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Further investigation of the N-demethylation of tertiary amine alkaloids using the non-classical Polonovski reaction

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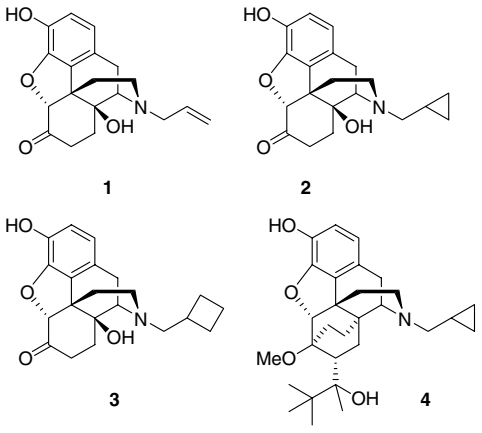
Abstract—The iron salt-mediated Polonovski reaction efficiently N-demethylates certain opiate alkaloids. In this process, the use of the hydrochloride salt of the tertiary *N*-methyl amine oxide was reported to give better yields of the desired N-demethylated product. Herein, we report further investigation into the use of *N*-oxide salts in the iron salt-mediated Polonovski reaction. An efficient approach for the removal of iron salts that greatly facilitates isolation and purification of the *N*-nor product is also described.

The *N*-methyl group is a characteristic moiety associated with many naturally occurring alkaloids of biological significance, including the prominent analgesic opiates morphine and codeine. Formation of the secondary amine in the opiate skeleton allows for substitution of the nitrogen atom, leading to the synthesis of pharmaceutically useful opiates such as naloxone (**1**), naltrexone (**2**), nalbuphine (**3**) and buprenorphine (**4**).[1] Thus, the formation of the N-demethylated derivative is an important intermediate in the synthesis of synthetic opiates.



A number of procedures have been reported for the N-demethylation of opiate alkaloids. These include reaction with cyanogen bromide (von Braun reaction)[2] or a substituted chloroformate[3] followed by cleavage of the resultant cyanamide or carbamate. Reaction with a dialkyl azodicarboxylate followed by hydrolysis has also been used to effect this conversion. Photochemical[4] and microbial[5] N-demethylation procedures are known, though the former has proven to be low yielding in the case of opiates.

In a recent preliminary communication, we reported an inexpensive and effective approach for the N-demethylation of opiate alkaloids which employed a modified iron salt-mediated Polonovski reaction.[6] This approach involved the conversion of the tertiary *N*-methyl amine to the corresponding *N*-oxide (by treatment with hydrogen peroxide or *m*-chloroperbenzoic acid) followed by treatment with iron sulfate. A range of opiates were successfully N-demethylated using this procedure in moderate to high yield. In all cases, the major by-product formed during the iron sulfate step was the parent *N*-methyl compound. It was found that isolation of the corresponding *N*-oxide as its hydrochloride salt prior to iron treatment afforded superior yields of the desired '*N*-nor' product. A high yielding example of this procedure is the conversion of codeine methyl ether (CME, **5a**) to the corresponding *N*-nor analogue **5b**, which proceeded in 87% yield over two steps (Scheme 1). More recently, an alternative method for the deoxygenative demethylation of tertiary amine-*N*-oxides has

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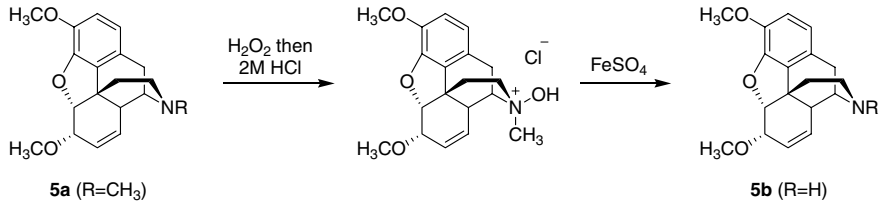


Scheme 1.

been reported which employed a 'column chromatography-like' setup comprised of different reaction zones.[7] This approach is yet to be trialed on opiate alkaloids.

One of the limitations of the iron salt-mediated variant of the Polonovski reaction is the difficulty in separating the product from the iron salts. The use of EDTA as an iron-chelating agent in the reaction work-up proved to be effective in removing iron salts in a number of cases.[6] However, the basic conditions (pH 10) that were required to ensure that metal coordination occurred were problematic for substrates with base-sensitive functionality.

The aim of this study was 2-fold; to further explore the scope of the use of amine-*N*-oxide salts in the non-classical Polonovski reaction, and to incorporate an alternative method of iron removal that would provide greater substrate tolerance and thus increased product yields.

A series of codeine methyl ether *N*-oxide salts were prepared in order to probe the effect of the anion on the iron salt-mediated Polonovski reaction. These salts were simply prepared by treating CME *N*-oxide with 1.1 equiv of the appropriate acid. The results following reaction with iron sulfate in methanol are summarised in Table 1.

In all cases, the combined isolated yields of nor-CME (**5b**) and CME (**5a**) were high, ranging from 82% to 100%. The ratio of these products varied greatly depending on the *N*-oxide salt used. Phthalate and chloride salts displayed the highest yields of nor-CME (82% and 79%, respectively) and the highest ratio of nor-CME to CME (4.6:1). Nitrate, hydrogen phosphate and perchlorate *N*-oxide salts were less selective, while the hydrogen sulfate salt afforded a higher proportion of CME.

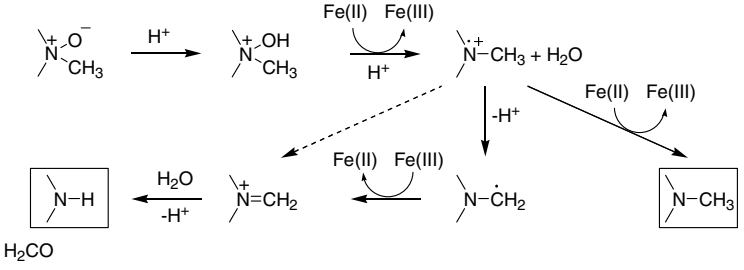
Table 1. Effect of anion on the N-demethylation of codeine methyl ether

Anion	nor-CME (**5b**) % yield[a]	CME (**5a**) % yield[a]	Ratio
Cl^-	82	18	4.6:1
Phthalate	79	17	4.6:1
NO_3^-	70	29	2.4:1
$H_2PO_4^-$	60	32	1.9:1
ClO_4^-	56	40	1.4:1
HSO_4^-	34	48	0.7:1

[a] Isolated yield after column chromatography.

The mechanism of the iron salt-mediated version of the Polonovski reaction is believed to involve two successive one-electron transfers involving Fe(II)/Fe(III) redox reactions (Scheme 2).[8] It is thought that the iron(II) initially coordinates to the protonated *N*-oxide which subsequently undergoes a one-electron reduction which results in cleavage of the N–O bond and formation of an aminium radical cation. This radical cation loses an α-proton and undergoes an electron reorganisation to form a more stable carbon centred radical (while still bound to iron). Oxidation of the carbon centred radical by iron(III) forms an iminium ion which undergoes hydrolysis to yield the N-demethylated product. An alternative mechanism has been proposed in which the aminium radical cation is converted to the iminium ion directly via transfer of a hydrogen atom to iron(III) which is reduced to iron(II) with the liberation of a proton.[9] The major by-product is the parent tertiary *N*-methylamine which is believed to form when the intermediate aminium radical cation dissociates from the oxidised iron complex and undergoes further reduction by iron(II).

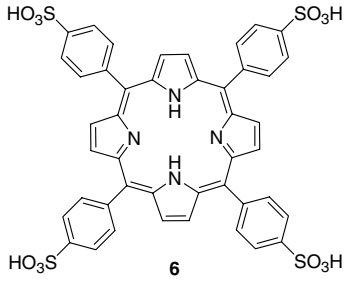
Although the anion effect of *N*-oxide salts has not been studied previously, the effect of different iron(II) anions on the iron-catalysed dealkylation of trimethylamine oxide has been investigated.[10] In that case, the yield of formaldehyde varied with the anion used (ClO_4^-, SO_4^{2-}, Cl^- and PO_4^{3-}). More specifically, as the stability constant of the anion with iron(III) increased, the yield of formaldehyde decreased. This led the authors to conclude that anions which complex more strongly with iron(III) may either (1) accelerate the reduction



Scheme 2. Proposed mechanism of the iron salt-mediated Polonovski reaction.

of the aminium radical cation or (2) decelerate the oxidation of the aminium radical cation by Fe(III), resulting in an enhanced yield of trimethylamine and a lower yield of formaldehyde. In our case, no correlation was observed between the stability constant of the *N*-oxide anion with iron(III) and the product ratio.

meso-Tetra(4-sulfophenyl)porphine (TPPS, **6**) was investigated as an alternative to EDTA under basic conditions for the removal of iron salts in the reaction work-up. TPPS was chosen for its high water solubility (as the corresponding salt), iron affinity and ease of synthesis. The sodium salt of TPPS was synthesised from sulfonation of *meso*-tetraphenyl porphine (TPP) using hot concentrated sulfuric acid, followed by aqueous work-up.[11] An additional advantage of using porphyrin systems is their ability to be demetallated to regenerate the free base porphyrin.[12]



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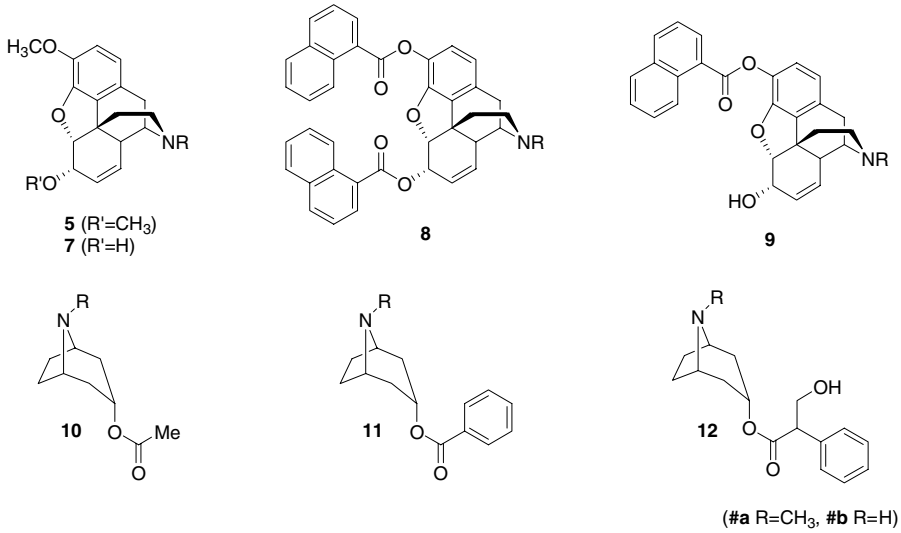
A range of substrates which possessed groups known to be base labile and/or groups which are known to coordinate to iron (primarily esters and hydroxyl groups, respectively) were evaluated using a procedure which employed TPPS for the removal of iron salts. Both opiate and tropane alkaloids were included in the test set. These substrates were efficiently and quantitatively oxidised using magnesium bis(monoperoxyphthalate). The resultant *N*-oxide, which was isolated as the phthalate salt, was then treated with iron sulfate to effect the N-demethylation. Once the reaction was complete, tetrasodium *meso*-tetra(4-sulfonatophenyl)porphine was added prior to chloroform extraction. In all cases, iron salts were cleanly extracted into the aqueous phase by the TPPS, greatly facilitating the isolation of organic products. N-Demethylated products were purified via column chromatography. The results of this study are summarised in Table 2. In all cases, the TPPS procedure for removal of iron salts gave comparable or superior results to the EDTA procedure. In the opiate examples, the improvement in yield was most notable in the isolation of norcodeine (**7b**) and normorphine di-(1-naphthoylate) (**8b**), while significantly improved yields were observed for all of the tropane alkaloids (**10b**, **11b** and **12b**).

In conclusion, the conversion of tertiary *N*-methyl alkaloids to the corresponding *N*-oxide followed by treatment with $FeSO_4{\cdot}7H_2O$ has proven to be an effective approach for N-demethylation and formation of the corresponding secondary amines. The isolation of the

Table 2. Modified Polonovski reaction of alkaloid *N*-oxides



5 (R'=CH_3)
7 (R'=H)

8

9

10

11

12

(**#a** R=CH_3, **#b** R=H)

Alkaloid	EDTA procedure *N*-Nor (NMe)[a]	TPPS procedure[13] *N*-Nor (NMe)[a]
5	77 (22)	78 (22)
7	49 (7)	62 (11)
8[14]	34 (15)	71 (18)
9[15]	55 (3)	59 (7)
10	10 (3)	56 (5)
11	16 (4)	61 (14)
12	16 (8)	51 (12)

[a] Isolated yields after column chromatography.

N-oxide salt following treatment with a variety of acids was found to have a marked effect on the amount of the desired *N*-nor product formed.

The use of the tetrasodium *meso*-tetra(4-sulfonatophenyl)porphine for the removal of iron as an alternative to basic EDTA significantly improved the yields of desired *N*-nor products. The TPPS procedure has demonstrated tolerance to acetyl, benzoyl and naphthoylate esters and hydroxyl groups. This modification has potential applications in large, scale processes, as the water, soluble porphyrin synthesis is straightforward and inexpensive, and has the added benefit of being recyclable through demetallation procedures, thus reducing costs and enhancing efficiency of the N-demethylation process.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.03.017.

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13. General method for TPPS procedure: Codeine methyl ether (0.20 g, 0.64 mmol) was dissolved in methanol (30 mL) and magnesium bis(monoperoxyphthalate) hexahydrate (80%, 0.38 g, 0.77 mmol) was added. The reaction mixture was stirred at rt for 45 min and then filtered (Celite pad). The Celite pad was washed with additional methanol and the filtrate was evaporated in vacuo to give CME–*N*-oxide as a phthalate salt. The crude *N*-oxide was redissolved in methanol (30 mL), $FeSO_4{\cdot}7H_2O$ (0.289 g, 0.96 mmol) was added and the reaction mixture was stirred for 6 h at rt. The methanol was evaporated and the resultant orange solid was dissolved in an aqueous solution of tetrasodium *meso*-tetra(4-sulfonatophenyl)porphine (1.14 g, 1.11 mmol in 25 mL) and extracted with $CHCl_3$ (4× 50 mL). The organic extract was dried ($MgSO_4$) and evaporated to afford a mixture of norcodeine methyl ether and codeine methyl ether (0.1987 g). Column chromatography using $CHCl_3$/MeOH/28% NH_4OH (89:10:1) as an eluent afforded pure norcodeine methyl ether in 78% yield.
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