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Solvent-free continuous flow reduction of aldehydes and ketones *via* mechanochemistry in a jacketed screw reactor

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We present a simple and efficient solvent-free method for the continuous flow reduction of aldehydes and ketones using sodium borohydride as a reducing agent at room temperature. By employing a jacketed screw reactor, this process achieves nearly complete conversion with residence times ranging from 2 to 10 minutes. The method has been demonstrated on ten representative aldehydes and ketones, highlighting its broad applicability and sustainability. This approach utilizes readily available starting materials, showcasing the potential of mechanochemistry for green and scalable chemical synthesis.

Introduction

In organic synthesis, reduction is one of the most fundamental reactions. The two most commonly used reducing agents are sodium borohydride (NaBH₄) and lithium aluminium hydride (LiAlH₄). NaBH₄ is widely used in industry due to its selectivity, safety, and versatility. The global sodium borohydride production reached around 826k tons in 2023.¹ It efficiently reduces aldehydes and ketones to alcohols under mild conditions, with minimal side reactions. It is also safer and more stable than LiAlH₄, making it easy to handle and compatible with protic and aprotic solvents. Industries use NaBH₄ in pharmaceutical synthesis,² paper bleaching,³ dye reduction,⁴ and hydrogen generation.⁵ It is cost-effective, aligns with green chemistry principles, and produces non-toxic by-products. Use of NaBH₄ along with catalysts can be extended further for enabling reductions of esters and nitriles. These features make it indispensable in pharmaceuticals, chemicals, textiles, and energy applications. Traditionally, flammable solvents such as ethanol, isopropanol (2-propanol), and methanol are used for reduction of aldehydes using NaBH₄.⁶ Use of solvents such as methanol, ethanol, and tetrahydrofuran (THF) is known for reducing

aldehydes and ketones using sodium borohydride. However, solvolysis can make aldehydes unstable in methanol or ethanol. Reduction in methanol needs a significant excess of NaBH₄.

In a recent study, Ishoni *et al.* have utilized a twin-screw reactor to reduce aldehydes in the presence of aqueous caustic solution as solvent.⁷ For synthesizing 18.76 grams of alcohol from an aldehyde, approximately 100 mL solvent was used,⁸ which needs to be neutralized later if implemented on a large scale. The literature also highlights that aldehydes can be directly reduced to alcohols in the presence of Lewis acids.

In 2022, Tanemura *et al.* demonstrated NaBH₄ reductions of aldehydes and ketones in methanol and ethanol with 99% conversion in 10–60 minutes.⁹ Despite this efficiency, conventional methods still require extended reaction times, large solvent volumes, and energy-intensive reflux. The reductions are strongly exothermic ($\Delta H \approx -530 \text{ kJ mol}^{-1}$), often necessitating semi-batch addition of NaBH₄ at low temperatures, which prolongs production.¹⁰ Over the past decade, various solvent-minimised strategies *viz.* grinding with solid acids, ball milling with liquid-assisted grinding, and sonication have been explored.^{11–21} While these methods exemplify that high reactivity can be used for accelerating the reaction, they suffer from limited scalability, variable reproducibility, and high energy demands (Table 1). Continuous processing offers clear advantages in handling exothermic reactions, as shown in systems employing Luche reagent or NaBH₄-packed columns^{22–24} but these often rely on solvents or sacrificial media. In contrast, solvent-free methods reduce waste, conserve energy, and often enhance selectivity and yield,^{25–29} though efficient handling of solid materials remains challenging. Screw reactors address this limitation and have been successfully applied to OLED materials, amides, esters, dyes, and APIs.^{30–36} Building on these advances, we explore their potential for continuous, solvent-free NaBH₄ mediated reductions.







In this communication, we discuss solvent-free solid–solid and solid–liquid reactions for reduction of aldehyde and ketone functional groups in a PTFE single continuous glass-jacketed

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Table 1 Various methods of reduction using NaBH₄ with no or with minimal solvent

Ref.	Solvent [additive]	Reactor type	Substrate(s)	Key remarks
7	Caustic solution (aq)		4-Chlorobenzaldehyde	Continuous flow, aqueous caustic solution used
8	MeOH		Benzylideneacetone	Uses solvent, requires distillation for recovery
9	Solvent-free		Benzaldehyde, vanillin, furfural	Scale-up <i>via</i> ball milling is not safe or feasible
10	Solvent-free		Furfural, 2-naphthaldehyde	Mechanochemical approach in batch
11	MeOH, EtOH, THF		Benzophenone, acetophenone	Solvent necessary for reaction
This work	Solvent-free [boric acid for ketones]		Aldehydes and ketones	Solvent-free, continuous, safer heat management

screw reactor. This approach facilitates the efficient processing of soft solid materials or pastes.

Reaction setup

Initially, the solvent-free synthesis was done in batch mode using a mortar and pestle. Subsequently, the experiments were performed in continuous mode using a single PTFE (polytetrafluoroethylene) screw reactor confined in a glass jacket (Fig. 1). All reactants were in solid or liquid forms, and the residence time was controlled by varying the speed of a calibrated motor and aligning the screw at different angles (vertical and horizontal). The glass jacket has a 39.6 mm outer diameter and an 18 mm inner diameter. It houses a 315 mm long PTFE screw with a diameter of 17.8 mm, which leaves a gap of only 0.2 mm between the jacket wall and the screw threads.

During the experiment, initially, the motor connected to the screw reactor was turned on followed by the motors for the two screws that fed the reactants. The reaction was observed to initiate immediately after the reactants came into contact with each other and the reaction continued to proceed from the inlet to the outlet. The speed was managed with a variable frequency drive motor (Remi, India). The extruder outlet discharges directly into a continuous stirred tank reactor (CSTR-1) with intense mixing, where water is continuously added to quench the alkoxide intermediate. The reaction mass was facilitated to exit the CSTR *via* overflow directly into CSTR-2, where ethyl acetate helped continuous extraction, followed by phase separation using a conventional layer separator and a Zyput membrane separator. The system was designed in-house and manufactured locally (Alpro Industries Pvt. Ltd, India).

Results & discussion

Initial batch experiments were carried out solely to confirm the feasibility of sodium borohydride-mediated reduction of carbonyl compounds and to identify suitable stoichiometric ranges. These reactions were performed using a mortar and pestle at room temperature. In some cases, methanol was used to assist mixing and monitoring; however, these batch experiments were not intended to directly define the conditions for continuous processing. Instead, they served as qualitative screening studies to understand the influence of sodium borohydride equivalents and substrate electronic effects on reaction time. It was observed that one equivalent of NaBH₄ typically resulted in complete aldehyde reduction within 15–30 min, whereas reducing the NaBH₄ loading to 0.5 or 0.25 equivalents significantly increased reaction time to 0.5–1 hour. On the other hand, electron-withdrawing substituents on the

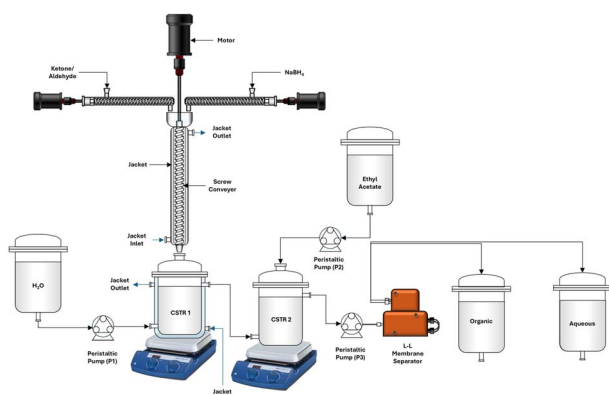


Fig. 1 Reaction set-up for continuous flow reduction of aldehydes and ketones.



aromatic ring facilitated reduction even at lower NaBH_4 equivalents. Since this approach lacks scalability and offers inefficient mixing as well as heat transfer, all further experiments were performed using a continuous mechanochemical approach using a single screw reactor.

Benzaldehyde was selected as the model substrate, and equimolar quantities of benzaldehyde and sodium borohydride were continuously fed into the reactor at room temperature. The screw rotation speed was systematically varied to control the residence time, while all other parameters were held constant. A hydride transfer reaction takes place in the screw reactor forming the corresponding benzyl alkoxide intermediate. Upon completion of the reduction, the extruder outlet discharges directly into a CSTR, where water is continuously introduced to quench the alkoxide intermediate, converting it to the corresponding alcohol. This reduction step is exothermic; heat is generated inside the screw reactor. Continuous stirring ensures efficient mixing and complete quenching. The quenched mixture exits the CSTR through an overflow outlet and is continuously transferred to CSTR-2, where ethyl acetate is added *via* (P-2). This mixture is then pumped by (P-3) to a liquid-liquid membrane separator for downstream phase separation occurs, and the organic layer containing the product is collected, while the aqueous layer is removed. This integrated setup enables uninterrupted continuous operation without the need to stop the extruder during downstream processing.

As summarized in Table 2, high screw speeds (180 rpm, 30 s residence time) resulted in incomplete conversion, affording only 25% isolated yield of benzyl alcohol (2a), due to the short residence time. Progressive reduction of the screw speed increased residence time and led to higher conversion: 42% yield at 120 rpm (45 s), 60% at 90 rpm (60 s), and 87% at 60 rpm (100 s). Optimal performance was achieved at 50 rpm, corresponding to a residence time of 120 s, yielding benzyl alcohol (2a) in 99% isolated yield. These conditions were selected as the optimized parameters for further studies. To monitor reaction progress and determine the optimal residence time, samples were collected directly from the extruder outlet at 30 s, 45 s, 60 s,

90 s, and 120 s residence times (as governed by the screw speed and feed rate). Each collected sample was immediately quenched with water and extracted with ethyl acetate, and the organic phase was analyzed by ATR-FTIR spectroscopy (Fig. 2). The disappearance of the characteristic aldehyde $\text{C}=\text{O}$ stretching band ($\sim 1700\text{ cm}^{-1}$) and the appearance of $\text{O}-\text{H}$ ($\sim 3350\text{ cm}^{-1}$) stretching bands confirmed the progressive conversion of benzaldehyde to benzyl alcohol. This systematic sampling allowed correlation of residence time with reaction completion and enabled identification of the optimal operating conditions. In conventional batch reactors, this often results in localized overheating or requires slow reagent addition. In contrast, the jacketed single-screw reactor used in our study provides continuous and efficient heat management. The screw reactor is equipped with an external jacket that allows the circulation of cooling fluid for temperature control. During operation, a modest exothermic increase of approximately $5\text{--}7\text{ }^\circ\text{C}$ was observed if operated in adiabatic mode. This exotherm can be efficiently dissipated by circulating cooling water through the reactor jacket to maintain the desired operating temperature. No hydrogen evolution was observed during extrusion. Hydrogen generation occurred only during the downstream aqueous quench, indicating complete formation of the alkoxide intermediate inside the screw reactor. ATR-FTIR spectra of material collected directly from the extruder further confirmed the disappearance of the aldehyde $\text{C}=\text{O}$ band prior to quenching (see the SI).

Optimization table

Optimization of reaction conditions for reduction of aldehyde compounds.

In a vertical single-screw reactor, under equimolar feed conditions (*i.e.* the flow rate is 2.40 mL min^{-1} for benzaldehyde and 0.88 g min^{-1} for NaBH_4 at room temperature) at a residence time of 60 s, it showed incomplete conversion on TLC, while for a residence time of 2 minutes, 99% yield of benzyl alcohol (2a) was obtained. The substrate scope for reducing aldehyde derivatives was investigated using the optimized conditions. However, the additional reaction time of 60 s ensured complete

Table 2 Conditions: benzaldehyde (1) (0.047 mol, one equivalent), sodium borohydride (0.047 mol, one equivalent), at room temperature

Entry	Screw (rpm)	Residence time (s)	Isolated yield (%)
1	180	30	25
2	120	45	42
3	90	60	60
4	60	100	87
5	50	120	99

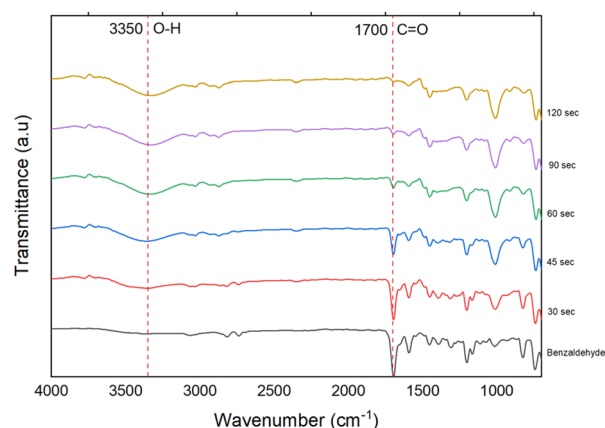
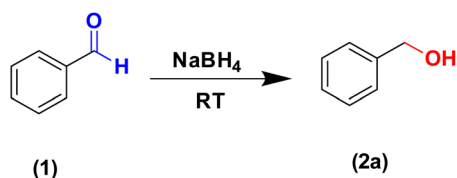


Fig. 2 Time-dependent ATR-FTIR spectra.



conversion, resulting in a 99% yield of benzyl alcohol (2a) after workup.

Using the optimized conditions, a wide range of aldehydes were subjected to a reduction reaction. Electron-rich aldehydes such as 3,4,5-trimethoxybenzaldehyde got reduced rapidly, achieving complete conversion within approximately 1 min and affording the corresponding alcohol (2c) in 99% isolated yield. Electron-deficient substrates, including nitro- and halogen-substituted benzaldehydes, also underwent efficient reduction within 1–2 min, providing products (2d–2e, 2h) in 96–99% yields.

In the case of bulky substrates such as 9-anthracenecarboxaldehyde, movement of the reaction mass inside the screw reactor was slow due to its sticky nature. Under these circumstances, the addition of a minimal amount (0.2 to 0.4 mL) of methanol for 9 g material was required solely to improve flow behavior, allowing complete conversion within 5 min and yielding 1-pyrenemethanol (2f) in 99% yield after workup. This solvent was not required for the chemical transformation itself. Ketones were found to be less reactive than aldehydes under identical conditions. To address this limitation, boric acid (30 mol%) was co-fed with the ketone substrate and sodium borohydride into the screw reactor, where it acts as a Lewis acid to activate the carbonyl group toward hydride transfer. Under these conditions, ketones such as acetophenone derivatives and trifluoromethyl ketones were successfully reduced within 6–8 min residence time, affording the corresponding alcohols (2i–2k) in 97–98% isolated yields.

Overall, the residence time required for complete conversion ranged from 1 to 10 min, depending on the substrate structure and reactivity, consistently delivering high isolated yields (90–99%). Increasing the NaBH_4 loading further accelerated the reaction but was not pursued due to economic considerations.

This process eliminates the need for column chromatography, as it achieves 100% conversion with the formation of a single product.

The scaled 50 mL screw reactor was operated continuously for 2 h under optimized conditions to evaluate operational stability. Benzaldehyde was continuously fed at a flow rate of $16.15 \text{ mL min}^{-1}$, while sodium borohydride was introduced at 5.9 g min^{-1} to maintain the required stoichiometric ratio. During this period, consistent conversion ($\approx 99\%$) was achieved without observable fouling, clogging, or performance decline. Based on the experimentally measured substrate throughput and isolated yield, approximately 2.06 kg of benzyl alcohol was produced during the 2 hour continuous operation, demonstrating the system's high productivity and stable performance.

The approach was also applicable to synthesis of various alcohol derivatives from aldehydes under optimized reaction conditions, *i.e.*, furfural alcohol (2m) and 1-hexanol (2l). The quantitative yield of all products was obtained following the straightforward workup procedure. The products were subsequently characterized using ^1H NMR and ^{13}C NMR spectroscopy, confirming their structural integrity and purity (Fig. 3).

The heat of the reduction reaction of any organic substrate using sodium borohydride varies in the range of -65 kJ mol^{-1} to -100 kJ mol^{-1} . This implies that for the given scale of

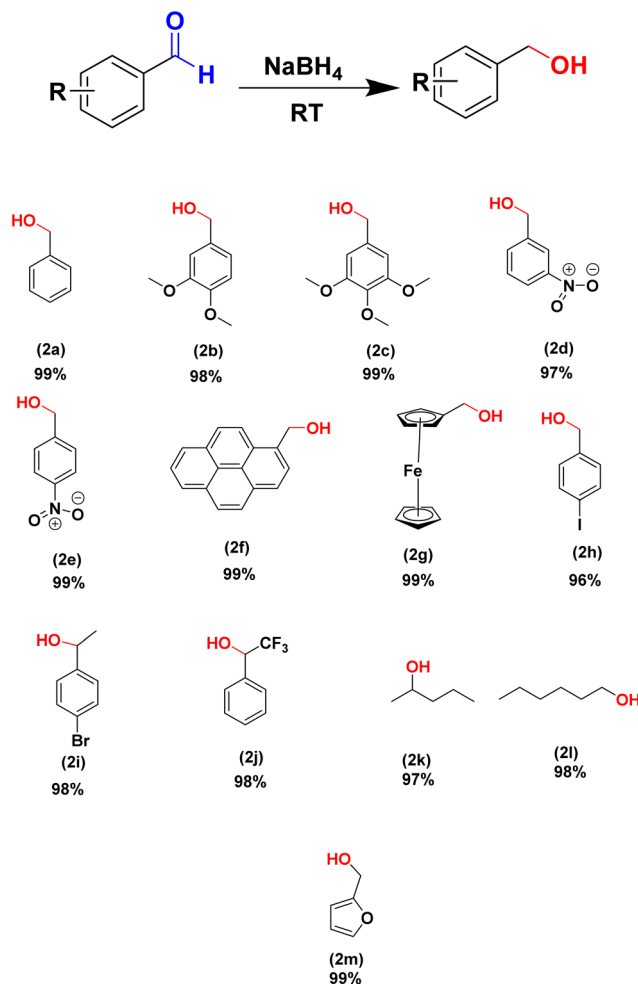


Fig. 3 Scope of derivatives for the reduction of aldehydes and ketones in a continuous flow mechanochemical process using a single screw reactor.

operation in the laboratory, the overall heat duty will vary from 0.243 kW to 1.122 kW, which is relatively manageable. However, upon scaling-up such a system by 100 times, one has to take care of 100 times higher heat duty as well as very steep heat generation rates. In such a situation, scale-up of screw reactors to a certain extent followed by numbering-up can be a realistic approach. We are exploring such approaches and the results will be reported separately to evaluate realistic scale-up options. In such a case, heat from this reaction can be effectively used for some useful purpose. Similarly, excess NaBH_4 would release hydrogen from the CSTR during its quenching, which can be compressed and used for other reduction reactions.

Conclusions

A simple and efficient solvent-free method for the continuous flow reduction of aldehydes and ketones using sodium borohydride as a reducing agent at room temperature in a single screw reactor is reported. Nearly complete conversion was achieved in 2 to 10 minutes for ten representative aldehydes and



ketones. More work on scale-up is in progress and will be reported in an appropriate engineering journal. Using a single screw reactor accelerates early stage developments due to its simplicity and compactness.

Conflicts of interest

The authors have filed a patent based on part of the information in this paper.

Data availability

The data that support the findings of this study are available in the supplementary information (SI) of this article. Supplementary information is available. See DOI: <https://doi.org/10.1039/d5mr00127g>.

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