanols **4** and **7**, respectively (Table 2, entries 2 and 4), similar to accounts of cinnamate reductions in the literature.[1a,8] Coumarin (**11**) and dihydrocoumarin (**9**) both provided alcohol **10** when subjected to the reaction conditions (Table 2, entries 5 and 6).

Isolated alkenes were left intact under the standard reaction conditions (Table 2, entry 9), which has also been described in Bouveault–Blanc literature.[2a,b,7c,9] Other substrates investigated included fatty acid ester **14** (Table 2, entry 8), sterically encumbered ester **18** (Table 2, entry 10), and indoleacetate **22** (Table 2, entry 12), which all provided alcohols in excellent yield. Using classic Bouveault–Blanc conditions, the reduction of amino acid esters was reported to provide amino alcohols in low yield.[10] Similarly, phenylalanine ester **20** resulted in low recovery of amino alcohol **21** using Na-SG(I) (Table 2, entry 11). The crude amino alcohol **21** was obtained in only 59% ee; however, after recrystallization the product could be obtained in 98% ee.

While the new method described efficiently transformed many esters to primary alcohols, other substrates resulted in incomplete reactions or complex mixtures when subjected to the standard conditions. Early reports by Bouveault and Blanc[11] indicated that the reduction of aromatic esters resulted in complex mixtures of products. Similarly, we found that when aromatic ester substrates **24**–**27** were treated using Na-SG(I) under the

---

(7) (a) Bouveault, L.; Blanc, G. *Bull. Soc. Chim. Fr.* **1904**, *31*, 1213–1215. (b) Bouveault, L.; Blanc, G. *Bull. Soc. Chim. Fr.* **1904**, *31*, 1210–1213. (c) Bouveault, L.; Blanc, G. *Compt. Rend.* **1903**, *137*, 328–329.

(8) (a) Brunner, O.; Singule, E. *Monatsh. Chem.* **1948**, *79*, 81–86. (b) Brunner, O.; Singule, E. *Monatsh. Chem.* **1947**, *77*, 251–258. (c) Bouveault, L.; Blanc, G. *Bull. Soc. Chim. Fr.* **1904**, *31*, 1206–1210.

(9) Kass, J. P.; Burr, G. O. *J. Am. Chem. Soc.* **1940**, *62*, 1796–1798.

(10) Gault, H. *Compt. Rend.* **1907**, *145*, 126–127.

(11) Bouveault, L.; Blanc, G. *Compt. Rend.* **1903**, *137*, 60–62.

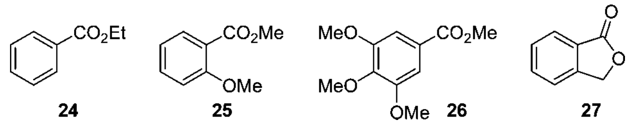


FIGURE 2. Aromatic esters that yielded mixtures under standard conditions.

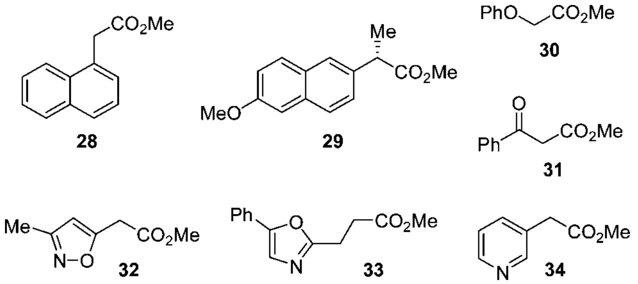


FIGURE 3. Other esters that yielded mixtures under standard conditions.

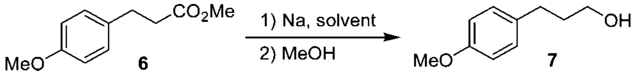
standard reaction conditions [(i) Na-SG(I), THF, 0 °C; (ii) MeOH], we obtained a complex mixture of products (Figure 2). Careful analysis of the reaction mixtures indicated that Birch reduction was competitive with ester reduction. The electron-rich substrate, ester **26**, was resistant to Birch reduction as well as ester reduction and was recovered from the reaction mixture mostly unchanged.

Naphthaleneacetates such as compound **28** and **29** (naproxen methyl ester) were found to yield mixtures under the standard conditions, presumably due to competitive Birch reduction (Figure 3). β-Keto ester **31** and pyridineacetate **34** also resulted in mixtures under the standard conditions. Both isoxazole (compound **32**) and oxazole (compound **33**) functionalities did not survive the reaction conditions. Similar to accounts of Bouveault−Blanc reductions of α-alkoxy esters,[7] phenoxyacetate **30** yielded a mixture containing mostly phenol, resulting from C−O bond reduction.

We were interested to see whether replacement of Na-SG(I) with sodium metal resulted in different reactivity (Table 3). Under the improved Bouveault−Blanc conditions in THF at 0 °C, ester **6** was reduced to yield alcohol **7** in excellent yield using Na-SG(I) (Table 3, entry 1). When Na-SG(I) was replaced with sodium metal, however, ester **6** was not fully consumed and alcohol **7** was obtained in only 61% yield (Table 3, 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 (Table 3, entries 2 and 4). Overall, the use of Na-SG(I) rather than sodium metal resulted in both cleaner and more complete reduction of the ester substrate.

The classic Bouveault−Blanc reduction has been largely avoided because of hazards associated with the use and handling of alkali metals, as well as the often violent reaction conditions that are necessary for the transformation. 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.

TABLE 3. Comparision of Na^0 and Na-SG(I)



entry	Na source[a]	solvent	temp (°C)[b]	yield[c]
1	Na-SG(I)	THF	0	99%
2	Na-SG(I)	toluene	60	29% conversion[d]
3	Na^0	THF	0	61%
4	Na^0	toluene	60	51% conversion[d]

[a] All reactions conducted using **6** (3 mmol), Na (42 mmol), and excess methanol. [b] Initial temperature; typically temperature increased by 10−15 °C during MeOH addition. [c] Isolated yield. [d] Determined from HPLC/NMR data.

Experimental Section

General Procedure for the Improved Bouveault−Blanc Reduction. Oleyl Alcohol (17).[12] Stage I sodium silica gel (27.1 wt % stage I, 3.56 g, 42.0 mmol) was added to a flame-dried flask fitted with an addition funnel and temperature probe. Anhydrous THF (45 mL) was added, and the mixture was cooled in an ice/H_2O bath under Ar to 0 °C. Ethyl oleate (**16**, 1.00 mL, 2.80 mmol) was added, followed immediately by the addition of anhydrous methanol (3.00 mL, 74.2 mmol) dropwise over 5 min. Some bubbling was observed, and the temperature of the mixture rose to 20−25 °C before falling. The ice/H_2O bath was removed, and after 30 min, H_2O (25 mL) was added (bubbling observed; exothermic). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with H_2O (40 mL) and brine (40 mL), dried, filtered, and concentrated to yield pure oleyl alcohol (**17**, 0.748 g, >99% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.35 (m, 2H), 3.64 (t, $J = 6.5$ Hz, 2H), 2.02 (m, 4H), 1.57 (m, 2H), 1.49 (br, 1H), 1.36−1.25 (m, 22H), 0.88 (t, $J = 7.0$ Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.9 (CH), 129.8 (CH), 63.0, 32.7, 31.9, 29.74, 29.72, 29.51, 29.49, 29.4, 29.31, 29.30, 29.2, 27.18, 27.16, 25.7, 22.7, 14.1 (CH_3) ppm. CI-MS *m/z*: $[M + H]^+$ 269 (96.4%), 139 (15.9%), 125 (46.5%), 111 (85.5%), 97 (100%), 95 (16.2%).

Acknowledgment. We would like to thank Michael Lefenfeld, Michael J. Costanzo, James L. Dye, James E. Jackson, and Partha Nandi for helpful scientific discussion.

Supporting Information Available: Experimental details and NMR spectra for all products shown in Tables 1 and 2 as well as for esters that were not commercially available. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802778Z

---

(12) For additional experimental guidelines on using sodium in silica gel, please see http://www.signachem.com/products/technical-documents/.