Sodium Tetraalkoxyborates: Intermediates for the Quantitative Reduction of Aldehydes and Ketones to Alcohols through Ball Milling with NaBH$_4$

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Stoichiometric molecular solid-state vibrational ball milling, solvent-free kneading ball milling, and mechanochemical ball milling of varied aldehydes and ketones with unmodified sodium borohydride under temperature control uses all hydrogen atoms of the reducing agent in fast reactions. It provides quantitative yields of thermally stable sodium tetraalkoxyborates. The easily isolated solids are extremely sensitive towards hydrolysis, leading to quantitative yields of the corresponding alcohols. The rapid syntheses are regiospecific

and stereoselective. Varied substituents are not attacked, including the bromine of α-bromo ketones. Conjugated aldehydes and ketones provide quantitative yields of the allylic alcohols free of contamination by saturated alcohols that would occur by reaction in solution. Depending on the stoichiometric ratio, benzil is quantitatively reduced to benzoin (4:1 ratio) or dihydrobenzoin (2:1 ratio).
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Introduction

Reduction of aldehydes and ketones (**1**) with NaBH$_4$ (**2**) to give the alcohols is a widely used technique.[1] It is mostly performed in protic solution, but the reactions are relatively slow and often proceed with low regioselectivity.[2] Only reductions with NaBH$_4$ in aprotic solvents allowed very tedious and unpractical isolation of a few tetraalkoxyborates.[3,4] There are also reports for the reduction of aldehydes and ketones with NaBH$_4$ under solvent-free conditions.[5] However, most of them have disadvantages for practical utility including excessive amounts of reducing agent, addition of catalysts, long reaction times, and the necessity of chromatographic workup. For example, benzophenone and a 10-fold molar amount of sodium borohydride were kept in a dry box at room temperature with occasional co-grinding of the reactants in an agate mortar with pestle for 5 d.[5a] More recently, solvent-free reductions of carbonyl compounds by sodium borohydride with added solid acids such as boric acid, benzoic acid, and 4-toluenesulfonic acid monohydrate[6] or wet silica have been reported.[7] All of these techniques, however, were not waste free, and the yields were less than quantitative. Highly versatile and varied stoichiometric ball milling at controlled temperature and moderate milling impact[8,9] has not yet

been used to improve the situation. Furthermore, other recent reviews (covering different reaction types, but homogeneous liquids should not be milled)[10] did not particularly stress these technical points, which increase yields and decrease milling times.[8,9] We report herein the sustainable, rapid, and quantitative stoichiometric ball milling of 32 aldehydes and ketones with complete use of all four hydrogen atoms of the reducing agent for obtaining the alcohols. This method has the additional benefit of possessing the easiest thinkable synthesis of the versatile solid intermediate sodium tetraalkoxyborates that escape detection and isolation in the presence of water or moisture or excessive amounts of NaBH$_4$.

Results and Discussion

A repetition of early grinding techniques with a fourfold excess amount of NaBH$_4$ (**2**)[5a] (1:1 mixture in the case of **1a**) gave only 36% yield of alcohol **4a**, whereas 10 min milling of such a mixture gave 100% yield after hydrolysis and workup. This appeared promising for the improvement of the reaction, as moisture- and solvent-free conditions would allow all four hydrogen atoms of **2** to be used, resulting in the isolation of tetraalkoxyborates **3**, and the use of excess amounts of **2** and inorganic waste would be avoided. The aldehydes used in Table 1 were either liquid (14 entries), solid (17 entries, m.p. 40–111 °C), or polymer (1 entry), but NaBH$_4$ (**2**) did not readily dissolve in them. Therefore, three types of milling procedures with substrates in a 4:1 ratio were used (Scheme 1, Table 1): (1) proper solvent-free kneading ball milling,[9] (2) proper solid-state molecular

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Table 1. Reduction of aldehydes and ketones by NaBH$_4$ under solvent-free stoichiometric (4:1 ratio) ball milling; the yield of solid or oily alcohols **4** was always >99% after hydrolysis of **3** and workup.

1	R^1	R^2	T [°C]	t [min]	M.p. of **4** [°C][a]
a	H	4-ClC$_6$H$_4$	25	10	68–70 (67–70)
b	H	4-BrC$_6$H$_4$	25	10	76–78 (77–78)
c	H	4-NO$_2$C$_6$H$_4$	25	10	94–96 (94)
d	H	3-NO$_2$C$_6$H$_4$	25	10	28–30 (30)
e	H	2-NO$_2$C$_6$H$_4$	25	10	70–72 (72)
f	H	4-CNC$_6$H$_4$	25	15	42–44 (42–44)
g	H	Ph	25	10	oil
h	H	4-MeC$_6$H$_4$	25	15	50–52 (50–52)
i	H	4-OMeC$_6$H$_4$	25	15	23–25 (23–25)
j	H	2-OMeC$_6$H$_4$	25	15	oil
k	H	4-OHC$_6$H$_4$	25	15	116–118 (115–118)
l	H	2-OHC$_6$H$_4$	25	15	71–73 (73)
m	vanillin		25	15	112–114 (114–115)
n	H	4-(Me)$_2$NC$_6$H$_4$	25	20	22–24 (24–25)
o	H	2-furanyl	25	15	oil
p	H	2-thiophenyl	25	15	28–30 (oil)
q	H	2-naphthyl	25	10	80–82 (79–83)
r	H	CH$_3$(CH$_2$)$_6$	25	15	oil
s	paraformaldehyde		25	20	liquid
t	H	CH$_3$CH=CH	25	15	oil
u	H	PhCH=CH$_2$	25	10	30–32 (32–33)
v	H	5-norbornen-2-yl	25	20	oil
w	Me	Ph	25	30	18–20 (19–20)
x	Me	4-NO$_2$C$_6$H$_4$	25	30	30–32 (oil)
y	Me	4-OHC$_6$H$_4$	60	60	134–136 (136)
z	Me	3-OHC$_6$H$_4$	60	30	115–117 (117–118)
α	Me	CH$_3$(CH$_2$)$_4$	25	30	oil
β	Ph	Ph	90	90	64–66 (65–67)
γ	Ph	CH$_2$Br	25	20	oil
δ	cyclohexanone		25	20	22–24 (26)
ε	cyclooctanone		60	30	20–23 (25)
ζ	Ph	PhC=O	70	90	136–137(135–137)[b]

[a] Melting points in parentheses are from refs.[13–16] [b] *rac*-Benzoin.

ball milling, and (3) mechanochemical ball milling (covalent bonds of paraformaldehyde **1s** were broken by mechanical action to provide free HCHO).[11] Solid-state reactivity for the second of these milling types was predicted for all compounds **1** with known crystal packing.[12]
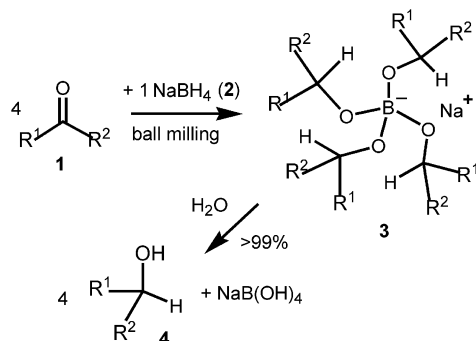
Scheme 1. Ball milling solvent-free reduction of carbonyl compounds via isolated, high-melting sodium tetraalkoxyborates **3**.

All reactions (Table 1) with a large number of diverse substituents on the aromatic, heterocyclic, and aliphatic residues proceeded quantitatively at the temperatures and times given, independent of the milling type, which is very favorable. A variety of aldehydes and ketones with a large selection of substituents varying from amino and methoxy to cyano and nitro in the aromatic, heterocyclic, aliphatic, and olefinic systems were not affected by the reduction procedure. The aldehydes reacted rapidly at 25 °C in less than 15 min, regardless of whether solid-state molecular ball milling, kneading ball milling, or mechanochemical ball milling was used. Some ketones required higher temperatures, but for the solid ketones (except **1β**) this temperature was well below their melting points. This also underlines the necessity to have temperature control in ball milling reactions. We note that this methodology is also successful with acetophenone (**1w**) and benzophenone (**1β**). Both compounds were practically unreactive when the reduction was attempted in solution or after 2 h grinding with an excess amount of **2**.[6]

Sodium Tetraalkoxyborates

The task of synthesizing easy-to-hydrolyze (even rapidly with atmospheric moisture) tetraalkoxyborates **3** by NaBH$_4$ reductions was not reasonably considered in the past. Thus, the report[3] was never cited in the literature and report[4] only three times, but only citing the alcohol formation, not

the intermediate. The reason is certainly the difficulty in the isolation of **3g** as a result of crystallization from THF or DMSO, respectively, with side products by reaction of the solvent in the latter case, and a tedious filtration–washing–drying procedure. The new ball milling technique is particularly useful, because it avoids all such difficulties, and pure solids **3** are quantitatively obtained in pure form (Scheme 1). Quantitative yield is safely judged from the quantitative isolation of the respective alcohols upon their purposeful hydrolysis. Salts **3** were most easily and safely collected from a laboratory-sized mill in a dry box and are stable in the absence of moisture (large mills would use internal gas cycle for the collection[8b]). All salts **3a**–**3ζ** had melting points >300 °C. The thermal stability of **3g** and **3δ** was evaluated. Their heating to 150 °C for 1 h in a vacuum did not change them. All compounds **3a**–ζ are very easily hydrolyzed. If a KBr pellet of **3a** was left in ambient air for 24 h its initial IR bands were lost and an almost pure spectrum of **4a** was obtained. Other qualities of **3a**–**3ζ** corresponded to those reported for **3g** and more extensive property studies and uses of **3** are now strongly facilitated and urged.

The present atom-economic ball milling technique provides a newer, easier, superior, and most sustainable way to pure compounds **3** by avoiding solvents and excess amount of reagents. The pure compounds are now directly obtained in the solid state and we have no problems with hydrolysis by filtration of voluminous precipitates from solution reactions in THF[3] or DMSO.[4] Other methods for the production of tetraalkoxyborates are the tedious addition of metal alkoxylates to boric acid esters in the respective alcohol,[17] or the alcohol exchange of tetraalkoxyborates.[18] Phenols and NaBH$_4$ (**2**) react to give related tetraaryloxyborates in THF,[19] or as a result of their low hydrolytic sensitivity, by reaction of boric acid with phenols.[20]

Hydrolysis of Sodium Tetraalkoxyborates

The reduction of aldehydes and ketones with an excess amount of NaBH$_4$ (**2**) in solution usually gives the corresponding alcohols together with much waste, also from further auxiliaries,[5–7] even though aqueous media appeared attractive.[1,2] Therefore, the quantitative hydrolysis of the now easily available pure tetraalkoxyborates **3** under very mild conditions by simple addition of water is rewarding. Filtration or extractive workup yields the alcohols and an aqueous solution of easily recycled stoichiometric sodium borate (Scheme 1). An interesting non-extractive workup is also possible if a stoichiometric amount of a salt with available crystal water such as Na$_2$SO$_4$·10H$_2$O is added and co-milled after the production of **3**. This technique is described in the Experimental Section for the isolation of methanol (**4s**) from **3s**. In any case, and unlike the contemporary reductions, all components can be easily recovered or recycled. The variation of this reduction technique is enormous (Table 1) and no organic side products but only uniform alcohols are quantitatively obtained.

Regiospecificity and Stereoselectivity

Table 1 contains several aldehydes and ketones that could have given different products. For example, the regioselectivity of the solvent-free NaBH$_4$ reduction was examined by reaction of ω-bromoacetophenone (**1γ**). The only product was 2-bromo-1-phenylethanol (**4γ**). No substitution of the bromine atom occurred and no phenyloxirane was formed by cyclizing elimination of HBr. It was reported that simple grinding in the absence or in the presence of a boric acid activator yielded only 20 or 50 % conversion, respectively, of **1γ** to give **4γ**.[6] This was probably due to organic side reactions.

Another problem with regioselectivity upon reductions with **2**, boron hydrides, or metal hydrides is competition of 1,2- and 1,4-hydrogenation of conjugated aldehydes and ketones. The syntheses of allylic alcohols (1,2-hydrogenation) rather than saturated alcohols (1,4-hydrogenation followed by tautomerization and another hydrogenation) are of importance, because allylic alcohols are intermediates in the production of pharmaceuticals, agrochemicals, and fragrances. Therefore, regioselective reduction of conjugated carbonyl compounds has been extensively studied in synthetic chemistry by using rather elaborate and diverse techniques, but often expensive reagents are employed and dangerous wastes are produced.[21–27] Fortunately, our versatile present technique exclusively provides the (*E*)-allylic alcohols when checked with (*E*)-crotonaldehyde (**1t**) and (*E*)-cinnamaldehyde (**1u**). Both kneading milling and solid-state molecular milling gave exclusively allylic alcohols **4t** and **4u**, respectively, with quantitative yield if only the safe and cheap unmodified reagent sodium borohydride (**2**) was used. Saturated alcohols were not detected at all (Scheme 2). This is a major advance, when it is recalled that sodium borohydride reductions of conjugated aldehydes and ketones in solutions generally lead to substantial amounts of the saturated alcohols.[21–27]
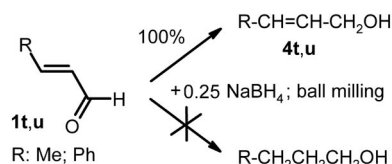
Scheme 2. Regiospecific reduction of α,β-unsaturated aldehydes **1t**,**u** by solvent-free stoichiometric ball milling with NaBH$_4$ (**2**).

Bifunctional benzil (**1ζ**) is quantitatively and specifically reduced by NaBH$_4$ (**2**) when used in a 4:1 stoichiometric ratio to give racemic benzoin (**4ζ**) without detectable amounts of dihydrobenzoin (**5/6**). This means that all the BH$_4^-$ anions have most rapidly reacted with one fourth of the available molecules of **1ζ** by transferring their first hydrogen atom, before such primary reduction product could react with another BH$_4^-$ anion. It also excludes intramolecular transfer of hydrogen to the second carbonyl group: the other three B–H bonds transferred to the rest of the stoichiometric molecules **1ζ**. Such a result has never been described in solution reactions of these reagents. Further-

more, both carbonyl groups of **1ζ** were quantitatively reduced if a 2:1 ratio of **1ζ** and **2** was applied under the otherwise identical conditions of Table 1. This stoichiometric synthesis provides *meso*-**5** and *rac*-**6** in 80 and 20% yield (¹H NMR spectroscopy; Scheme 3). This stereoselectivity compares with the reported 100:0 ratio in methanol (2 h at 25 °C)[28] and the 85:15 ratio of **5/6** in ethanol (1 **1ζ** + 2 **2**, overnight).[29]
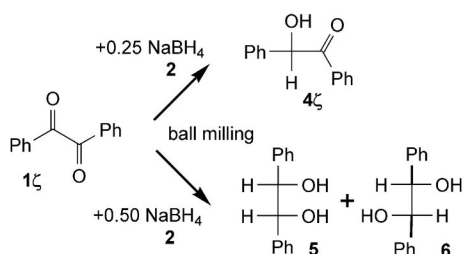
Scheme 3. Specific and stereoselective solvent-free reduction of benzil (**1ζ**) with NaBH₄ by ball milling.

Conclusions

Temperature-controlled milling of aldehydes and ketones with a stoichiometric amount of NaBH₄ (**2**) (4:1 ratio) under varied conditions in a commercially available ball mill is the easiest, fastest, and simplest path to varied sodium tetraalkoxyborates **3**. These very-high-melting, stable solids with extreme sensitivity towards hydrolysis are regiospecifically formed and can be of practical use for the chemisorption of gases up to the purification of inert gases from trace impurities,[30] for chemical sensors (ion-recognition sites),[19] and for industrial purposes such as their use as polymerization catalysts.[31] Further uses of hitherto not reasonably available salts **3** do suggest themselves. Also, alcohols **4** that are liberated upon water treatment of **3** are quantitatively obtained and it is particularly useful that no side reactions occur even with the highly active bromine of phenacylbromide (**1γ**). α,β-Unsaturated aldehydes (**1t,u**) react smoothly and quantitatively to give highly versatile allylic alcohols as synthetic building blocks that are now easily isolated and unspoiled from saturated alcohols as a result of the absence of any competition of 1,4-hydrogenation with our new technique. Also, the specific reduction of benzil (**1ζ**) to give benzoin (**4ζ**) is unusual and important. These new processes are of uppermost sustainability and synthetic use as temperature-controlled ball milling is executed. So-called high-speed ball milling without temperature control "in open atmosphere" (speed not specified) led to inferior results at fourfold excess of B–H bonds in the reduction of **4b,c,g,h,w,x** with **2** to give the primary (65–70%) and secondary alcohols (70%) after 1 and 6 h milling, respectively.[5e] Similarly, the reduction of aromatic esters (LiBH₄, 17 h) led to only 32–85% yield.[5e] An improvement is to be expected when optimized ball milling would be applied. Missing temperature control in vibrational mills and excessive milling impact[32] may also have led to inferior yields and very long milling times (compare ref.[9]). The use of

high-speed and planetary mills still seems to be governed by undue literature claims of "mechanochemistry" (implying "molecular activation") when only intermolecular bonds are mechanically broken in solvent-free reactions.[33] However, too high an impact is often detrimental even in reactions with mechanical breaking of chemical bonds.[11]

The excellent performance of the solvent-free milling technique in the NaBH₄ reductions would suggest its use in stereochemical studies with 1,2-, 1,3-, 1,4- and other diketones or polyketones. This will certainly provide interesting bis- or poly(sodium tetraalkoxyborates) and probably other stereoselectivities of the diols that will be obtained upon hydrolysis than those obtainable in the corresponding solution reactions. More studies on the application of the present methods and further use of state-of-the-art ball milling in organic synthesis are therefore in progress and will be presented in due course.

Experimental Section

General Methods: All chemicals were purchased from Merck, Aldrich, or Fluka and used as received except for benzaldehyde (**1g**) that had been freshly distilled. The ball mill was a Retsch MM 200 swing mill with its 3D-driving of the balls. A 10-mL stainless steel double-walled beaker with fittings for circulating liquids was applied. Two stainless steel balls with 12-mm diameter were used, and the milling frequency was at 20–25 Hz at the temperatures given in Table 1 and provided by circulating water of the appropriate temperature. In the absence of temperature control, the temperature would rise within the milling beaker from 25 to about 30 °C even for these short times. Melting points were measured in capillary tubes with an electrothermal 9200 apparatus and are uncorrected. Low melting points close to room temperature were measured in the storage flask by slow approach to the melting point in a thermostatted bath. Analytical TLC was carried out by using Merck 0.2 mm silica gel 60 or F-254 Al-plates for the detection of the conversions. IR spectra were recorded with a Perkin–Elmer 1720-X FTIR spectrometer by using KBr pellets. ¹H (500 MHz) and ¹³C NMR (125 MHz) spectra were obtained by using a Bruker DRX-500 Avance spectrometer, all in CDCl₃ (but [D₆]DMSO for **3**) at ambient temperature. Vapor-phase chromatography (VPC) for purity checks were recorded with a Perkin–Elmer 8420 capillary gas chromatograph. All of the already known products were characterized by comparison of their melting points and IR and NMR spectroscopic data with those reported in the literature.[13–16]

General Procedure for the Synthesis of Sodium Tetraalkoxyborates 3a–ζ: A clean, dry, temperature-controlled, 10-mL ball-mill vessel with 2 stainless steel balls was charged with aldehydes **1a–v** (**1s** as paraformaldehyde) or ketones **1w–ζ** (2.00 mmol) and NaBH₄ (**2**; 0.5 mmol). Diketone **1ζ** (2.00 mmol) was also reacted with **2** (1.00 mmol). The vessel was closed, and the milling was started at the temperatures given in Table 1 at a speed of 20–25 Hz. TLC was used to monitor the progress of the reaction. The milling was continued until the reaction was complete. Solid sodium tetraalkoxyborates **3** were collected from the milling beaker in a moisture-free glove box and handled in the glove box for the melting point sampling, KBr pellet preparation, NMR solution preparation, and other manipulations, because they rapidly became sticky with atmospheric moisture. All solids **3a–ζ** melted above 300 °C. ¹H NMR spectra in dry [D₆]DMSO were of little use due to strongly broadened peaks. Yields and purities of **3** were derived from the yields

of pure alcohols that were quantitatively isolated upon hydrolysis. Compounds **3w**, **3β**, sodium tetra-(2-propoxy)borate,[3] and **3g**[4] were previously characterized. The reported "solubility" of **3g** in cyclohexane[4] could however not be confirmed.

Typical Example. Sodium Tetra(4-chlorobenzyloxy)borate (3a): M.p. >300 °C. IR (dried KBr): $\tilde{v}$ = 2900, 1659, 1434, 1079, 956, 603, 549, 438 cm^{-1}; the KBr pellet when exposed to ambient air for 24 h completely lost the bands of **3a** and exhibited all of the known IR bands of **4a** with some minor additional bands and a significant band at 986–939 cm^{-1}. ^{1}H NMR ([D₆]DMSO): δ = 7.54, 4.69 ppm (br., 4:2 ratio).

Thermal Stability Tests of 3: About 50 mg of **3g**, or **3δ** in a 50-mL evacuated flask, were heated to 150 °C for 1 h. IR analysis in dried KBr indicated no change.

Isolation of Alcohols 4: Solid milling products **3a**–**ζ** were hydrolyzed with water. Insoluble solid alcohols were filtered off and dried. Soluble and liquid alcohols were isolated by extraction (3 to 5 times) from the water with ethyl ether in a small separating tube device and dried with MgSO₄·2H₂O that was filtered off and washed with ethyl ether for thermal reactivation. The solvent was recovered by isothermal distillation in a closed system, and the residue was freed from trace amounts of solvent by short-path distillation or sublimation. The purity of products **4** was confirmed by VPC analysis, and their identity was confirmed by comparison of their spectroscopic data and melting points with those in the literature (Table 1). The sodium borate content in the aqueous phases was ready for recycling as Na₂B₄O₇·10H₂O by evaporation and recrystallization, as no poisonous auxiliaries were used in the reduction process.

Isolation of Methanol from 3s after Hydrolysis with Na₂SO₄·10H₂O: After the milling of paraformaldehyde (**1s**; 90 mg, 3.0 mmol) with NaBH₄ (**2**; 28.5 mg, 0.75 mmol) at 25 °C for 20 min to give **4s** (m.p. >300 °C), Na₂SO₄·10H₂O (97 mg, 0.3 mmol) was added and milling was continued for 10 min. The hydrolytically liberated methanol was distilled to a cold trap at 77 K by vacuum pumping directly from the milling beaker to give a yield of 96 mg (100%) methanol. Similarly, most of the other alcohols in Table 1 might be isolated by this vacuum distillation technique with appropriate heating of the milling beaker if the use of extraction by an organic solvent should be avoided, even though the recycling of Na₂B₄O₇·10H₂O would not be facilitated by the addition of a different salt with crystal water. However, similar use of borax would remove this problem.

Test Run by Grinding of 1a with NaBH₄: 4-Chlorobenzaldehyde (**1a**; 140 mg, 1.0 mmol) and NaBH₄ (**2**; 38 mg, 1.0 mmol) were continuously ground in an agate mortar with pestle for 30 min. The mixture took up moisture from the air and a 36% ^{1}H NMR spectroscopic yield of 4-chlorobenzyl alcohol (**4a**) was obtained after extraction as above together with unreacted **1a** (64%).

Acknowledgments

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