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ARTICLE

Utility of iron nanoparticles and a solution-phase iron species for the *N*-demethylation of alkaloids

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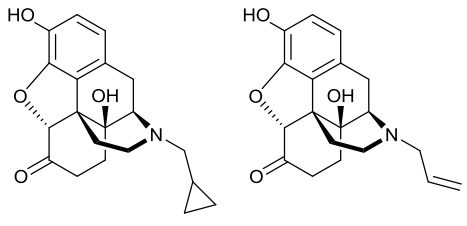
The *N*-demethylation of selected *N*-methylalkaloids using a modified Polonovski reaction can be accomplished using a novel green methodology employing nanoscale zero-valent iron, nZVI, in isopropanol. Use of nZVI promotes a much faster conversion to *N*-demethylated products due to much higher surface area on the metal surface as shown by SEM analysis. Rates of conversion can be further enhanced using catalytic quantities of the solubilised iron(0) species triiron dodecacarbonyl, $Fe_3(CO)_{12}$.

Introduction

The opiate alkaloids morphine and codeine, which are extracted from the opium poppy, *Papaver somniferum*, are common analgesics that have been used for thousands of years for the treatment and control of pain.[1] In addition to being used clinically as therapeutic agents in their own right, they can be used as starting materials in the production of semi-synthetic opioid pharmaceuticals, such as naltrexone, naloxone and buprenorphine.[2] These particular opioids are useful as therapeutic agents for the treatment of opiate or alcohol dependence, opiate overdose and in pain management. Specifically, naloxone hydrochloride is used to reverse the acute symptoms of opioid overdose and studies have found it to be a cost-effective strategy.[3] The rate of drug overdose deaths increased by 140% between the years 2000 and 2014, an increase driven by opioid overdose and, since 2013, in large part due to synthetic opioids including fentanyl.[4] A key feature in the synthesis of semi-synthetic opioid pharmaceuticals is the loss of the *N*-methyl group, which is replaced by a variety of alkyl groups, such as a cyclopropylmethyl group in naltrexone and buprenorphine, or an allyl group in naloxone (**Figure 1**). Inclusion of a non-methyl *N*-alkyl group is rationalized by the "message-address" concept, where varying this "message" group typically allows control of agonist or antagonist activity.[5]

Despite the medical utility of these semi-synthetic opioids, *N*-demethylation has traditionally been a difficult step on the industrial scale. The most commonly used methods for the *N*-demethylation of tertiary *N*-methylamines involved the use of cyanogen bromide (von Braun reaction)[6] and chloroformate reagents.[7] Both of these methods have significant drawbacks; cyanogen bromide is a highly toxic reagent,[8] whilst the more effective chloroformate reagents, such as vinyl chloroformate, are quite expensive. In both cases, the resulting product must be further processed in order to return the *N*-nor product; in the case of the von Braun reaction to hydrolyse the resulting cyanamide group, and with the Polonovski reaction to cleave the resulting carbamate.

The *N*-demethylation of a range of alkaloids has also been achieved using the non-classical Polonovski reaction. Galanthamine was *N*-demethylated in good yield by first oxidising this alkaloid with *m*CPBA and subsequently treating the resultant *N*-methylamine oxide with ferrous sulfate.[9] Iron catalysts have also been successfully investigated and developed into efficient catalysts for the *N*-demethylation of opiate alkaloids utilizing what has been proposed as a non-classical Polonovski-type mechanism.[10] Further development of this work showed that the use of solid iron powder as the catalyst allowed its easy removal from the reaction mixture *via* filtration.[11]



Naltrexone (**1**) Naloxone (**2**)

Fig. 1. Semi-synthetic opioid pharmaceuticals used for treatment of opioid overdose.

In addition to this, the reaction returns the free *N*-nor compound without the need for further reaction, therefore avoiding additional steps. This system has been subsequently

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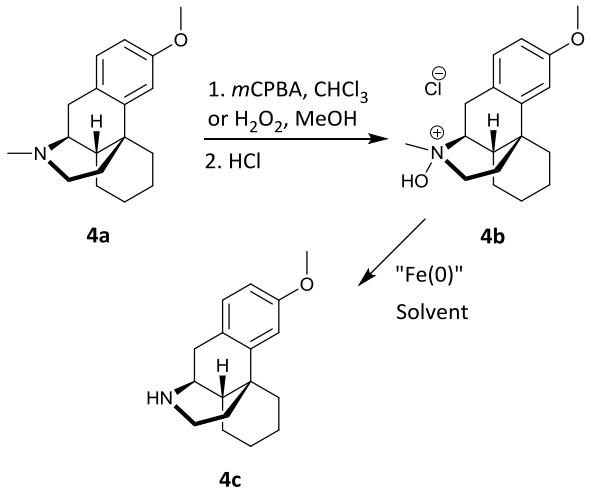
adapted by Nakano *et al.* in a flow process using iron/sand columns, again demonstrating the utility of using these catalysts.[12]

The optimised process requires the formation of the alkaloid *N*-oxide, which can be readily accomplished using a variety of oxidants, such as hydrogen peroxide or *m*CPBA on a laboratory scale.[10] This is then converted to the hydrochloride salt, which was previously found to be an important factor, as the additional proton is essential in the proposed mechanism.[10] Furthermore, the anion used in the salt formation is also important, as departure from the chloride anion results in a reduction in yield.[13] While the reaction will still proceed using the free *N*-oxide, the yields obtained are suboptimal.[14] Solvent also plays an important role, with chloroform ($CHCl_3$) giving the highest yield of the solvents tested.[15]

The precise nature of the catalytic system is also important. The optimised loading is described as 13 mol% Fe(0) powder with an additional 2 mol% Fe^{3+} in the form of $FeCl_3$.[11] It was demonstrated that while increasing the loading of Fe(0) has little impact on the yield, increasing the loading of Fe^{3+}, or even switching to an Fe^{2+} species, results in suboptimal yields. Finally, allowing the reaction to proceed in open air increases the reaction rate, while under an inert nitrogen atmosphere the reaction rate is adversely affected.[11] All these factors may be implemented in an industrial setting for cost-effective, relatively safe, and efficient *N*-demethylation of opiates for conversion to other clinically useful drugs (**Scheme 1**).

While previously described advances have been extremely useful, we have a continued interest in the development of iron catalysts in *N*-demethylations, either for industrial or synthetic purposes. While the Fe(0)/Fe(III) system we described earlier is efficient, both in terms of yield and cost, the use of $CHCl_3$ is undesirable as it is toxic and a potential carcinogen.[16] Furthermore, it is potentially fatal if absorbed or ingested in larger quantities.



Scheme 1. *N*-Demethylation of DXM, **4a**, *via* *N*-oxide hydrochloride, **4b**.

Therefore, its use on an industrial scale is highly undesirable. Seeking a solvent replacement is not always a simple task. Reaction kinetics, thermodynamics and yield may be affected by the balance of solvent polarity and protic nature. More specifically in the case of *N*-demethylations, molecular oxygen dissolved in the solvent can also impact on reaction rate and yield.[11] The work previously conducted by our group has extensively explored various iron powders, iron salts, as well as steel alloy powders under a variety of conditions.[10,11,14,15,17,18] In the present study, we present the use of two new iron species as alternatives for the *N*-demethylation of alkaloids whilst also exploring the use of "greener" solvents for this reaction.

Nanoscale zero-valent iron (nZVI) has been prepared using a variety of methods and employed in several different types of reactions.[19,20,21] The majority of literature reports involving nZVI describe the remediation of ground water and the removal of contaminants such as arsenic(III),[22] chromium(VI),[23] and *E. coli* bacteria.[24] There are a number of reports where nZVI has been used in catalytic applications.[21,25,26] The efficacy of these methods is due in part to the extremely high surface area-to-volume ratio of nZVI. This property, along with our experiences using iron(0) as a catalyst in the modified Polonovski reaction, prompted us to investigate its use for *N*-demethylation reactions. A number of "green" advantages are also presented through the use of nZVI in these systems. The high surface area of nZVI was anticipated to lead to faster reaction rates for *N*-demethylation of the *N*-oxides used in these reactions. Furthermore, the preparation of nZVI can be accomplished in water using minimally toxic sodium borohydride ($NaBH_4$) and subsequent catalytic demethylations can be conducted in alcoholic solvents such as isopropanol (*i*-PrOH).

A number of procedures have been reported for the preparation of nZVI. The most common technique involves reduction of an iron(II) or iron(III) salt, such as iron(II) sulfate or iron(III) chloride, to iron(0) using $NaBH_4$ in aqueous media. This procedure is relatively non-toxic, inexpensive, uncomplicated and can yield nanoscale iron(0) particles in the size range of 10–50 nm.[27] The effects of iron and $NaBH_4$ concentration, atmospheric *versus* inert conditions, the rate of agitation during reaction, the rate of $NaBH_4$ addition, and how the iron is dried and stored have been extensively studied and optimised.

Triiron dodecacarbonyl ($Fe_3(CO)_{12}$) is an unusual iron species, typically used as a source of reactive Fe(0) for the synthesis of various iron complexes, or as a reagent. Its utility as a catalyst has, to our knowledge, not been previously described. Previously investigated catalysts tend to be heterogeneous due to the insolubility of iron and iron salts in the tested solvents. In contrast to these, $Fe_3(CO)_{12}$ is soluble in non-polar organic solvents, with limited solubility in more polar solvents. Furthermore, the carbonyl ligands are easily displaced by Lewis bases, potentially allowing for better interaction with the substrate and hence higher rates of reaction.

Synthesis of iron nanoparticles can also be achieved using $Fe_3(CO)_{12}$. Previous examples demonstrate that under relatively harsh conditions, $Fe_3(CO)_{12}$ may undergo controlled decomposition to form either nZVI or magnetite nanoparticles.[28,29] A solution of $Fe_3(CO)_{12}$ and PPh_3 in hexane may form graphite coated iron nanoparticles under strong UV irradiation over an extended period of time.[28] $Fe_3(CO)_{12}$ may

form magnetite nanoparticles upon prolonged reflux in diethylene glycol, diethyl ether, and oleic acid.[29] Both of these methods result in nanoparticles that have an organic coating. As we are interested in "bare" nZVI, these methods were not utilised.

Industrial adoption of any new method for the *N*-demethylation of alkaloids depends on appropriate selection of a green solvent. The environmental impact and waste involved in the synthesis of active pharmaceutical ingredients (API's) is of considerable concern to the pharmaceutical industry.[30] With solvents contributing 80–90% of the non-aqueous waste generated, reduction in toxic waste solvent is critical to reducing health and environmental damage. Solvents, nonetheless, are still required for the production of API's, and therefore need to be replaced with greener options. To that end, GSK have assembled a toolkit to assist in the selection of solvents suitable for large-scale industrial applications.[30] It has also been suggested that initial reaction development could be guided by this solvent selection process, as this would save both time and money further down the line when optimising such reactions for industrial purposes. With this in mind, we have chosen to approach the problem primarily using greener options.

Herein, we report the use of nZVI and $Fe_3(CO)_{12}$ as Fe(0) sources for the modified Polonovski reaction in which the *N*-demethylation of various alkaloids in green solvents is demonstrated. The reaction systems have been optimised for the use of *i*-PrOH, a green solvent that is directly compared to the use of the "non-green" solvent $CHCl_3$ as well as other solvent combinations. The use of nZVI represents an improved green approach to this reaction in that the rate of reaction is significantly enhanced *versus* iron dust while maintaining ease of isolation of products and the use of a green iron(0) catalyst. $Fe_3(CO)_{12}$, although less green than using nZVI, has favourable solubility properties, allowing for catalytic amounts to be employed in conjunction with the use of *i*-PrOH. The extension of the methodology to a selected array of *N*-methylalkaloids is also reported.

Results and discussion

nZVI was prepared using a previously reported procedure in which ferric sulfate heptahydrate was reduced in aqueous medium using $NaBH_4$ with mechanical stirring, washed with 50% aqueous methanol *via* repetitive centrifugation, decantation and replacement of solvent.[27] The isolated nZVI was then suspended in the reaction solvent to be used for the modified Polonovski reactions. nZVI prepared using this method could be carefully isolated under inert atmosphere to prevent oxidation, as far as possible, followed by characterisation using scanning electron microscopy (SEM) (**Figure 2**). The SEM image shows spherical, monodisperse particles of approximately 75 nm in diameter, forming chain-like secondary structures. Comparison with the SEM of iron dust used in previous studies shows distinctly smaller particle size (i.e. 75 nm vs. 40 μm) and therefore significantly higher surface area of the iron(0) surface upon which reaction can occur.

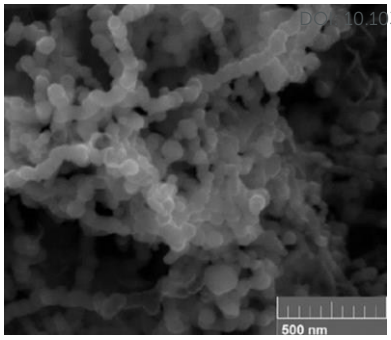


Fig. 2. SEM image of synthesised nZVI.

The pseudo-opioid dextromethorphan (DXM), **4a**, was chosen as an ideal substrate for preliminary reactions investigating optimisation of reaction conditions. DXM, contained in many common cough medications due to its anti-tussive properties, is structurally similar to naturally occurring opiates possessing an *N*-methyl group, and is a member of the morphinan family of compounds. Unlike naturally occurring opiates, it is not a highly controlled substance and is hence readily available as its hydrobromide salt from commercial sources. DXM hydrobromide is an atmospherically stable solid at room temperature making it easy to manipulate in a laboratory setting. DXM is easily transformed into its *N*-oxide and *N*-oxide hydrochloride derivative, **4b**, in high yields. *N*-Oxidation of **4a** and isolation of the hydrochloride salt **4b** was achieved by treatment of **4a** with either *m*CPBA or H_2O_2, followed by addition of aqueous HCl using a variation of a literature procedure.[14] In general, *m*CPBA in $CHCl_3$ was employed as the oxidant as it afforded the desired *N*-oxide after a short reaction time (~ 1 h). However, H_2O_2 in MeOH has previously been used as a greener alternative for this transformation.[10,13,18] Despite this, literature procedures tend to vary significantly in equivalents added and the reaction time required. Initial screening using titrated H_2O_2 showed that 10 eq. was sufficient to afford conversion of **4a** to **4b** overnight. Excess H_2O_2 was then degraded to water using minimal MnO_2. After filtration and removal of the organic solvent *in vacuo*, the HCl salt was subsequently generated by adding dilute acid and removing the excess water using a freeze-dryer. Increasing the molar ratio of H_2O_2 to 20 eq. and 30 eq. offered no significant advantage in terms of reaction time. Overall, this procedure gave comparable yields of the *N*-oxide and eliminated the need for chlorinated solvents, replacing them with MeOH and water.

The *N*-oxide **4b** was subsequently converted to corresponding N-nor derivative **4c**. Typically, **4b** was dissolved or suspended in the selected solvent system and nZVI or $Fe_3(CO)_{12}$ was then added as a solution/suspension in the appropriate solvent and the reaction was stirred at room temperature for the prescribed period of time. The results of these experiments are summarised in Tables 1 and 2. Reaction of **4b** in *i*-PrOH gave a good yield of the *N*-demethylated product, **4c,** using a stoichiometric amount of nZVI (Table 1, Entry 1). Use of this green solvent afforded slightly lower yields

than when $CHCl_3$ was used (Table 1, Entry 2), likely due to differences in solubility of the substrate molecules. Switching the solvent to methanol resulted in a noticeable decrease in yield of **4c** (Table 1, Entry 3). It has previously been postulated that iron acts as a catalyst in the modified Polonovski reaction.[10] When a catalytic amount of nZVI (i.e. 10 mol%) was employed, there was a pronounced decrease in the yield of the *N*-demethylated product, **4c** (Table 1, Entries 4 – 6), regardless of the solvent used. We believe this is due to catalyst poisoning/deactivation as the *N*-demethylated product builds up in the reaction. The coordination of the Lewis basic product, **4c**, to iron prevents further substrate molecules from interacting with the iron catalyst. Conversion of **4b** to **4c** was unsuccessful when nZVI were employed using water as a solvent.

Table 1. *N*-Demethylation of various alkaloid *N*-oxide hydrochlorides using nZVI.

Entry	nZVI (mol %)	Substrate (*N*-oxide)	Solvent / Conditions[A]	Time (h)	% yield[B] (N-nor)
1	100	DXM (**4b**)	*i*-PrOH	0.75	**4c**, 84
2	100	DXM (**4b**)	$CHCl_3$	1	**4c**, 92
3	100	DXM (**4b**)	MeOH	3	**4c**, 59
4	10	DXM (**4b**)	*i*-PrOH	21	**4c**, 78
5	10	DXM (**4b**)	$CHCl_3$	1	**4c**, 67
6	10	DXM (**4b**)	MeOH	3	**4c**, 34
7	100	Noscapine (**5b**)	*i*-PrOH	24	-[C]
8	100	Atropine (**6b**)	*i*-PrOH	3	**6c**, 85
9	100	Tropine (**7b**)	*i*-PrOH	24	-[C]
10	100	Pivaloyltropine (**8b**)	*i*-PrOH	14	**8c**, 59
11	100	Benzoyltropine (**9b**)	*i*-PrOH	14	**9c**, 58

[A] 10 mL of solvent per 100 mg substrate at ambient temperature (measured to be 21°C on average) under an atmosphere of argon. Reactions were stirred using a 12 mm magnetic bead at 900 RPM.
[B] Isolated yield following column chromatography.
[C] NMR of crude product mixture showed no evidence of any conversion of *N*-oxide starting material to *N*-nor product.

$Fe_3(CO)_{12}$ proved to be an efficient catalyst for the *N*-demethylation of **4b**. In $CHCl_3$, good yields were achievable with low catalyst loadings and drastically reduced reaction times. As seen in Table 2, the optimal yield was obtained using 5 mol% $Fe_3(CO)_{12}$ (Table 2, Entry 1), with increases in catalyst loading resulting in slightly reduced yield. When less than 5 mol% of $Fe_3(CO)_{12}$ is used, the reaction never goes to completion, even if left for extended periods of time. We again rationalise this to be due to poisoning of the catalyst. We suspect that **4c** may be forming stronger coordination bonds to iron than the native carbonyl ligand at the conclusion of the catalytic cycle.

Following optimisation of the reaction in $CHCl_3$, we proceeded to assess various greener solvents in order to ascertain the ability of $Fe_3(CO)_{12}$ to perform under alternative conditions. To this end, various ester solvents were tested, with the addition of MeOH to increase the solubility of the substrate. Ester solvents (Table 2, Entries 4, 6, 7 and 8) afforded generally good results for the reaction with **4b**. Dimethyl carbonate (DMC) (Table 2, Entry 5) proved to be the exception, with very low recovery of the product. Although DMC is known to be a methylating agent, its ability to alkylate is only evident under relatively harsh conditions. Therefore, we suspect that methylation of **4c** under the tested conditions is unlikely to occur. Rather, this solvent may simply not be amenable to this particular reaction. The effect of substituting *i*-PrOH for MeOH in these solvent mixtures was also explored. EtOAc/*i*-PrOH (Table 2, Entry 8) gave higher yields compared to the EtOAc/MeOH mixture (Table 2, Entry 7). Indeed, when used as the bulk solvent, *i*-PrOH gave surprisingly good results (Table 2, Entry 3). Although reaction times were longer, the yields obtained were improved.

Table 2. *N*-Demethylation of various alkaloid *N*-oxide hydrochlorides using $Fe_3(CO)_{12}$.

Entry	$Fe_3(CO)_{12}$ (mol %)	Substrate (*N*-oxide)	Solvent / Conditions[A]	Time (h)	% yield[B] (N-nor)
1	5	DXM (**4b**)	$CHCl_3$	0.1	**4c**, 86
2	10	DXM (**4b**)	$CHCl_3$	0.1	**4c**, 73
3	5	DXM (**4b**)	*i*-PrOH	0.7	**4c**, 92
4	5	DXM (**4b**)	MeOAc/MeOH (9:1)	0.1	**4c**, 76
5	5	DXM (**4b**)	DMC/MeOH (9:1)	0.1	**4c**, 15
6	5	DXM (**4b**)	*t*BuOAc/MeOH (9:1)	0.1	**4c**, 83
7	5	DXM (**4b**)	EtOAc/MeOH (9:1)	0.1	**4c**, 74
8	5	DXM (**4b**)	EtOAc/*i*-PrOH (9:1)	0.1	**4c**, 81
9	5	Noscapine (**5b**)	$CHCl_3$	24	**5c**, 28
10	5	Noscapine (**5b**)	EtOAc/MeOH (9:1)	17	**5c**, 26
11	5	Noscapine (**5b**)	EtOAc/*i*-PrOH (9:1)	2	**5c**, 30
12	5	Noscapine (**5b**)	*i*-PrOH	120	-[C]
13	5	Atropine (**6b**)	EtOAc/MeOH (9:1)	22	**6c**, 66
14	5	Atropine (**6b**)	EtOAc/*i*-PrOH (9:1)	19	**6c**, 79
15	5	Tropine (**7b**)	*i*-PrOH	2.5	-[C]
16	5	Pivaloyltropine (**8b**)	$CHCl_3$	2	**8c**, 83
17	5	Pivaloyltropine (**8b**)	*i*-PrOH	17	**8c**, 63
18	5	Pivaloyltropine (**8b**)	EtOAc/MeOH (9:1)	0.1	**8c**, 66
19	5	Pivaloyltropine (**8b**)	EtOAc/*i*-PrOH (9:1)	0.1	**8c**, 63

[A] 10 mL of solvent per 100 mg substrate at ambient temperature (measured to be 21°C on average) under an atmosphere of argon. Reactions were stirred using a 12 mm magnetic bead at 750 RPM.
[B] Isolated yield following column chromatography.
[C] NMR of crude product mixture showed no evidence of any conversion of *N*-oxide starting material to *N*-nor product.

Following the demonstration of nZVI and $Fe_3(CO)_{12}$ as effective catalysts for the demethylation of **4b**, we sought to establish whether the methodology could be applied to other

biologically interesting alkaloids. We therefore investigated the demethylation of the *N*-oxide hydrochlorides of noscapine (**5a**), atropine (**6a**), tropine (**7a**), pivaloyltropine (**8a**), and benzoyltropine (**9a**) (**Figure 3**) using nZVI and $Fe_3(CO)_{12}$. Compound **5a** is interesting as a potential starting material for synthesis. Its complex array of carbocycles and heterocycles makes it an attractive starting point for more complex products. Furthermore, **5a** has gained interest as a starting material for the synthesis of potential anti-cancer agents.[31,32] Previous studies in our group have already indicated the potential use of *N*-substituted noscapine analogues as more potent anti-cancer agents, which obviously necessitates the preparation of *N*-nornoscapine, **5c**, as an intermediate.[31] Compound **6a**, like many opioids, has been a historically important drug, present in various plant sources, particularly *Atropa belladonna*, from which the drug gets its name. It is also used as a starting material for various pharmaceuticals; *N*-noratropine, **6c**, is an important intermediate for the synthesis of ipratropium bromide, a bronchodilator.[33] Improved *N*-demethylation methods for both **5a** and **6a** could be utilized for rapid and easy access to the *N*-nor compounds. Compound **7a** was tested as an interesting synthon that may be included in various drugs (such as Granisetron, Hyoscyamine and Tropisetron), while **8a** and **9a** represent more "drug-like" compounds with increased organic solubility.

N-Demethylation of these alternative test substrates gave variable, but promising results (Table 1, Entries 7 – 11, Table 2, Entries 9 – 19). Compound **5b**, for example, failed to give increased yields of **5c** when $Fe_3(CO)_{12}$ was used as the catalyst compared to previously established literature methods.[31] However, the reaction did go to completion (Table 2, Entries 9-11). Using *i*-PrOH, no product was observed when either nZVI or $Fe_3(CO)_{12}$ were used (Table 1, Entry 7 and Table 2, Entry 12). Once again, we believe this to be due to the limited solubility of the substrate in the selected solvents. Furthermore, **5a** may be a particularly difficult substrate for this particular process as the *N*-methyl group is quite sterically hindered. Upon oxidation to **5b**, further steric hindrance may occur, preventing approach of the catalyst to the required site for the radical oxidation to occur.

Using **6b** as a test substrate, very good yields were obtained when nZVI was used in *i*-PrOH (Table 1, Entry 8), while only moderate yields were observed when using $Fe_3(CO)_{12}$ in EtOAc/*i*-PrOH (Table 2, Entry 13 & 14). Lower yields were observed when using MeOH instead of *i*-PrOH in the mixture, which is consistent with previous results. Conversion of **7b** to *N*-nortropine proved unsuccessful under all tested conditions, including using *i*-PrOH as the solvent (Table 1, Entry 9 & Table 2, Entry 15).

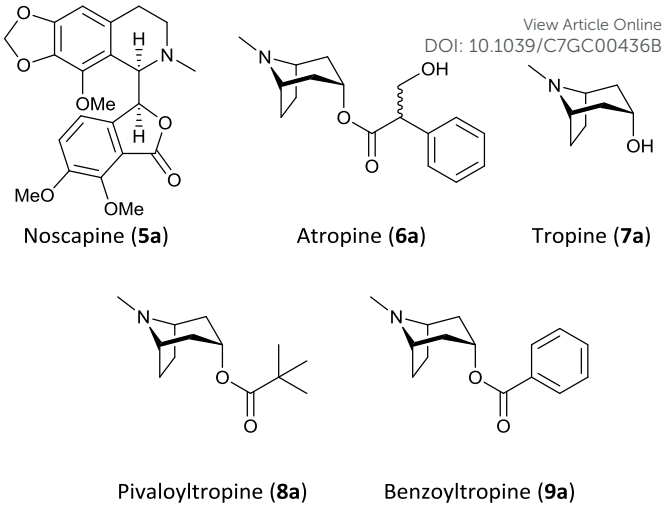


Fig. 3. Alternative alkaloid substrates for *N*-demethylations.

The more soluble **8b** gave variable results compared to those previously obtained using nZVI or $Fe_3(CO)_{12}$. Whereas previous substrates gave good yields in a mixture of 9:1 (*v/v*) EtOAc/*i*-PrOH, conversion to **8c** was suboptimal in this system compared to in $CHCl_3$ (Table 2, Entry 16). Switching to **9b** did not result in any appreciable increase in yield when using nZVI (Table 1, Entry 11). The yields are, nevertheless, comparable to those obtained for previous attempts at *N*-demethylation of tropane alkaloids, but with a significantly reduced reaction time.[33] Although some optimisation may be required, these results highlight the possibility of using greener solvent substitutes without a significant compromise in yield.

Reactions using nZVI and $Fe_3(CO)_{12}$ were observed to proceed much faster in $CHCl_3$ than in greener solvents such as *i*-PrOH. Furthermore, these two iron sources seemed to considerably enhance the rate of the *N*-demethylation reactions to a far greater degree than other iron sources investigated earlier by our research group. For example, *N*-demethylation of **4b** appeared complete within 5 min when conducted using $Fe_3(CO)_{12}$, and within 1 h when using nZVI in $CHCl_3$. Hence, we endeavoured to measure the relative rates of conversion for each of the iron sources. In order to make direct comparisons and also to emphasize the compatibility of our systems in green solvent systems, the study of relative conversions of **4b** to **4c**, using the different iron catalysts, were conducted in *i*-PrOH. Ferric sulfate did not give 100% conversion into nor-DXM, **4c**, even after 30 h (**Figure 4**). As we reported earlier, the use of iron(0) dust improved this reaction and resulted in essentially 100% conversion after almost 30 h.[15]

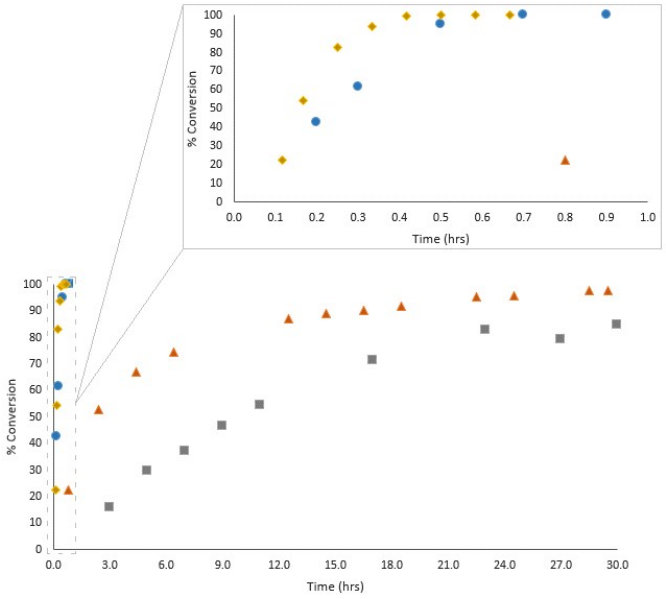


Fig. 4. Percentage conversion *versus* time for various iron catalysts. $FeSO_4$ (■), Fe(0) dust (▲), nZVI (●), $Fe_3(CO)_{12}$ (◆).

As anticipated, the use of nZVI, with far greater surface area, afforded 100% conversion after only 40 min. Lastly, the use of $Fe_3(CO)_{12}$ afforded the fastest rate of conversion for all iron sources trialled, with 100% conversion of **4b** to **4c** in just over 30 min.

Conclusions

The green attributes of the modified Polonovski reaction, through which the *N*-demethylation of various alkaloids is achieved, have been significantly improved in comparison to previously reported methodologies. The use of nZVI as a green catalyst and *i*-PrOH as a green solvent afforded enhanced rates of conversion to nor-alkaloid products. Although less green, the use of $Fe_3(CO)_{12}$ as a catalyst affords even faster rates of conversion to demethylated, nor-alkaloid products. The solubility properties of this compound allow for genuinely catalytic amounts to be employed, while still permitting the use of *i*-PrOH. This methodology has been successfully applied to a number of *N*-methylated alkaloids, with the possibility of being further extended to the *N*-demethylation of opiates of social significance, used in the commercial preparation of naltrexone, naloxone and buprenorphine.

Experimental

All solvents were used as provided by the manufacturer (Fisher Scientific, Alfa Aesar, Sigma-Aldrich). TLC was performed using aluminium-backed silica plates (Merk, Silica gel 60Å f254), with compounds visualised using a UV lamp, or *via* polymolybdate or $KMnO_4$ staining. ^1H and ^{13}C NMR spectra were recorded at 400 and 101 MHz or 300 and 75 MHz (Bruker Avance Nanobay III 400 MHz Ultrashield Plus or Bruker Avance III HD), respectively. Chemical shifts were referenced to residual solvent peaks according to Gottlieb *et al.*[34] Alkaloids were purchased from the supplier and used as provided (Sigma-Aldrich, Alfa Aesar), except for dextromethorphan, which was washed with base (2 x 5 % aqueous NaOH) to return the free base before *N*-oxidation according to literature procedure.[14] Triirondodecacarbonyl and ferric sulfate heptahydrate were purchased from Sigma-Aldrich.

General procedure for *N*-oxidation of alkaloids using *m*CPBA.

Alkaloid *N*-oxide hydrochloride salts were generated using variations of a literature procedure.[14] The alkaloid free amine was dissolved in $CHCl_3$ and cooled to (-5–0° C, typically 20 mL per gram of alkaloid). *m*CPBA (typically 1.2 eq.) was then added in a single portion and the reaction allowed to stir until reaction completion as determined by TLC analysis, after which time the mixture was worked up using one of the following procedures:
A. The volume of $CHCl_3$ was doubled and *i*-PrOH was added to make the solution a 3:1 (*v/v*) mixture of $CHCl_3$/*i*-PrOH. This was then washed successively with 1:4 (*v/v*) 2 M NaOH/brine (5 × 5 mL), followed by 1:4 (*v/v*) 2 M HCl/brine (5 × 5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered, and the solvent removed *in vacuo* to give the alkaloid *N*-oxide hydrochloride salt.
B. The reaction mixture was extracted with 1 M HCl (3 × 10 mL). The combined aqueous extracts were washed with $CHCl_3$ (2 × 10 mL) and the resulting aqueous phase reduced *in vacuo* to give the alkaloid *N*-oxide hydrochloride salt.

Procedure for *N*-oxidation of DXM using H_2O_2

DXM free amine (366 mg, 1.35 mmol, 1 eq.) was dissolved in MeOH (5 mL) and cooled to 0°C. H_2O_2 (26% w/w in H_2O, 1.766 g, 13.5 mmol, 10 eq.) was then added dropwise and the reaction allowed to stir at room temperature for 18 h. The reaction was then diluted with MeOH and excess H_2O_2 deactivated with MnO_2. The reaction was filtered through Celite and the solvent removed *in vacuo*. Aqueous HCl (0.1 M, 50 mL) was then added, and the resulting solution freeze-dried to give **4b** as the hydrochloride salt (412 mg, 94%).

General procedure for *N*-demethylation of alkaloid *N*-oxides using nZVI.

Following a modified procedure,[27] an appropriate amount of $FeSO_4 \cdot 7H_2O$ (see Table 1) was dissolved in aqueous methanol (two parts deionized water, one part methanol, 8 mL per 0.50 mmol $FeSO_4 \cdot 7H_2O$) and stirred at 450 RPM using a mechanical stirrer in an appropriately sized round-bottom flask while a 0.12 M aqueous solution of $NaBH_4$ was added dropwise at a rate of approximately 1 drop every 5 sec (0.8 mL per 0.50 mmol $FeSO_4 \cdot 7H_2O$). As drops were added, the solution turned an increasingly darker green until finally a black precipitate was formed. The suspension of black precipitate was stirred for an additional 5 min before being transferred into a 15 mL centrifuge tube. The washing process next consisted of five repetitions of centrifugation (5 min each at 3200 RPM) and decantation of the supernatant fluid. Before each centrifugation, the tubes were shaken vigorously such that the iron particles were re-suspended in the solvent. After the initial

centrifugation and decantation, the tube was filled to the 5 mL mark with 2 mL of water and 3 mL of methanol, centrifuged and decanted. The same washing process was then repeated. The tube was then filled with 5 mL of the solvent to be used in the *N*-demethylation reaction, centrifuged and decanted. The same washing process was repeated one more time. At this point the nZVI was suspended in the appropriate solvent (5 mL) and added to the *N*-demethylation reaction flask. The alkaloid *N*-oxide hydrochloride salt (0.50 mmol) was previously dissolved or partially dissolved in the selected solvent (10 mL) in the reaction flask, giving a total of 15 mL of solvent, along with the *N*-oxide hydrochloride salt and suspended nZVI. This mixture was stirred for the appropriate amount of time (see Table 1) at room temperature. Upon completion of reaction, the solvent was removed under reduced pressure and the residue dissolved in 3:1 (*v/v*) $CHCl_3$/*i*-PrOH (26 mL). The resulting organic phase was washed with 2 M NaOH (2 × 2 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent removed *in vacuo*. The resulting residue was purified by silica column chromatography to give the corresponding *N*-nor compounds.

General procedure for *N*-demethylation of alkaloid *N*-oxides using $Fe_3(CO)_{12}$.

The alkaloid *N*-oxide hydrochloride salt (100 mg) was dissolved or partially dissolved in the selected solvent (9 mL) and an appropriate amount of $Fe_3(CO)_{12}$ (see Table 2) was added as a solution/suspension in the solvent (1 mL). The reaction was allowed to stir until reaction completion (see Table 2). Where solvent mixtures with 10% MeOH or *i*-PrOH were used, the alkaloid was dissolved in the appropriate alcohol (1 mL) first, followed by the bulk solvent (8 mL). The iron species was then delivered as a suspension/solution in the bulk solvent (1 mL). Upon reaction completion, the solvent was removed *in vacuo* and the residue dissolved in 3:1 (*v/v*) $CHCl_3$/*i*-PrOH (26 mL). The resulting organic phase was washed with 2 M NaOH (2 × 2 mL), dried over anhydrous Na_2SO_4, filtered, and the solvent removed *in vacuo*. The resulting residue was purified by silica column chromatography and evaporated from DCM to give the corresponding *N*-nor compounds.

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N-demethylation of selected *N*-methylalkaloids using a modified Polonovski reaction can be accomplished employing nanoscale zero-valent iron, nZVI, in isopropanol.