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Ammonia-free Birch reductions with sodium stabilized in silica gel, Na-SG(I)

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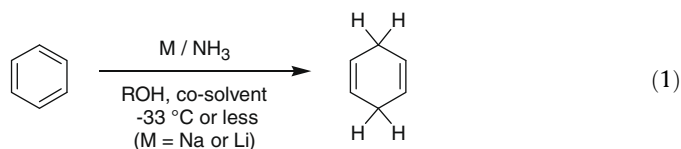
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ABSTRACT

Ammonia-free Birch reduction conditions were developed based upon sodium stabilized in silica gel for a variety of substrates. In general, the yields were similar to those reported for lump sodium in liquid ammonia.

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The reduction of aromatic compounds by alkali metals in liquid ammonia is a synthetically powerful and versatile method that has been in use since its discovery in 1937 by Wooster and Godfrey.¹ The full scope and limitations of this method were expanded through the efforts of Birch, hence it now bears his name (Eq. 1).^{2a–d}



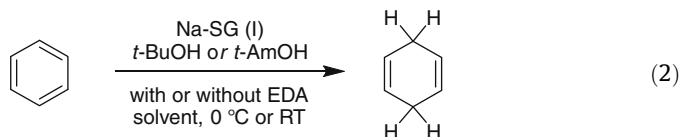
The Birch reduction is one of only a few methods that can readily convert aromatic synthons into alicyclic structures and has been used in the synthesis of drugs and complex natural products.^{3a–d} Despite its great utility, the classic Birch reduction has several undesirable attributes that have limited its use, particularly on a large scale.^{4a,b} Primary among these are the inherent dangers of handling elemental alkali metals, the practicality and hazards of running cryogenic reactions, and the high toxicity of ammonia.^{5a,b}

Consequently, researchers have sought alkali-metal reduction conditions that avoid the use of liquid ammonia. Benkeser et al. have successfully reduced aromatic substrates with lithium metal in neat low molecular weight amines. These include primary amines, primary and secondary amine mixtures, and ethylenediamine (EDA) without a cosolvent or an alcohol present to serve as a proton donor.^{6a,b} This method, known as the Benkeser reduction, is generally a more powerful reducing system than the Birch reduction and frequently results in over-reduced product mixtures. However, greater selectivity can be achieved in neat mixtures of primary and secondary amines. In a second method, Donohoe et al. have reported on the ammonia-free reductions of electron-deficient (i.e., activated) hetero- and carbocyclic aromatic com-

pounds with lithium metal.^{7a,b} This reduction is performed in a mixture of THF and bis-(methoxyethyl)-amine at $-78\text{ }^\circ\text{C}$ with either di-*tert*-butyl-biphenyl or naphthalene serving as an electron carrier. One major advantage of this ammonia-free method over the classic Birch reduction is the ability to subsequently react the intermediate anions with electrophiles (e.g., alkyl halides, acid chlorides, and aldehydes) that may otherwise react with ammonia under the standard Birch conditions.

Recently, we have developed a technology for encapsulating alkali metals into nano-structured porous oxides, such as silica gel and alumina.^{8a,b} Encapsulation reduces the dangers associated with the handling of alkali metals while still retaining the reducing power of the metal. Stage I sodium and sodium-potassium alloys in silica gel (Na-SG, Na₂K-SG, and K₂Na-SG) are free-flowing black powders that are typically loaded with 35–40 wt % of the neat alkali metal.⁹ These reagents have demonstrated applications in ester reductions,¹⁰ detosylations,¹¹ desulfurizations,^{8a} and the cleavage of arylphosphines to metal phosphides.¹²

Herein we describe a safer and more practical modification of the classic Birch reduction that avoids the use of liquid ammonia and cryogenic temperatures (Eq. 2). Central to this modification is the use of Stage I sodium in silica gel, Na-SG(I), as the reducing agent. Na-SG(I) is a more convenient and safer form of metallic sodium than either lump sodium or sodium sand because it can be easily handled in the open air without loss of activity and it is safer to quench.



The Birch reductions of 16 different substrates with Na-SG(I) under ammonia-free conditions were examined and compared with literature values for sodium in liquid ammonia (Table 1). These substrates fall into 4 compound classes, including polycyclic aromatic hydrocarbons (1a–4a), aromatic hydrocarbons (5a–7a), aryl ethers (8a–12a), and polycyclic aromatic heterocycles (13a–16a).

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Table 1
Comparison of the Birch reduction of aromatic substrates with Na-SG(I) under ammonia-free conditions with lump sodium in liquid ammonia

Entry	Substrate (a)	Major Product (b)	Na-SG(I) method ^a	Rxn equiv ^b	Time (h)	Na-SG(I) Prod. ^c /Yield ^d (%)	Na/NH ₃ (lit.) ^e Prod./Yield ^d (%)
1			A	3.5	2.0	96/70	—/85 ^f
2			A	2.0	1.0	87/83	—/97 ^g
3			B	3.5	2.5	99/94	—/96 ^g
4			C	2.7	4.0	63/34	52/20 ^h
5	Ph—C≡C—Ph	Ph—CH ₂ —CH ₂ —Ph	A	3.5	2.0	100/83	—/80–90 ⁱ
6	Ph—CH=CH—Ph	5b	A	3.5	2.0	100/82	—/80–90 ⁱ
7			D	14	24	9/—	—/63 ^j
8			D	14	24	30/—	—/74 ^k
9			A	3.5	24	12/—	—/19 ^l
10			A	3.5	24	68/43	—/— ^m
11			D	14	24	85/68	—/74 ⁿ
12			E	5.6	24	—/56 ^o	—/— ^p
13		12b	E	5.6	24	—/58 ^o	—/69 ^q
14			D	14	48	94/62	—/15 ^r
15			F	3.5	2.0	89/38	—/— ^s
16			F	3.5	2.0	77/40	—/89 ^t
17	8a	8b	G	3.5	2.5	92/80	—/74 ^k

^a Methods A–F are ammonia-free conditions and method G (entry 17) was run in liquid ammonia; all methods are described in detail in Ref. 14.

^b Number of Na-SG(I) reaction equivalents (2 moles of Na are required per mole of substrate).

^c Percent product in the crude reaction mixture as estimated by GC/MS (either EI or CI detection).

^d Isolated yield after purification.

^e Literature values.

^f Ref. 15.

^g Ref. 16; performed in either Et₂O or THF at room temperature instead of liquid ammonia.

^h Ref. 17; percent conversion as estimated by GC (FID).

ⁱ Ref. 18.

^j Ref. 19.

^k Ref. 20.

^l 2,5-Dihydroanisole obtained through demethoxylation followed by Birch reduction was reported as the major product in Ref. 20 (37% by GC).

^m A crude yield of 90% of 1,4-dimethoxycyclohexa-1,4-diene was reported in Ref. 21.

ⁿ Ref. 22.

^o Unidentified products, presumably a mixture of Birch reduction isomers by NMR (*m/z* 122) were also isolated for entries 12 and 13, however they were inseparable from 2-ethylphenol by GC/MS.

^p No literature values exist for Na/NH₃, however a 95% yield of 2-ethylphenol was reported for Li/NH₃ in Ref. 23.

^q Ref. 24.

^r The major products as reported in Ref. 25 were 1-methylindoline (15%) and 4,7-dihydro-1-methylindole (20%).

^s No literature values exist for the preparation of 1,2,3,4-tetrahydroquinoline with Na/NH₃, however a 36% yield was reported for Li/NH₃ in Ref. 26.

^t Ref. 27.

Several sets of ammonia-free reaction conditions (methods A–F, Table 1) were developed and optimized for each compound. Like the Benkeser reduction, most of our conditions use an amine, ethylenediamine (EDA), to facilitate the reduction. However unlike the classic Benkeser conditions, our reaction conditions use only 1 mole of amine per mole of sodium rather than a large excess of amine as the solvent. In addition, our conditions employ an alcohol as the proton source instead of an amine, as in the Benkeser conditions. Although some of the substrates studied can be quickly and cleanly reduced with Na–SG(I) without EDA, the presence of EDA generally shortened the reaction times and increased the product yields. In addition, we found *t*-amyl alcohol (2-methyl-2-butanol) to be more convenient to use than *t*-butanol because of its lower melting point (–12 °C vs 26 °C), although there were some instances where *t*-butanol gave better results. All of the Na–SG(I) reductions shown in Table 1 were run either in THF at 5 to 5 °C or in 1,4-dioxane at room temperature. However, depending upon the solubility of the substrate, other aprotic solvents can be used. These include heptanes, cyclohexane, toluene, methyl *t*-butyl ether (MTBE), 1,2-dimethoxyethane (DME), and 2-methyltetrahydrofuran. Usually 2.0–3.5 reaction equivalents of sodium as Na–SG(I) were needed to completely consume the starting substrate, which is typical for classical Birch conditions with sodium in liquid ammonia. Some slower reactions required more than 3.5 reaction equivalents of sodium to proceed to completion because of the competitive decomposition of sodium from reaction with the alcohol.

The results given in Table 1 show that the yields using Na–SG(I) under ammonia-free conditions are generally similar to those reported in the literature for lump sodium in liquid ammonia, although there are some notable exceptions. The polycyclic aromatic hydrocarbons indene (**1a**) and naphthalene (**2a**) were cleanly and quickly reduced in the presence of EDA to **1b** and **2b** in 71% and 83% yields, which are similar to the literature yields of 85% and 97%, respectively. Anthracene (**3a**) was reduced with Na–SG(I) in the absence of EDA to furnish **3b** in 94% yield. In contrast, reduction of anthracene (**3a**) with lump sodium metal under otherwise identical conditions provided **3b** in only 14% conversion. The Na–SG(I) reduction of phenanthrene (**4a**) to **4b** under optimal conditions required the formation of the intermediate dianion at low temperature (–74 °C) before addition of the proton source (*t*-butanol), otherwise a substantial amount of over-reduced side products were obtained. Still, the 34% yield of **4b** was comparable with the literature yield (20%).

The reductions of diphenylacetylene (**5a**) and *trans*-stilbene (**6a**) with excess Na–SG(I) under the ammonia-free conditions cleanly provided **5b** in yields of 83% and 82%, respectively, which are analogous to the literature yields (80–90%). In sharp contrast, the reductions of toluene (**7a**) and anisole (**8a**) gave low conversions of **7b** (9% vs 63% lit.) and **8b** (30% vs 74% lit.), even when a large excess (14 reaction equiv) of Na–SG(I) was used. A control reduction of anisole (**8a**) was performed with Na–SG(I) in liquid ammonia according to the literature procedure for lump sodium (entry 18). Under these conditions, compound **8b** was produced in 92% yield, which is somewhat improved over the literature yield (74%) obtained with lump sodium. Hence, the poor conversion of anisole (**8a**) to **8b** is due to the ammonia-free solvent conditions rather than from using Na–SG(I) instead of lump sodium. Although the reduction of 1,2-dimethoxybenzene (**9a**) gave **9b** in only 12% conversion, it was still similar to the literature yield (19%). 1,4-Dimethoxybenzene (**10a**) and 6-methoxy-1,2,3,4-tetra-hydro-naphthalene (**11a**) gave reasonable yields of **10b** (43%) and **11b** (68%), respectively. The results for **8a–11a** suggest that the yields for anisole derivatives are highly dependent upon the substitution pattern.

The reductive dealkylation of aromatic ethers with alkali metals is well known in the literature and is highly dependent upon the

reaction conditions.¹³ For example, the reductions of 2,3-dihydro-benzofuran (**12a**) and benzofuran (**13a**) with excess Na–SG(I) under ammonia-free conditions both provided 2-ethylphenol (**12b**) as the major product (56% and 58% yields, respectively). In general, we found that increasing the amount of alcohol and EDA minimized the amount of dealkylation observed with aryl ethers.

The reduction of certain aromatic heterocycles with Na–SG(I) under ammonia-free conditions was also investigated. While the reduction of *N*-methylindole (**15a**) was somewhat sluggish (48 h), it provided **15b** in 62% yield, which is a dramatic improvement over the 15% yield reported in the literature. Quinoline (**15a**) and isoquinoline (**16a**) were quickly reduced with excess Na–SG(I) to **15b** and **16b**, respectively, although the yield for **16b** (40%) was lower than the literature yield (89%).

In conclusion, we have developed ammonia-free modifications of the classic Birch reduction based upon sodium encapsulated in silica gel, Na–SG(I). Na–SG(I) is a more convenient and safer form of metallic sodium than either lump sodium or sodium sand because it can be easily handled in the open air without loss of activity. In general, the yields for a variety of substrates using Na–SG(I) under ammonia-free conditions were similar to those reported for lump sodium in liquid ammonia.

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Supplementary data

Supplementary data (Experimentals and NMR data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.040.

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14. *Method A*: 1.0 mmol of substrate, 7.0 mmol of Na-SG(I), 7.0 mmol of EDA, 8.4 mmol of *t*-AmOH in THF at 5–5 °C; *Method B*: 1.0 mmol of substrate, 7.0 mmol of Na-SG(I), 7.6 mmol of *t*-BuOH in 1,4-dioxane at rt; *Method C*: 1.0 mmol of phenanthrene and 7.0 mmol of Na-SG(I) in THF at rt for 15 min, cool to –74 °C, add 7.0 mmol of EDA, stir at –74 °C for 45 min, add 4.2 equiv of *t*-BuOH and stir at –74 °C for 2–3 h; *Method D*: 1.0 mmol of substrate, 28 mmol of Na-SG(I), 30 mmol of EDA, 36 mmol of *t*-AmOH in THF at 5–5 °C. *Method E*: 1.0 mmol of substrate, 11.2 mmol of Na-SG(I), 11.2 mmol of EDA, 8.4 mmol of *t*-AmOH in THF at 5–5 °C. *Method F*: Same as Method B except run at 5 to 5 °C in THF. *Method G*: 1.0 mmol of anisole, 7.0 mmol of Na-SG(I), 3.2 mmol of EtOH in liquid ammonia at –33 °C. *General procedure*: Na-SG(I) was suspended in solvent (1.75 mL), cooled to 0 °C, treated with EDA and stirred for 15 min. The alcohol was added dropwise at <5 °C and stirred for 5 min. A solution of the substrate (1 mmol) in solvent (0.25 mL) was added and the reaction mixture was stirred for the specified time. The reaction mixture was carefully quenched by treatment with 0.6 mL of MeOH/H₂O (9:1) followed by stirring for 2 h. The mixture was filtered through paper and the filtrate was diluted with water and extracted twice with EtOAc. The combined organic extracts were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo.
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