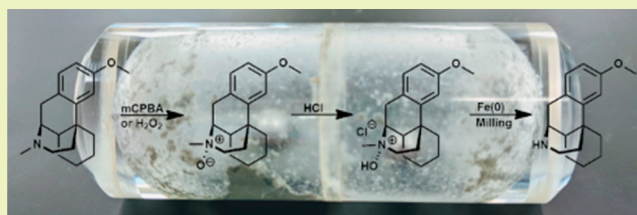


Liquid Assisted Grinding for the *N*-Demethylation of AlkaloidsJon Kyle Awalt,<sup>†,§</sup> Peter J. Scammells,<sup>‡,§</sup> and Robert D. Singer<sup>\*,†,§</sup><sup>†</sup>Atlantic Centre for Green Chemistry, Department of Chemistry, Saint Mary's University, 923 Robie Street, Halifax, Nova Scotia B3H 3C3, Canada<sup>‡</sup>Medicinal Chemistry, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria 3052, Australia

## Supporting Information

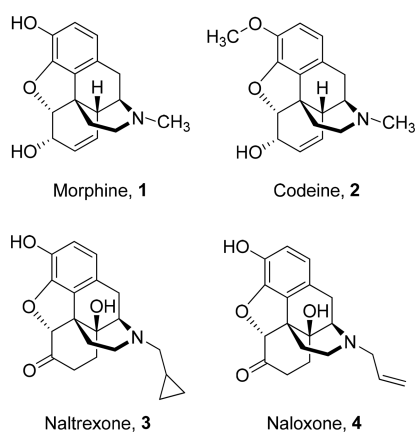
**ABSTRACT:** A mechanochemical approach has been demonstrated for the selective cleavage of nitrogen–carbon bonds in the *N*-demethylation of various alkaloids relevant in the pharmaceutical industry. This methodology employs a range of so-called “liquid additives” used in microliter quantities in liquid assisted grinding rather than “solvents” used in solution phase reactions. Green liquid additives such as alcohols, water, PEG and ionic liquids as well as a nonchemical, mechanical approach for the generation of nanoscale Fe<sup>0</sup> dust significantly improve the green attributes of the *N*-demethylation process.

**KEYWORDS:** Liquid assisted grinding, Mechanochemistry, *N*-Demethylation, Alkaloid, Liquid additive



## INTRODUCTION

A key step in the synthesis of semisynthetic opioid pharmaceuticals is the removal of the *N*-methyl group found in naturally occurring opiates such as morphine, **1**, and codeine, **2**, allowing for new functionality to be installed at the nitrogen atom. This strategy is evident in drugs such as naltrexone, **3**, and naloxone, **4**, which contain *N*-cyclopropylmethyl and *N*-allyl groups, respectively (Figure 1).



**Figure 1.** Naturally occurring opiate alkaloids and semisynthetic opioid pharmaceuticals used for treatment of opioid overdose.

Inclusion of a nonmethyl *N*-alkyl group is rationalized by the “message-address” concept, where varying this “message” group typically allows control of agonist or antagonist activity.<sup>1</sup> Traditional methods for the *N*-demethylation of alkaloids include the von Braun reaction<sup>2</sup> and the use of chloroformate reagents,<sup>3</sup> both of which have significant drawbacks. The von Braun reaction utilizes cyanogen bromide while other reactions

rely on the use of acid anhydrides or chlorides, both of which can be toxic and expensive.

Furthermore, in both cases the resulting intermediate must be further processed in order to yield the *N*-nor product. These shortcomings resulted in the need for a new method of *N*-demethylation and the development of the nonclassical Polonovski reaction.<sup>4</sup> This reaction utilizes an iron catalyst to afford the *N*-nor product with no further modification necessary, thereby reducing the number of synthetic steps. Several iron catalysts have been investigated including FeSO<sub>4</sub>,<sup>4</sup> and Fe<sup>0</sup> sources,<sup>5</sup> with nanoscale zerovalent iron (nZVI) and Fe<sub>3</sub>(CO)<sub>12</sub> being the most efficient catalysts reported to date.<sup>6</sup> When these catalysts were employed in the green reaction solvent, *i*-PrOH, isolated yields of greater than 85% of the *N*-nor product were achieved in under 1 h for the *N*-demethylation of the pseudo-opioid dextromethorphan (DXM), **5a** (Figure 2). This represents a significant improvement when compared to a 21 h reaction time when using Fe<sup>0</sup> dust and over 30 h when using FeSO<sub>4</sub>.<sup>6</sup> Use of green solvents also represents a dramatic improvement compared to chlorinated solvents utilized previously.

Though the choice of solvent to be used in a reaction is an important consideration, so too is the total volume of solvent used. In the pharmaceutical industry, 80–90% of the nonaqueous waste generated is due to solvents.<sup>7</sup> Hence, a reduction in solvent usage can substantially lower the environmental impact of a given chemical process. The use of mechanochemistry addresses these issues.<sup>8</sup> The process of grinding solid components to induce chemical transformations can be traced back centuries but it has only been in the last 25

Received: March 27, 2018

Revised: May 29, 2018

Published: June 21, 2018

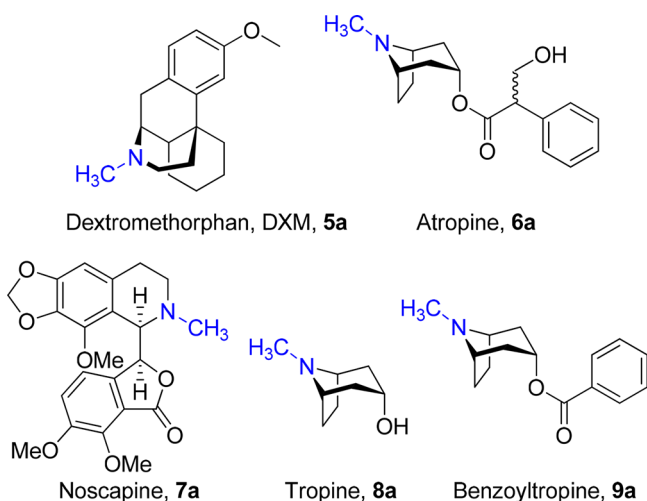


Figure 2. *N*-Methyl alkaloids used in this study.

years that a period of rediscovery in mechanochemistry has begun to take place.<sup>9</sup> Mechanochemistry is broadly defined as “chemical synthesis enabled or sustained by mechanical force” and can be achieved in a number of practical ways.<sup>10</sup> Commonly, an agate mortar-and-pestle is used to manually grind solid materials together. This technique is generally referred to as grinding and though it is simple and effective in some circumstances it does not allow for a reproducible set of parameters to be applied and thus can lead to inconsistent results.<sup>11</sup> A more sophisticated approach, referred to as milling, utilizes a shaker or planetary ball-mill. The use of a ball-mill allows for an experiment to be conducted in a closed vessel, a milling jar, often made of either stainless steel, zirconia, tungsten carbide, polytetrafluoroethylene (Teflon) or poly(methyl)methacrylate (PMMA).<sup>10</sup>

Automation of the grinding process through ball-milling ensures controllable and reproducible experimental conditions; milling speed (measured in Hz), composition of milling jars and milling balls, and medium-to-sample weight ratio are all easily tunable. Additionally, there is no practical limit on the length of milling time as with manual grinding.

Liquid assisted grinding (LAG), also known as solvent-drop grinding,<sup>12,13</sup> is an extension of traditional solvent-free mechanochemical techniques in which a small amount of liquid is used as an additive to enhance or control reactivity.<sup>10</sup> An important parameter of LAG experiments is the ratio of solid sample to liquid additive ( $\mu\text{L}/\text{mg}$ ), denoted  $\eta$ . A value of  $\eta = 0$  represents neat, or dry grinding whereas  $\eta \geq 10$  represents a typical reaction in solution. To be considered an example of LAG,  $\eta$  is usually between 0 and 1.<sup>10</sup> Studies have shown its effectiveness in synthesizing crystalline supramolecular structures such as cocrystals, making it an important technique for the screening of solid-state drugs.<sup>12,14,15</sup> Patents filed since the year 2000 show a dramatic increase in the use of mechanochemistry in areas such as the development of batteries, medical and personal care and catalysis.<sup>9</sup> Several organic transformations have been shown to proceed via LAG including fluorination of 1,3-diketones,<sup>16</sup> Suzuki cross-couplings,<sup>17</sup> so-called click reactions<sup>17</sup> and many others.<sup>8,17,18</sup> As well, it has been shown that organic reactions performed in planetary ball mills are amenable to scale-up to industry-scale mills.<sup>10</sup>

Though LAG has been shown to enhance and expose new reactivity, it also plays a significant role in the field of sustainable chemistry. Organic syntheses using ball mills have been shown to use less energy than common alternatives such as traditional heating, microwaves and ultrasound.<sup>19</sup> Furthermore, a typical LAG reaction typically requires only microliters of liquid additive compared to a solvent-phase reaction, which requires several milliliters of solvent. Solvent selectivity is another important consideration in green and sustainable chemistry where LAG offers an advantage. It has been shown that in certain circumstances, unlike in slurry ( $1 \leq \eta \leq 10$ ) or solvent-phase reactions ( $\eta > 10$ ), solubility of reactants is decoupled from reactivity when performing LAG.<sup>10</sup> This enables the experimenter a wider range of applicable solvents and potentially greener, more sustainable, options. For example, the effects of solubility on the formation of cocrystals by LAG has been studied extensively and it has been shown that cocrystallization was insensitive to all but the largest variations in component solubilities.<sup>20</sup> As pharmaceutical companies attempt to move away from toxic solvents such as tetrahydrofuran (THF), toluene and dichloromethane (DCM), toward those considered more sustainable, such as 2-propanol, ethanol and ethyl acetate, this feature of LAG can be highly advantageous.<sup>21,22</sup>

Though our previous work demonstrated that nZVI and  $\text{Fe}_3(\text{CO})_{12}$  out-perform  $\text{Fe}^0$  dust, there remain some shortcomings with each of these iron sources. Iron nanoparticles were prepared using a chemical reduction, “bottom-up” approach, using sodium borohydride, adding extra steps to the methodology, whereas  $\text{Fe}_3(\text{CO})_{12}$  is inherently toxic. Conversely,  $\text{Fe}^0$  dust is available for purchase directly from chemical suppliers, is inexpensive, and is comparatively nontoxic. By utilizing  $\text{Fe}^0$  dust in a mechanochemical reaction, it may be possible to eliminate or drastically reduce solvent use as well as to achieve the additional reactivity provided by nZVI by means of a nonchemical, “top-down” approach, to nanoparticle synthesis; namely,  $\text{Fe}^0$  nanoparticles may be generated from  $\text{Fe}^0$  dust in a ball mill. Hence, we anticipated that the nonclassical, iron-mediated Polonovski reaction would be amenable to neat grinding or liquid assisted grinding.

Herein, we report the use of liquid assisted grinding (LAG) to facilitate nonclassical Polonovski reactions using  $\text{Fe}^0$  dust as an iron source for the *N*-demethylation of alkaloids. Experiments were carried out in a shaker-type ball mill with reaction times between three and 6 h. Multiple “green” liquid additives were examined including various alcohols, water, polyethylene glycol, and the ionic liquids 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide ([BMPyr][NTf<sub>2</sub>]) and 1-butyl-1-methylpyrrolidinium tetrafluoroborate ([BMPyr][BF<sub>4</sub>]). The extension of the methodology to a selected array of *N*-methylalkaloids is also reported (Figure 2).

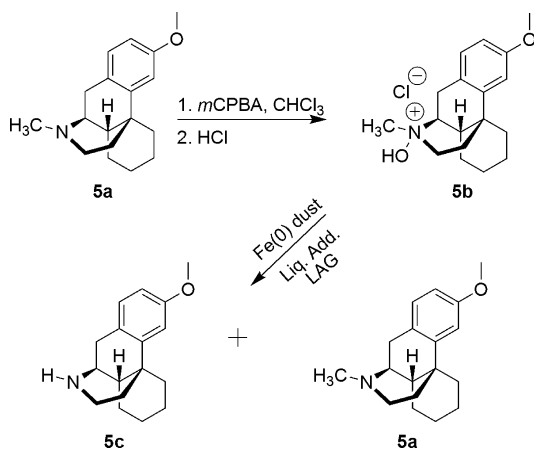
## RESULTS AND DISCUSSION

Dextromethorphan, **5a**, and other alkaloids, **6a–9a**, were first converted into their *N*-oxide hydrochloride derivatives, **5b–9b**, and isolated as previously described.<sup>5</sup> Generally, alkaloids were oxidized to their *N*-oxides using comparatively toxic *m*CPBA in  $\text{CHCl}_3$  because this procedure afforded short reaction times (ca. 1 h). *N*-Oxide hydrochloride salts could then be obtained by treatment with aqueous HCl and could be stored as powders under ambient conditions where they are stable for more than 3 months. Alternatively, a more sustainable approach utilizes  $\text{H}_2\text{O}_2$  in MeOH for this transformation.<sup>4,23,24</sup>

We previously reported that use of titrated H<sub>2</sub>O<sub>2</sub> showed that 10 equiv could efficiently oxidize **5a** overnight.<sup>6</sup> Increasing the amount of H<sub>2</sub>O<sub>2</sub> to 20 or 30 equiv showed no improvement in reaction times. Any excess H<sub>2</sub>O<sub>2</sub> could be easily degraded by the addition of a small amount of MnO<sub>2</sub> in each case. Filtration followed by removal of solvent, *in vacuo*, then reaction with aqueous HCl afforded the *N*-oxide hydrochloride **5b** after freeze-drying. Hence, use of MeOH and water afforded comparable yield of *N*-oxide allowing the elimination of toxic CHCl<sub>3</sub>. The use of HCl is significant, as departure from the chloride anion results in a reduction in yield during the formation of the *N*-nor product.<sup>23</sup> Yields will also be reduced if the *N*-nor product is formed from the free *N*-oxide.<sup>25</sup>

At the onset of this study, the *N*-oxide hydrochloride salts, **5b–9b**, were converted to their *N*-nor derivatives by either neat dry-grinding or liquid assisted grinding (LAG) using an agate mortar and pestle. DXM *N*-oxide hydrochloride, **5b**, and 1 mol equiv of Fe<sup>0</sup> dust were transferred to a mortar and manually dry-ground for 45 min with a pestle. During the grinding process a red-brown oil formed in the mortar. The crude reaction mixture containing unreacted starting material and desired product was dissolved in MeOH and analyzed by HPLC-DAD. Analysis indicated 15% conversion of **5b** into a mixture of the desired free *N*-nor derivative, **5c**, and the original free tertiary amine, **5a**, in a 5:1 ratio (Scheme 1).

**Scheme 1.** Conversion of DXM, **5a**, to Its *N*-Oxide Hydrochloride Derivative, **5b**, and Subsequently to its *N*-nor Derivative, **5c**, via LAG



Although an encouraging result, this manual grinding technique did not allow for consistent and reproducible results. This outcome was improved using a vortex grinding<sup>26</sup> technique that afforded a 100% conversion to products with a 9:1 ratio of **5c**:**5a**. However, reproducible results were also difficult to obtain using this technique.

The final and most reproducible technique employed involved the use of a shaker-type ball mill. This allowed for the reaction vessel/milling jar to be shaken at a consistent, rapid rate, making sure that the mixing balls contacted the entire reaction vessel evenly and were never immobilized. Both LAG and dry grinding experiments were conducted in the ball mill using PMMA reaction vessels, or milling jars, and two stainless steel milling balls. In a typical experiment the milling balls, 0.5 mmol of the alkaloid *N*-oxide hydrochloride, **5b–9b**, 1 mol equiv of Fe<sup>0</sup> dust and either 0, 50 or 100  $\mu$ L of an appropriate liquid additive were transferred to the milling jar.

The milling jar was then sealed and locked into place in the ball mill which was set to run for either 3 or 6 h at 25 Hz. The first set of experiments conducted compared the effectiveness of LAG, using a number of different liquid additives, relative to a neat, dry-grinding reaction (Table 1). Each experiment was

**Table 1.** *N*-Demethylation of DXM *N*-Oxide Hydrochloride<sup>a</sup>, **5b**, Using LAG

Entry	Liquid Additive	$\eta$	Time (h)	%Conv.	Ratio <b>5c</b> : <b>5a</b>
1	N/A	0	6	75	8.0:1
2	<i>i</i> -PrOH	0.26	6	100	8.8:1
3	<i>i</i> -PrOH	0.52	3	100	13.6:1
4	MeOH	0.52	3	100	2.8:1
5	EtOH	0.52	3	100	7.2:1
6	H <sub>2</sub> O	0.52	3	100	1.8:1
7	PEG-400 <sup>b</sup>	0.52	3	100	16.2:1
8	[BMPyr][NTf <sub>2</sub> ] <sup>c</sup>	0.52	3	84	13.3:1
9	[BMPyr][BF <sub>4</sub> ] <sup>d</sup>	0.52	3	100	9.8:1

<sup>a</sup>All reactions conducted using 0.500 mmol (162 mg) DXM *N*-oxide hydrochloride with 0.50 mmol (28 mg) Fe<sup>0</sup> dust. <sup>b</sup>Polyethylene glycol, 380–420 g/mol. <sup>c</sup>*N*-butyl-*N*-methylpyrrolidinium bis-((trifluoromethyl)sulfonyl)amide. <sup>d</sup>*N*-butyl-*N*-methylpyrrolidinium tetrafluoroborate.

performed using DXM *N*-oxide hydrochloride, **5b**, as the model substrate. When no liquid additive is used and the ball mill is run for 6 h, **5b** undergoes a 75% conversion to products in an 8:1 ratio of **5c**:**5a** (Table 1, Entry 1). Comparatively, when 50  $\mu$ L of *i*-PrOH is added to the milling jar, giving  $\eta$  = 0.26, **5b** undergoes 100% conversion to products with a similar ratio of **5c**:**5a** (Table 1, Entry 2). *i*-PrOH was chosen as a liquid additive based on its effectiveness as a green solvent in previous work.<sup>6</sup> When the volume of liquid additive was increased to 100  $\mu$ L, giving  $\eta$  = 0.52, milling time could be reduced to only 3 h to achieve 100% conversion to products with an improved ratio of 13.6:1 for **5c**:**5a** (Table 1, Entry 3).

Encouraged by these results, alternative, green and sustainable liquid additives were trialed. Methanol and ethanol both afforded 100% conversion of the starting *N*-oxide hydrochloride, **5b**, but with less selectivity for the nor-DXM product, **5c** (Table 1, Entries 4 and 5). Interestingly, the three simple alcohols tested, MeOH, EtOH and *i*-PrOH produced product ratios of 2.8:1, 7.2:1 and 13.6:1 respectively, apparently increasing with the lipophilicity of the alcohol additive used. The use of water as the additive also resulted in a complete conversion but gave the poorest product ratio of any liquid additive tested at 1.8:1 (Table 1, Entry 6). To expand the scope of sustainable liquid additives further, polyethylene glycol (PEG-400) and two ionic liquids were employed (Table 1, Entries 7, 8 and 9). The hydrophobic ionic liquid [BMPyr][NTf<sub>2</sub>] and the water-soluble ionic liquid [BMPyr][BF<sub>4</sub>] were chosen for their different properties including relatively low viscosity, making them easier to work with than other, more viscous, ionic liquids. Of these less conventional liquid additives, PEG-400 was the most effective, converting 100% of **5b** to products with a ratio of 16.2:1 for **5c**:**5a**, the best product ratio obtained. [BMPyr][NTf<sub>2</sub>] afforded a 13.1:1 ratio of **5c**:**5a** with only an 84% conversion while [BMPyr][BF<sub>4</sub>] afforded a 100% conversion with a poorer product ratio of 9.8:1.

Following the successful *N*-demethylation of DXM using LAG, we sought to expand the scope of the methodology to

additional biologically and synthetically interesting *N*-methylalkaloids. Atropine **6a**, noscapine, **7a**, tropine, **8a**, and benzoyltropine, **9a**, were selected based upon their ease of availability and relevance in medicinal synthesis and applications. Compound **6a** is found in various plant sources, particularly *Atropa belladonna*, and has been a historically important drug. *N*-Noratropine, **6c**, is an intermediate in the synthesis of ipratropium bromide, a bronchodilator.<sup>27</sup> Compound **7a** is relevant as a potential starting material for anticancer agents as well as other pharmaceuticals due to its complex arrangement of carbocycles and heterocycles.<sup>28,29</sup> Varying the functional group in noscapine derivatives has proven pharmacologically relevant, thus establishing the significance of an efficient *N*-demethylation methodology.<sup>28</sup> Compounds **8a** and **9a** are “drug-like” molecules and **8a** could serve as a starting material for drugs such as Granisetron, Hyoscyamine and Tropisetron. Each of these additional substrates were first isolated as their *N*-oxide hydrochloride salts, **6b–9b**, and subsequently *N*-demethylated using LAG (Scheme 1).

In each case, LAG products were purified via column chromatography affording isolated yields where possible (Table 2). Compound **5b** was also isolated in this manner to

**Table 2.** *N*-Demethylation of Various Alkaloid *N*-Oxide Hydrochlorides Using LAG

Entry	Substrate ( <i>N</i> -oxide HCl)	Liquid Additive	$\eta$	Cat. (equiv)	% Yield <sup>a,b</sup>
1	DXM, <b>5b</b>	<i>i</i> -PrOH	0.52	1	88, <b>5c</b>
2	DXM, <b>5b</b>	PEG-400	0.52	1	76, <b>5c</b>
3	DXM, <b>5b</b>	<i>i</i> -PrOH	0.61	0.1	80, <b>5c</b>
4	Atropine, <b>6b</b>	<i>i</i> -PrOH	0.50	1	79, <b>6c</b>
5	Atropine, <b>6b</b>	<i>i</i> -PrOH	0.58	0.1	50, <b>6c</b>
6	Noscapine, <b>7b</b>	<i>i</i> -PrOH	0.38	1	35, <b>7c</b>
7	Noscapine, <b>7b</b>	<i>i</i> -PrOH	0.42	0.1	40, <b>7c</b>
8	Tropine, <b>8b</b>	<i>i</i> -PrOH	0.80	1	–
9	Tropine, <b>8b</b>	<i>i</i> -PrOH	1.00	0.1	–
10	Benzoyltropine, <b>9b</b>	<i>i</i> -PrOH	0.57	1	48, <b>9c</b>
11	Benzoyltropine, <b>9b</b>	<i>i</i> -PrOH	0.66	0.1	20, <b>9c</b>

<sup>a</sup>Isolated yield following column chromatography. <sup>b</sup>All reactions conducted for 3 h.

obtain an 88% isolated yield of **5c** (Table 2, Entry 1) comparable to previous reports employing solution based reactions.<sup>5,6</sup> For comparison, the isolated yield of **5c** was also obtained when PEG-400 was used as the liquid additive (Table 2, Entry 2). Chromatographic separation of **5c**, **5a** and PEG-400 proved challenging, requiring successive aqueous washes to remove residual PEG-400 from products. This resulted in an overall lower isolated yield of 76% for **5c**. Thus, *i*-PrOH afforded higher isolated yield when used as a liquid additive; hence, all additional substrates were trialed using *i*-PrOH as the liquid additive. Compound **6b** was successfully *N*-demethylated and isolated in 79% yield, comparable to previous work (Table 2, Entry 3).<sup>6</sup> Despite the relatively low isolated yield of 35% obtained for compound **7c** (Table 2, Entry 5), we were encouraged by this result due to the fact that this compound had been previously difficult to synthesize and isolate.<sup>6</sup> Attempts at isolating compound **8c** were unsuccessful, consistent with previous work.<sup>6</sup> Finally, compound **9c** was isolated in 48% yield, slightly lower than previous reports using other methodologies (Table 2, Entry 10).<sup>6</sup> Optimization of

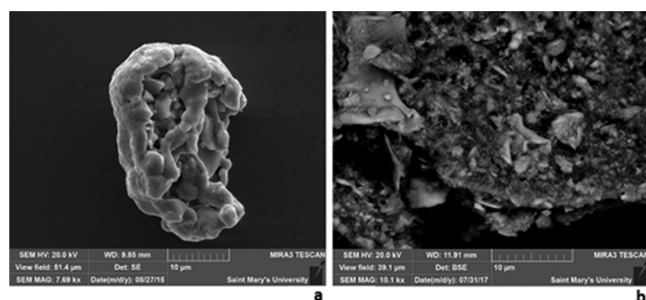
parameters such as the nature of the liquid additive, the value of  $\eta$ , shaking frequency, and LAG time are the subject of ongoing experiments.

Based on earlier reports for the modified Polonovski reaction being promoted by stainless steel,<sup>30</sup> the possibility that the stainless steel milling balls were promoting *N*-demethylation of the *N*-oxide hydrochloride starting materials was considered. Indeed, a number of examples of metal catalyzed reactions promoted by stainless steel<sup>31–33</sup> or copper<sup>34</sup> milling balls have been reported in the literature. Hence, a number of control experiments were conducted. The use of identical conditions employed for Table 1, Entry 3, with the exception of zirconia in place of stainless steel milling balls resulted in 100% conversion to products with an 8.9:1 ratio of **5c**:**5a**. This product ratio represented a significantly lower proportion of the desired *N*-nor product produced compared to when stainless steel balls were used (Table 1, Entry 3). This result indicated that the stainless steel milling balls influenced the outcome of the LAG methodology, likely resulting from the iron content of the stainless steel. Next, the conditions of Table 1, Entry 3 were again employed, this time with the omission of Fe<sup>0</sup> dust. This created conditions in which the only source of iron was the stainless steel milling balls themselves. Hence, after 3 h of milling, 25% of **5b** was converted to products with a ratio of 13.1:1. This indicated that the stainless steel was promoting the reaction, albeit at a much slower rate, presumably due to a decrease in available surface area at Fe<sup>0</sup>. Interestingly, the product ratio was similar to Table 1, Entry 3.

Earlier studies conducted in our laboratories demonstrated the catalytic nature of the iron source, either Fe<sup>2+</sup> or Fe<sup>0</sup>, used in these reactions.<sup>4–6</sup> Hence, when a substoichiometric amount (i.e., 10 mol %) of Fe<sup>0</sup> dust was employed for the *N*-demethylation of **5b**, an isolated yield of 80% was obtained for the nor-DXM product, **5c** (Table 2, Entry 3). When the same substoichiometric amount of Fe<sup>0</sup> dust was used for the *N*-demethylations of **6b**, **7b** and **9b**, isolated yields of 50, 40 and 20% were obtained for *N*-nor products **6c**, **7c** and **9c**, respectively (Table 2, Entries 5, 9 and 11). These yields are similar or lower than what were obtained for corresponding reactions in which a stoichiometric amount of Fe<sup>0</sup> dust was utilized. This indicates that the iron source is somehow becoming deactivated during the reaction, perhaps due to buildup of impurities and other reaction byproducts. Hence, a stoichiometric amount of Fe<sup>0</sup> dust is optimal for these reactions. This is not regarded as a serious issue given the inexpensive nature of Fe<sup>0</sup> dust relative to other transition metal catalysts.

We next sought to determine whether ball milling of Fe<sup>0</sup> dust resulted in the formation of nanoscale iron dust, hence providing a much more sustainable, nonchemical, “top-down” approach to Fe<sup>0</sup> nanoparticle formation. When commercially available Fe<sup>0</sup> dust was observed using SEM, particles exceeding 10  $\mu\text{m}$  in each dimension were observed (Figure 3). After 3 h of milling the Fe<sup>0</sup> dust under similar conditions as used for all other experiments, submicrometer particles were prevalent as observed by SEM (Figure 3).

The methodology reported herein describes the improvement in the sustainability for one step of a multistep process for the conversion of alkaloids to their *N*-demethylated analogues. Features such up to a 10<sup>3</sup>-fold decrease in solvent use, use of greener liquid additives, and mechanochemical generation of iron nanoparticles all represent increases in sustainability. Noteworthy is the fact that a number of other



**Figure 3.** SEM images of Fe<sup>0</sup> dust particles (a) premilling and (b) postmilling.

steps in this methodology remain comparatively poor in terms of sustainability and warrant further development along these lines.<sup>35</sup> Those steps utilizing chlorinated solvents, especially for purification, must be more adequately addressed. We are currently investigating LAG synthesis for the *m*CPBA oxidation of *N*-methyl alkaloids in addition to more sustainable purification protocols for these systems.

## CONCLUSIONS

The use of liquid assisted grinding (LAG) for the nonclassical Polonovski reaction for the *N*-demethylation of various alkaloids has facilitated a significant decrease in the amount of solvent/liquid additive used. The use of stoichiometric amounts of Fe<sup>0</sup> dust lead to optimal results comparable to those systems in which reactions were performed in solution. Conversions from *N*-oxide hydrochlorides, **5b–9b**, to nor-alkaloid products, **5c–9c**, occurred within the same time span with comparable isolated yields using LAG. However, use of substoichiometric amounts of Fe<sup>0</sup> dust resulted in lower isolated yields of nor-alkaloid products. Furthermore, the sustainability of the nonclassical Polonovski reaction for the *N*-demethylation of various alkaloids have been enhanced through the use of liquid assisted grinding (LAG) employing a range of green and sustainable liquid additives. Additional enhancement of sustainable attributes for this system have been realized through the generation of nanoscale Fe<sup>0</sup> particles via a nonchemical, “top-down” approach from inexpensive, commercially available iron dust.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.8b01393.

Experimental section and characterization data (PDF)

## AUTHOR INFORMATION

### Corresponding Author

\*R. D. Singer. E-mail: Robert.Singer@smu.ca.

### ORCID

Peter J. Scammells: 0000-0003-2930-895X

Robert D. Singer: 0000-0002-2708-9485

### Present Address

<sup>§</sup>Medicinal Chemistry, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Victoria 3052, Australia

## Funding

Natural Sciences and Engineering Research Council of Canada – Discovery Grant.

## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

The authors thank the Natural Sciences and Engineering Research Council of Canada (NSERC Discovery to R.D.S.) for financial support for this research. Financial contributions from Saint Mary’s University are also gratefully acknowledged. The authors thank Professor Tomislav Friščić of McGill University for the loan of a milling machine. A fruitful discussion with Marc MacKinnon of Memorial University of Newfoundland is also acknowledged.

## ABBREVIATIONS

LAG, Liquid Assisted Grinding; PEG, polyethylene glycol; nZVI, nanoscale zerovalent iron; *i*-PrOH, isopropanol (2-propanol); DXM, dextromethorphan; PMMA, poly(methyl)-methacrylate; [BMPyr][NTf<sub>2</sub>], 1-butyl-1-methylpyrrolidinium bis(trifluoromethylsulfonyl)imide; [BMPyr][BF<sub>4</sub>], 1-butyl-1-methylpyrrolidinium tetrafluoroborate; HPLC-DAD, high performance liquid chromatography–diode array detector

## REFERENCES

- Portoghesi, P. S.; Sultana, M.; Nagase, H.; Takemori, A. E. Stereochemical aspects of phenylethanolamine analogs as substrates of phenylethanolamine *N*-methyltransferase. *J. Med. Chem.* **1988**, *31*, 281–282.
- von Braun, J. Die Einwirkung von Bromcyan auf tertiäre Amine. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 1438–1452.
- Cooley, J. H.; Evain, J. E. Amine Dealkylations with Acyl Chlorides. *Synthesis* **1989**, *1989*, 1–7.
- McCamley, K.; Ripper, J. A.; Singer, R. D.; Scammells, P. J. Efficient *N*-Demethylation of Opiate Alkaloids Using a Modified Nonclassical Polonovski Reaction. *J. Org. Chem.* **2003**, *68*, 9847–9850.
- Kok, G. B.; Pye, C. C.; Singer, R. D.; Scammells, P. J. Two-Step Iron(0)-Mediated *N*-Demethylation of *N*-Methyl Alkaloids. *J. Org. Chem.* **2010**, *75*, 4806–4811.
- Awalt, J. K.; Lam, R.; Kellam, B.; Graham, B.; Scammells, P. J.; Singer, R. D. Utility of iron nanoparticles and a solution-phase iron species for the *N*-demethylation of alkaloids. *Green Chem.* **2017**, *19*, 2587–2594.
- Henderson, R. K.; Jiménez-González, C.; Constable, D. J. C.; Alston, S. R.; Inglis, G. G. A.; Fisher, G.; Sherwood, J.; Binks, S. P.; Curzons, A. D. Expanding GSK’s solvent selection guide – embedding sustainability into solvent selection starting at medicinal chemistry. *Green Chem.* **2011**, *13*, 854–862.
- James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friščić, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C. Mechanochemistry: opportunities for new and cleaner synthesis. *Chem. Soc. Rev.* **2012**, *41*, 413–447.
- Friščić, T. Supramolecular concepts and new techniques in mechanochemistry: cocrystals, cages, rotaxanes, open metal–organic frameworks. *Chem. Soc. Rev.* **2012**, *41*, 3493–3510.
- Do, J.-L.; Friščić, T. Mechanochemistry: A Force of Synthesis. *ACS Cent. Sci.* **2017**, *3*, 13–19.
- Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B. Ball milling in organic synthesis: solutions and challenges. *Chem. Soc. Rev.* **2011**, *40*, 2317–2329.
- Cheney, M. L.; McManus, G. J.; Perman, J. A.; Wang, Z.; Zaworotko, M. J. The Role of Cocrystals in Solid-State Synthesis:

Cocrystal-Controlled Solid-State Synthesis of Imides. *Cryst. Growth Des.* **2007**, *7* (4), 616–617.

(13) Cheney, M. L.; Zaworotko, M. J.; Beaton, S.; Singer, R. D. Cocrystal Controlled Solid-State Synthesis. A Green Chemistry Experiment for Undergraduate Organic Chemistry. *J. Chem. Educ.* **2008**, *85* (12), 1649.

(14) Caira, M. R.; Nassimbeni, L. R.; Wildervanck, A. F. Selective formation of hydrogen bonded cocrystals between a sulfonamide and aromatic carboxylic acids in the solid state. *J. Chem. Soc., Perkin Trans. 2* **1995**, *12*, 2213–2216.

(15) Friščić, T.; Trask, A. V.; Jones, W.; Motherwell, W. D. S. Screening for Inclusion Compounds and Systematic Construction of Three-Component Solids by Liquid-Assisted Grinding. *Angew. Chem., Int. Ed.* **2006**, *45*, 7546–7550.

(16) Howard, J. L.; Sagatov, Y.; Repousseau, L.; Schotten, C.; Browne, D. L. Controlling reactivity through liquid assisted grinding: the curious case of mechanochemical fluorination. *Green Chem.* **2017**, *19*, 2798.

(17) Wang, G.-W. Mechanochemical organic synthesis. *Chem. Soc. Rev.* **2013**, *42*, 7668.

(18) Mack, J.; Shumba, M. Rate enhancement of the Morita–Baylis–Hillman reaction through mechanochemistry. *Green Chem.* **2007**, *9*, 328–330.

(19) Stolle, A. Technical Implications of Organic Syntheses in Ball Mills. In *Ball Milling Towards Green Synthesis: Applications, Projects, Challenges*; Ranu, B., Stolle, A., Eds.; The Royal Society of Chemistry: Cambridge, UK, 2015.

(20) Friščić, T.; Childs, S. L.; Rizvi, S. A. A.; Jones, W. The role of solvent in mechanochemical and sonochemical cocrystal formation: a solubility-based approach for predicting cocrystallisation outcome. *CrystEngComm* **2009**, *11*, 418–426.

(21) Constable, D. J. C.; Jimenez-Gonzalez, C.; Henderson, R. K. Perspective on Solvent Use in the Pharmaceutical Industry. *Org. Process Res. Dev.* **2007**, *11* (1), 133–137.

(22) Prat, D.; Hayler, J.; Wells, A. A survey of solvent selection guides. *Green Chem.* **2014**, *16*, 4546–4551.

(23) Thavaneswaran, S.; Scammells, P. J. Further investigation of the N-demethylation of tertiary amine alkaloids using the non-classical Polonovski reaction. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2868–2871.

(24) Dong, Z.; Scammells, P. J. New Methodology for the N-Demethylation of Opiate Alkaloids. *J. Org. Chem.* **2007**, *72*, 9881–9885.

(25) Kok, G. B.; Ashton, T. D.; Scammells, P. J. An Improved Process for the N-Demethylation of Opiate Alkaloids using an Iron(II) Catalyst in Acetate Buffer. *Adv. Synth. Catal.* **2009**, *351*, 283–286.

(26) Elacqua, E.; Kummer, A. K.; Groeneman, R. H.; Reinheimer, E. W.; MacGillivray, L. R. Post-application of dry vortex grinding improves the yield of a [2 + 2] photodimerization: Addressing static disorder in a cocrystal. *J. Photochem. Photobiol., A* **2016**, *331*, 42–47.

(27) Pham, D. D.; Kelso, G. F.; Yang, Y.; Hearn, M. T. W. One-pot oxidative N-demethylation of tropane alkaloids with hydrogen peroxide and a FeIII-TAML catalyst. *Green Chem.* **2012**, *14*, 1189–1195.

(28) Debono, A.; Xie, J.; Ventura, S.; Pouton, C.; Capuano, B.; Scammells, P. J. Synthesis and Biological Evaluation of N-Substituted Noscaine Analogues. *ChemMedChem* **2012**, *7*, 2122–2133.

(29) DeBono, A.; Mistry, S.; Xie, J.; Muthiah, D.; Phillips, J.; Ventura, S.; Callaghan, R.; Pouton, C.; Capuano, B.; Scammells, P. J. The Synthesis and Biological Evaluation of Multifunctionalised Derivatives of Noscaine as Cytotoxic Agents. *ChemMedChem* **2014**, *9*, 399–410.

(30) Kok, G. B.; Scammells, P. J. Further investigations into the N-demethylation of oripavine using iron and stainless steel. *Org. Biomol. Chem.* **2011**, *9*, 1008–1011.

(31) Sawama, Y.; Niikawa, M.; Yabe, Y.; Goto, R.; Kawajiri, T.; Marumoto, T.; Takahashi, T.; Itoh, M.; Kimura, Y.; Sasai, Y.; Yamauchi, Y.; Kondo, S.-i.; Kuzuya, M.; Monguchi, Y.; Sajiki, H. Stainless-Steel-Mediated Quantitative Hydrogen Generation from

Water under Ball Milling Conditions. *ACS Sustainable Chem. Eng.* **2015**, *3*, 683–689.

(32) Sawama, Y.; Kawajiri, T.; Niikawa, M.; Goto, R.; Yabe, Y.; Takahashi, T.; Marumoto, T.; Itoh, M.; Kimura, Y.; Monguchi, Y.; Kondo, S.-i.; Sajiki, H. Stainless-Steel Ball-Milling Method for Hydro-/Deutero-genation using H<sub>2</sub>O/D<sub>2</sub>O as a Hydrogen/Deuterium Source. *ChemSusChem* **2015**, *8*, 3773–3776.

(33) Štefanić, G.; Krehula, S.; Štefanić, I. The high impact of a milling atmosphere on steel contamination. *Chem. Commun.* **2013**, *49*, 9245–9247.

(34) Tireli, M.; Maračić, S.; Lukin, S.; Kulcsár, M. J.; Žilić, D.; Cetina, M.; Halasz, I.; Raić-Malić, S.; Užarević, K. Solvent-free copper-catalyzed click chemistry for the synthesis of N-heterocyclic hybrids based on quinoline and 1,2,3-triazole. *Beilstein J. Org. Chem.* **2017**, *13*, 2352–2363.

(35) Sheldon, R. A. Metrics of Green Chemistry and Sustainability: Past, Present, and Future. *ACS Sustainable Chem. Eng.* **2018**, *6*, 32–48.