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

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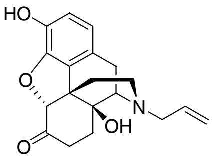
Abstract—The iron salt-mediated Polonovski reaction efficiently N-demethylates certain opiate alkaloids. In this process, the use of the hydrochloride salt of the tertiary *N*-methyl amine oxide was reported to give better yields of the desired N-demethylated product. Herein, we report further investigation 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.



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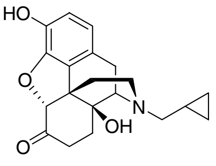

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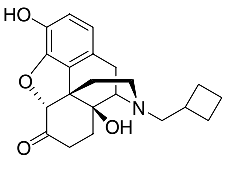

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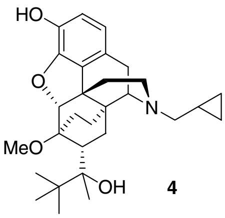

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A number of procedures have been reported for the N-demethylation of opiate alkaloids. These include reaction with cyanogen bromide (von Braun reaction)[2] or a substituted chloroformate[3] followed by cleavage of the resultant cyanamide or carbamate. 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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Keywords: N-demethylation; Non-classical Polonovski reaction.

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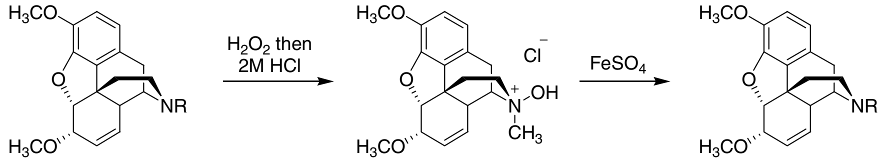


5a (R=CH$_3$)

5b (R=H)

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.

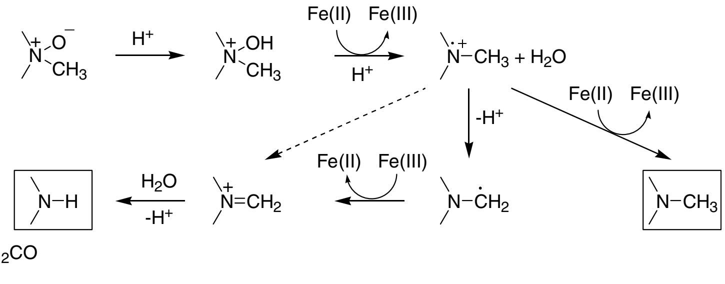
Table 1. Effect of anion on the N-demethylation of codeine methyl ether

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.