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Alternative methods for the MnO_2 oxidation of codeine methyl ether to thebaine utilizing ionic liquids

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Abstract—The MnO_2 oxidation of codeine methyl ether, CME, to thebaine has been accomplished via the use of the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate, $bmimBF_4$. The ionic liquid has been used to remove or extract excess MnO_2 and associated impurities from the reaction mixture to afford thebaine in 36 to >95% yield. © 2001 Elsevier Science Ltd. All rights reserved.

Thebaine (Fig. 1) is a minor opium alkaloid found in the poppy *Papaver somniferum* and has no known direct medicinal applications. However, thebaine has seen ample use as a synthetic precursor to many opiate derivatives, such as buprenorphine, that are used in the treatment of opiate and alcohol addiction as well as opiate overdose.[1] Although thebaine can now be isolated in large quantities from the poppy plant there is frequently a higher demand for thebaine to prepare opiate derivatives than can be met from these sources. Hence, we have sought to develop a synthetic method with which thebaine can be prepared in an economical fashion and in useful quantities.

There are a number of procedures described in the literature for the synthesis of thebaine.[2] Most notable is that by Barber and Rapoport in which it is reported that codeine methyl ether (Fig. 1) can be oxidized with γ-MnO_2 to afford an 80% yield of thebaine (67% overall from codeine).[2b] This method makes use of 25 equiv. of γ-MnO_2 and is conducted in tetrahydrofuran under a nitrogen atmosphere. We have found it difficult to reproduce such a high yield of thebaine via this methodology (Table 1; entry 1). We believe that thebaine is strongly adsorbing to the surface of the MnO_2 particles and that use of such a large excess of oxidizing agent in this methodology makes isolation of thebaine extremely problematic.

Most recently, a new class of solvents known as ionic liquids has been gaining popularity for use in a number of synthetic applications. Ionic liquids have been utilized in a wide range of reactions as a solvent[3] and have seen limited use as an extractant.[4] It is this latter application of ionic liquids that we wished to exploit. Specifically, we have used ionic liquids to extract, or remove, excess γ-MnO_2 and associated impurities from the reaction mixture in which codeine methyl ether is oxidized to thebaine. We have utilized the ionic liquid 1-butyl-3-methylimidazolium tetrafluroborate,[5] bmim-

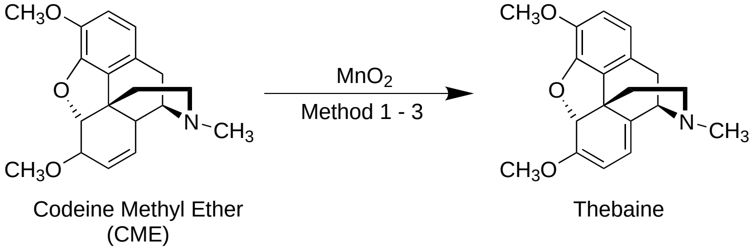

Figure 1. Oxidation of codeine methyl (CME) ether to thebaine.

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Table 1. MnO_2 oxidation of codeine methyl ether to thebaine[7,8]

Entry	Equiv. MnO_2	Reaction conditions[a,b]	Reaction time (h)	Yield (%) (% recovery)[c]
1	25	THF	24	25 (58)[d]
2	10	$BmimBF_4$, sonication	120	38 (80)
3	10	$BmimBF_4/Et_2O$ (biphasic), sonication	168	36 (100)
4	10	THF, sonication	144	>95 (100)

[a] In entries 2–4, MnO_2 was extracted/immobilized in $bmimBF_4$; opiates extracted into EtOAc layer.

[b] All reactions were monitored by TLC until no further change was discernible.

[c] Total recovery of opiates (Thebaine and unreacted CME)

[d] Best result obtained after repeated attempts.

BF_4, in our initial studies and are currently investigating the use of other air and moisture stable ionic liquids for this application (Fig. 2).

We have demonstrated three methods employing ionic liquids in the MnO_2 oxidation of CME to thebaine (Table 1; entries 2–4).[6] First, the MnO_2 oxidation of CME was performed in the ionic liquid alone. In this case, it was anticipated that use of the ionic liquid as a reaction medium/solvent might enhance the rate of this oxidation reaction in addition to facilitating the separation of products from excess MnO_2, impurities and unwanted by-products. After extended reaction times under sonication (ca. 120 h), thebaine and unreacted CME were easily extracted from the reaction mixture using ethyl acetate. MnO_2 and other impurities remained in the bottom ionic liquid layer of this extraction process. CME underwent a 38% conversion to thebaine under these conditions with approximately 80% of combined opiate components (i.e. thebaine and CME) isolated as determined via ^1H NMR analysis, and comparison to authentic samples. Hence, the use of ionic liquids as solvents for this oxidation reaction does not appear to enhance the rate of reaction appreciably under those conditions examined here. Further investigation using a wider range of ionic liquids as solvents (see Fig. 2) may allow the realization of this goal. However, it has been demonstrated that this strategy does allow easy isolation of opiate components from an otherwise intractable mixture of reaction products.

The second method in which ionic liquids were used in the MnO_2 oxidation of CME to thebaine employed a biphasic solvent system. The CME starting material was dissolved in diethyl ether giving a clear solution that formed an upper layer when combined with the more dense ionic liquid containing the MnO_2 oxidant. Utilization of this method afforded comparable results compared to those obtained using that employed previously (Table 1; entry 2). Under these biphasic conditions, CME underwent a 36% conversion to thebaine after extended reaction time under sonication (ca. 168 h) as determined via ^1H NMR analysis, and comparison to authentic samples, with a quantitative isolation of combined opiate components. We believe that CME did not partition very favorably between the etherial upper layer and the lower ionic liquid layer that contained the oxidant. This resulted in the low conversion to thebaine. Once again, we envisage that use of a wider range of ionic liquids, or perhaps even the addition of a phase transfer reagent, may enable better conversion of CME to thebaine in a biphasic, organic/ionic liquid system.

Finally, the oxidation was performed in a conventional covalent solvent (i.e diethyl ether or tetrahydrofuran) in which the CME was initially dissolved followed by addition of excess MnO_2. The heterogeneous mixture was then sonicated for an extended reaction time (ca. 144 h). The separation of MnO_2 and other troublesome impurities from the unreacted CME and the desired product, thebaine, was then accomplished by adding an appropriate amount of ionic liquid and extracting the organic components from the inorganic components (contained in the ionic liquid) using ethyl acetate and/or diethyl ether.[7] Under these conditions, CME underwent a >95% conversion to thebaine after extended reaction time under sonication (ca. 144 h) as determined via ^1H NMR analysis, and comparison to authentic samples, with a quantitative isolation of combined opiate components. It is obvious that this method is far superior to all others performed so far. In essence, this method has combined the use of a good solvent for this oxidation reaction (i.e. dry THF under inert atmosphere) with use of an excellent selective extractant for the unreacted MnO_2 and other inorganic impurities.

It is possible that the ionic liquid dissolves MnO_2 and other inorganic impurities present in these reactions, forms some kind of colloid with the MnO_2 particles, or

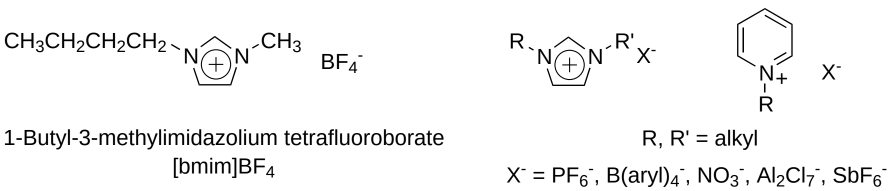

Figure 2. 1,3-Dialkylimidazolium and *N*-alkylpyridinium based ionic liquids.

simply adsorbs to the surface of the MnO_2 particles preferentially to CME or thebaine. Regardless of the interaction between the ionic liquid and MnO_2, the inorganic components of these reactions preferentially partition into the ionic liquid layer versus the upper organic layer into which the opiate components preferentially partition. This allows the facile isolation of all opiates in high yields; hence, the major drawbacks of previous methods for the MnO_2 oxidation of CME to thebaine have been overcome. Our method requires the use of less than half the amount of γ-MnO_2 as reported elsewhere[2b] and has proven to be easily reproducible. The use of sonication has also resulted in decreased reaction times required for the reaction to go to completion as compared with unsonicated reactions. Hence, our method offers significant advantages from an industrial point of view, especially in the context of disposal of unreacted MnO_2. Depending on the method used, CME can be converted into thebaine in varying degrees. It has been reproducibly demonstrated that using the ionic liquid strictly as an extractant for inorganic impurities and by-products in those reactions in which CME is converted to thebaine in a covalent, molecular solvent affords high yields of thebaine. The actual nature of the interaction between the ionic liquid and MnO_2 is a topic of current investigations. Also noteworthy is the fact that these reactions represent one of the first examples of an oxidation reaction conducted in an ionic liquid.[3c,8]

Acknowledgements

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7. **Typical procedure:** γ-MnO_2 Oxidation of CME to thebaine: CME (0.50 g, 1.6 mmol) was dissolved in 10 mL of freshly dried and distilled THF followed by addition of γ-MnO_2 (0.70 g, 8.0 mmol). The heterogeneous mixture was then sonicated at ambient temperature for 48 h, under N_2, after which time TLC analysis showed incomplete reaction. An additional 5 equiv. of γ-MnO_2 (0.70 g, 8.0 mmol) was then added and the mixture sonicated for a total of 144 h. 10 mL of 1-butyl-3-methyl-imidazolium tetrafluoroborate, $bmimBF_4$, were then added to the reaction mixture to extract the MnO_2, impurities and unwanted by-products into a bottom ionic liquid layer. The reaction mixture was then extracted, first with diethylether (3×30 mL), and then with ethyl acetate (3×30 mL) that had formed an upper organic layer above the ionic liquid layer. The combined organic extracts were then washed with distilled water to remove residual ionic liquid, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford 0.5 g of yellow solid. ^1H NMR analysis and comparison to authentic samples then showed >95% conversion of CME to thebaine with essentially 100% recovery of opiate from the reaction mixture. Less than 5% of CME was the only other component present in the reaction product mixtures determined by ^1H NMR. The yellow color of the products can be attributed to this unreacted CME. The yellow color of the crude product could be easily removed via recrystalization from ethanol with a 93% recovery from crude to give pure thebaine with a white color.
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