Mechanically induced oxidation of alcohols to aldehydes and ketones in ambient air: Revisiting TEMPO-assisted oxidations

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Abstract

The present work addresses the development of an eco-friendly and cost-efficient protocol for the oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones by mechanical processing under air. Ball milling was shown to promote the quantitative conversion of a broad set of alcohols into carbonyl compounds with no trace of an over-oxidation to carboxylic acids. The mechanochemical reaction exhibited higher yields and rates than the classical, homogeneous, TEMPO-based oxidation.

Introduction

Aldehydes and ketones constitute some of the most powerful and versatile building blocks that are available for a variety of synthetic transformations [1]. The reason for this lies in the capability of the carbonyl group to generate other possible functional groups through more or less complex chemical transformations [2]. The ubiquity of the carbonyl group in biomolecules adds further value to its chemistry, which is crucial for strategic areas of science related to biochemistry and biotechnology [3,4].

In principle, the oxidation of alcohols represents a convenient option for preparing aldehydes and ketones, as alcohols are among the most abundant naturally occurring organic compounds [5,6]. Although the literature provides a plethora of
generic indications and detailed recipes on this subject [7-10], the selective oxidation of primary alcohols to the corresponding aldehydes is one of the most difficult transformations to control because of the marked propensity towards over-oxidation to the respective carboxylic acid [11,12]. In addition, the appeal of this reaction is reduced by the need to use stoichiometric amounts of strong oxidising agents that are extremely toxic, hazardous, and expensive [13-17]. The use of the stable tetraalkylnitroxyl radical TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) as the catalytic oxidising agent (Anelli–Montanari reaction) has been the main driving force behind the successful development of greener oxidation procedures [18,19]. The classic Anelli–Montanari oxidation requires aqueous NaOCl (bleach) as a co-oxidant, and it works in a CH₂Cl₂/H₂O two-phase system buffered at pH 8.5–9.5 [20]. Over the years, bleach has been replaced with an impressively long list of other co-oxidants [21], which are sometimes very expensive, and exhibit a wide spectrum of effectiveness (Scheme 1) [22,23]. Recently, Stahl [24] developed a practical Cu²⁺/TEMPO-based catalyst for the selective oxidation of primary alcohols to aldehydes under ambient aerobic conditions (Scheme 1) [25,26]. The procedure is operationally simple and extremely effective in terms of both chemoselectivity and reaction yield [27,28]. Gao (2016) further improved this methodology by replacing the bpy/Cu²⁺/NMI catalyst system with Fe(NO₃)₃·9H₂O (10 mol %), 9-azabicyclo[3.3.1]nonane-1-oxyl (ABNO, 3 mol %), CH₃CN, air. c) Gao (2016) protocol: [Cu(MeCN)₄]OTf (5 mol %), bpy (5 mol %), TEMPO (5 mol %), NMI (10 mol %), CH₃CN, air. c) Gao (2016) protocol: Fe(NO₃)₃·9H₂O (10 mol %), 9-azabicyclo[3.3.1]nonane-1-oxyl (ABNO, 1–3 mol %), CH₃CN, air.

Despite the advances, the choice of solvent for TEMPO-based oxidative procedures remains a crucial issue in the development of greener alternatives to traditional alcohol oxidation reactions [32-34]. In particular, the lack of a green option significantly decreases the attractiveness of the proposed synthetic routes, as the solvent is the main component of the reaction system and, thus, the main source of waste in organic synthesis [35]. By far, performing the oxidation of alcohols under solvent-free conditions represents the best strategy to radically eliminate possible drawbacks in regard to waste disposal [36,37]. In this respect, the mechanical activation of solids [38-42], in the absence of solvents [43], or in the presence of catalytic amounts of liquid [44,45], holds significant promise [46-58].

Rooted in ancient practices from the dawn of civilization, a thin historical thread twisting across human history connects powder metallurgy and mineralurgy with science and engineering at the cutting edge of research in the fields of materials science and chemistry [59]. Presently, mechanochemistry is one of the fastest growing areas of investigation that aims to provide alternative methods to traditional syntheses in organic and inorganic chemistry [49,60,61]. Mechanochemistry is also used in supramolecular chemistry [62] and metal-organic chemistry [63].

In this work, we show that mechanical processing by ball milling can represent a viable solution to the selective oxidation of alcohols to aldehydes. Specifically, we investigated the potential of a mechanically activated TEMPO-based oxidative procedure [64].

Results and Discussion
We began our investigation with an attempt to replicate Gao’s procedure in a stainless steel reactor of a commercial ball mill in the presence of stainless steel balls and air, and in the absence of solvent. The oxidation of solid 4-nitrobenzyl alcohol (1a) to 4-nitrobenzaldehyde (2a) was selected as a model reaction. Unfortunately, the alcohol-to-aldehyde conversion was very low (<15%), and the use of larger amounts of the catalyst as well as molecular oxygen instead of air did not result in a significant improvement (Scheme 2, left side). To our great surprise, using Stahl’s catalyst, the mechanically activated oxidation of the model substrate 1a under solvent-free conditions proceed so quickly and selectively that it was complete within just a few minutes. The progress of the reaction was monitored by TLC and GC–MS analysis until the completion of the reaction. The experimental protocol involved two stages, namely the preparation of the catalytic system and the final oxidation reaction. During the first stage [Cu(MeCN)₄]OTf (5 mol %), 2,2’-bipyridine (5 mol %), NMI (10 mol %), and TEMPO (5 mol %) were milled (1 min) in a stainless steel reactor using four stainless steel balls of different sizes. Following the mechanical treatment, the catalyst uniformly covered the reactor walls forming a dark red/brown thin film. Subsequently, solid
was only achieved after solvent extraction. A minor modification to the synthetic protocol, involving the use of additional zirconia balls (four balls × 5 mm Ø, 7 balls × 12 mm Ø) and opening the jar (3 min) to air during the time interval between two consecutive cycles, gave 2b in 96% overall yield even on the gram scale. On the gram scale, the mechanical activation no longer required an additional solvent to recover the final aldehyde during purification. With the optimized reaction conditions in hand, a series of common benzyl alcohols 1b–n with different functional groups was then tested in order to examine the scope of the reaction (Scheme 3). To our satisfaction, very high yields (>90%) were obtained with all tested compounds, except 2n (39%).

Next, we replaced the starting stainless-steel grinding jar and balls with a zirconia jar (45 mL) and six zirconium oxide balls (5 and 12 mm Ø) with the aim of avoiding contamination due to metal release. Under these conditions, it was possible to reduce the loading of [Cu(MeCN)4]OTf, 2,2′-bipyridine and TEMPO to 3 mol % and NMI loading to 7 mol % without affecting the reaction time or the product yield. Interestingly, the alcohol-to-aldehyde oxidation under ball milling conditions was faster (15 min overall) than that in solution (1 h) [25]. In addition, the absence of a solvent facilitated the purification of the final aldehyde. Specifically, the reaction crude was transferred from the reactor into a beaker containing an aqueous 10% citric acid solution [66,67], and the desired product precipitated as a solid. If necessary, the crude product could be further purified via filtering on a short pad of silica gel to give final aldehyde 2a with a higher degree of purity (>95% as determined by GC–MS analysis).

Since most common alcohols are, unfortunately, liquids at room temperature, their mechanical activation requires using a versatile dispersant. Ideally, a dispersant should not interfere with the oxidation reaction, and should be inexpensive and eco-friendly, if possible. As a first choice, we dispersed benzyl alcohol (1b) on alumina and silica gel. However, the reaction did not go to completion. In contrast, it proceeded smoothly (10 min) and in high yields when Na2SO4 and NaCl [68] were used as dispersants. Furthermore, the use of sodium chloride (500 mg per mmol of alcohol) facilitated the transfer of the reaction mixture from the reactor to the separating funnel containing the aqueous 10% citric acid solution. On the microscale (2 mmol), the full recovery of benzaldehyde was only achieved after solvent extraction. A minor modification to the synthetic protocol, involving the use of additional zirconia balls (four balls × 5 mm Ø, 7 balls × 12 mm Ø) and opening the jar (3 min) to air during the time interval between two consecutive cycles, gave 2b in 96% overall yield even on the gram scale. On the gram scale, the mechanical activation no longer required an additional solvent to recover the final aldehyde during purification. With the optimized reaction conditions in hand, a series of common benzyl alcohols 1b–n with different functional groups was then tested in order to examine the scope of the reaction (Scheme 3). To our satisfaction, very high yields (>90%) were obtained with all tested compounds, except 2n (39%).

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prolonged milling times led to the decomposition of the final aldehyde. These promising results prompted us to undertake additional studies on secondary alcohols. The optimised ball milling protocol was applied to alcohols 1o–v. Excellent yields of the ketones 2o–v were obtained (Scheme 4). Notably, the product yield was not significantly affected by the position or electronic nature of the substituents on the aromatic ring of the alcohols.

Encouraged by the facile oxidation of benzyl alcohols, the scope of the reaction was finally extended to the formation of more challenging aliphatic aldehydes. Unfortunately, non-acti-
vated aliphatic alcohols did not react efficiently under the reaction conditions, and very low alcohol-to-aldehyde conversions occurred. The extension of milling times to 3 h failed to result in improved yields of all tested substrates: 3-phenyl-1-propanol, cyclohexanol and nonanol. Despite several attempts to improve the alcohol-to-aldehyde conversion, by, for instance, milling under an oxygen atmosphere and the use of more reactive co-oxidant catalysts [69], no significant improvements were observed.

Conclusion

We have developed a TEMPO-based oxidative procedure for the air oxidation of primary and secondary benzyl alcohols to the corresponding aldehydes and ketones under ball milling conditions. A library of common alcohols was efficiently converted into carbonyl compounds with no trace of over-oxidation to the carboxylic acids. The final products could be easily separated/purified from the crude reaction mixture without using toxic organic solvents. Under mechanical activation conditions, the reactions provided better yields and proceeded faster than classical, homogeneous phase TEMPO-based oxidations. Studies are underway to identify more effective TEMPO-based catalysts that are also capable of promoting the oxidation of non-activated alcohols.

Experimental

General procedure to prepare carbonyl compounds 2a–v.

| Compound | Yield | Purity |
|----------|-------|--------|
| 2a       | 195 mg, 92% | >93% by GC analysis |
| 2b       | 104 mg, 78% | >93% by GC analysis |

The air oxidation of primary and secondary benzyl alcohols was monitored by TLC analysis. The progress of the reaction was monitored by TLC analysis. The final products could be easily separated/purified from the crude reaction mixture without using toxic organic solvents. Under mechanical activation conditions, the reactions provided better yields and proceeded faster than classical, homogeneous phase TEMPO-based oxidations. Studies are underway to identify more effective TEMPO-based catalysts that are also capable of promoting the oxidation of non-activated alcohols.

Supporting Information

Supporting Information File 1

Experimental part and NMR spectra.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-13-202-S1.pdf]

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In 2015, Mal et al. reported the first example of a very interesting solvent free ball-milling oxidation of activated primary alcohols to aldehyde using NBS (1.5 equiv) or oxone (0.6 equiv) as co-oxidising agents. This paper has laid the foundation for further studies on this topic.

The formalism for mechanochemically activated reactions was proposed here.

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