A Simple and Practical Method for the Oxidation of Thebaine to 14-Hydroxycodeinone by V_2O_5–H_2O_2

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Abstract: An efficient, practical and expeditious method has been developed for the oxidation of thebaine to 14-hydroxycodeinone in excellent yield by employing 20 mol% of V_2O_5 in the presence of 30% H_2O_2 in aqueous medium. The method provides a clean technological process for the preparation of a key drug intermediate, 14-hydroxycodeinone.

Key words: 14-hydroxycodeinone, thebaine, vanadium pentoxide, hydrogen peroxide, catalytic oxidation

The development of efficient methods for the synthesis of opioid derivatives which have pain-relieving properties and are devoid of side effects, such as addiction, has been a strong challenge to organic chemists.[1] The introduction of the 14-hydroxyl group onto the morphine alkaloid structure improves its pharmacological properties. Many such derivatives are clinically used as analgesic and antitussive agents, and for the treatment of opiate abuse, opiate overdose and alcohol addiction. For example, oxycodone (Eucodal; **1**) is finding increasing application as an analgesic and antitussive agent,[2a] whereas naltrexone (**2**) and naloxone (**3**) are used to treat opiate abuse,[2b] opiate overdose[2c] and alcohol addiction.[2d] 14-Hydroxycodeinone (**4**) is the key 14-hydroxylated intermediate for the synthesis of these drug molecules (Figure 1).

Thebaine (**5**, Figure 1), a minor opium alkaloid found in the poppy *Papaver somniferum*, has no direct medicinal application.[3] However, thebaine has been widely used as the starting material for the synthesis of many 14-hydroxylated opiates. In this context, a number of improved methods have been reported in the literature for the oxidation of thebaine to 14-hydroxycodeinone. Rapoport et al.[4a] accomplished the oxidation of thebaine to 14-hydroxycodeinone in very low yield (25%) by employing a cold H_2CrO_4/H_2SO_4 mixture as the oxidizing agent. Hauser et al.[4b] reported the oxidation of thebaine by *m*-chloroperoxybenzoic acid in a mixture of AcOH–TFA in 74% yield. But, Iijima et al.[4c] reported that this reaction did not give reproducible yields and furnished only 24.3% of the desired product along with many undesirable side products. Kraßnig et al.[4d] oxidized thebaine by using the $H_2O_2/HCO_2H/H_2SO_4$ system in 74.7% yield. Photooxidation of thebaine in TFA/CH_2Cl_2 produced the 14-hydroxycodeinone salt in 61% yield.[4e] 14-Hydroxycodeinone can also be obtained in high yield (90%) from thebaine bitartrate monohydrate, but the preparation of the starting material from codeine phosphate hemi-hydrate requires multi-step reacions.[4f] The synthesis of 14-hydroxycodeinone can also be achieved by the oxidation of codeinone or codeine. For example, the oxidation of codeinone by $Co(OAc)_3$ in AcOH furnished 14-hydroxycodeinone in 51% yield,[4g] whereas oxidation by $MnSO_4$ in the presence of sodium thiosulfate afforded 14-hydroxycodeinone in 85% yield.[4h] In addition to these methods, Madyastha et al.[4i] carried out a microbial transformation of codeine into 14-hydroxycodeinone by employing *Bacillus* sp. in 53% yield accompanied by the formation of 14-hydroxycodeine as a side product (yield 9%).

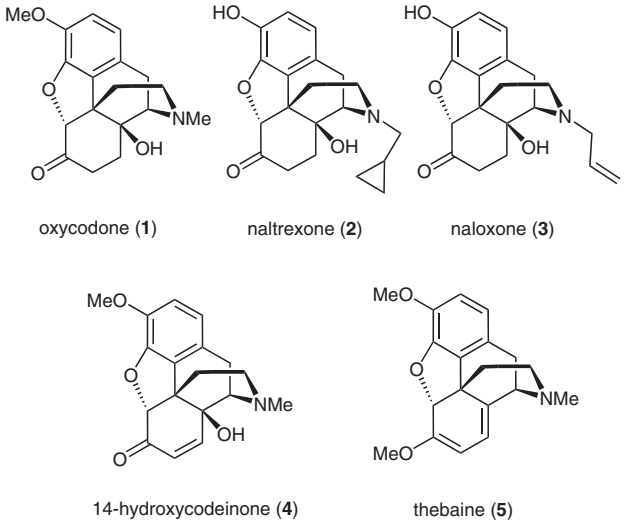

Figure 1

These reported methods suffer from low yields,[4a–e,g,i] harsh reaction conditions,[4a–c] use of toxic[4a] and stoichiometric amount of reagents,[4b–d,f,g] formation of byproducts,[4a–c,i] use of acids,[4a–g] long reaction times[4a–c,f–h] and the need for extensive chromatography in order to purify the final product.[4i] It is therefore desirable to develop a practical, efficient, environmentally acceptable and catalytic method for the oxidation of thebaine to 14-hydroxycodeinone, which eliminates the drawbacks stated above.

Recently, the combination of V_2O_5–H_2O_2 has emerged as a powerful oxidizing system for the oxidation of various organic substrates under mild conditions.[5] This system is

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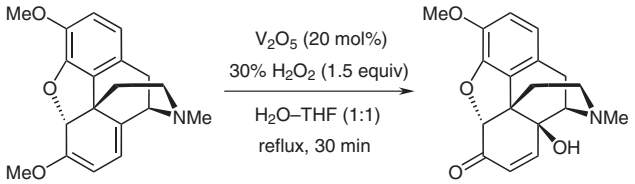
cheap, non-toxic and easy to handle. In a continuation of our efforts to develop clean and environmentally friendly synthetic methods[6] for various organic transformations we wish to report herein an efficient, practical and eco-friendly method for the oxidation of thebaine (**5**) to 14-hydroxycodeinone (**4**) by employing 20 mol% V_2O_5 in the presence of 30% H_2O_2 in a refluxing THF–H_2O mixture in excellent yield (Scheme 1).



5 **4**

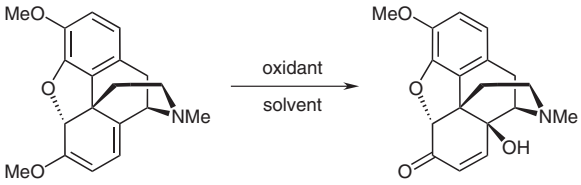
Scheme 1

In order to carry out the oxidation of thebaine in aqueous medium, we initiated our studies by adding 50 mol% of V_2O_5 and 1.5 equivalents of 30% H_2O_2 to a flask containing thebaine in water. Unfortunately, no reaction was observed even after six hours reflux (entry 1, Table 1). Since the reason may be due to the insolubility of the thebaine in water, the solubility problem was addressed by using a mixture of organic solvent (THF) and water. However, the resulting yield was very poor after 14 hours of stirring at room temperature (entry 2, Table 1). But under reflux conditions, the desired 14-hydroxycodeinone was obtained in excellent yield in a much shorter reaction time (entry 3, Table 1). The reaction conditions were then optimized by employing a range of catalyst loadings and solvent systems. The results are documented in Table 1. It was established that either V_2O_5 or H_2O_2 alone were not able to oxidize thebaine (entries 9 and 10, Table 1); the presence of both was indispensable for this oxidation process. The best result was achieved by carrying out the reaction with 20 mol% of V_2O_5 in the presence of 1.5 equivalents of H_2O_2 in a THF–H_2O (1:1) mixture under reflux (entry 5, Table 1).

We then turned our attention to the effects of different oxidizing agents on the oxidation of thebaine. To this end, a series of metal oxidants were tried. Among those tested, only $Ce(SO_4)_2{\cdot}4H_2O$ afforded the desired product (7% yield). Other oxidants [MnO_2, $Mg(ClO_4)_2$, $FeCl_3$, $Cu(OAc)_2{\cdot}H_2O$, $CuCl_2{\cdot}2H_2O$, KIO_3, $KMnO_4$, $Fe(NO_3)_3{\cdot}9H_2O$ and $NaNO_2$] were completely ineffective in this transformation as no product was detected in any case. The experimental procedure is very simple: thebaine (1 mmol) was mixed with 20 mol% of V_2O_5 and 30% H_2O_2 (1.5 equiv) in a mixture of H_2O–THF (1:1, 10 mL). The reaction mixture was then refluxed for 30 min, then worked-up to produce 14-hydroxycodeinone in excellent yield (Scheme 1). The reaction was very clean and no side-product was formed.

Though it is difficult to speculate on the mechanism of the reaction at this stage, it is envisaged that thebaine reacts with peracid (**A**)[5b] to form 14-hydroxycodeinone (Scheme 2).

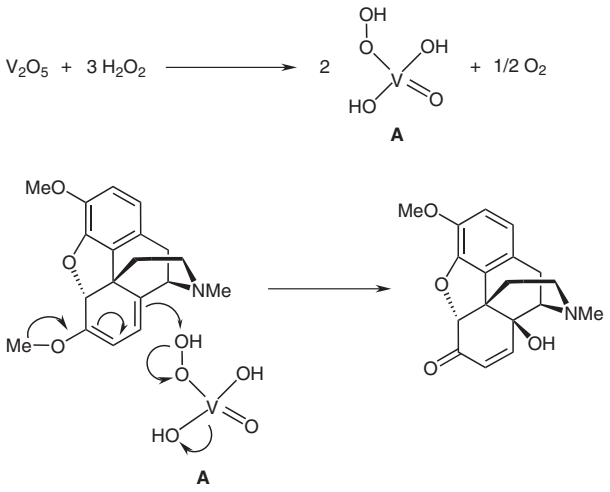
Table 1 Oxidation of Thebaine to 14-Hydroxycodeinone Using V_2O_5 and H_2O_2 in a Range of Solvents under Reflux



Entry	Oxidizing system		Solvents	Time (h)	Yield (%)[a]
	V_2O_5 (mol%)	H_2O_2 (equiv)[d]			
1	50	1.5	H_2O	6.0	n.r.[b]
2	50	1.5	THF + H_2O (1:1)	14.0	20[c]
3	50	1.5	THF + H_2O (1:1)	0.3	86
4	25	1.5	THF + H_2O (1:1)	0.3	86
5	20	1.5	THF + H_2O (1:1)	0.3	86
6	15	1.5	THF + H_2O (1:1)	0.4	84
7	10	1.5	THF + H_2O (1:1)	1.0	81
8	5	1.5	THF + H_2O (1:1)	1.3	76
9	20	0	THF + H_2O (1:1)	4.0	n.r.[b]
10	0	1.5	THF + H_2O (1:1)	4.0	n.r.[b]
11	20	1.5	THF + H_2O (2:1)	0.3	86
12	20	1.5	THF + H_2O (1:2)	0.3	83
13	20	1.5	THF	2.3	72
14	20	1.5	MeCN + H_2O (1:1)	0.4	83
15	20	1.5	MeOH + H_2O (1:1)	0.4	79
16	20	1.5	EtOH + H_2O (1:1)	0.35	80

[a] Isolated yield.
[b] No reaction. No spot detected by TLC.
[c] Reaction was carried out at 25 °C.
[d] 30% H_2O_2 was used for every reaction.

In conclusion, a practical, straightforward and environmentally acceptable clean technological process has been developed for the preparation of a key drug intermediate, 14-hydroxycodeinone, from thebaine by employing 20 mol% of V_2O_5 in the presence of 30% H_2O_2 (1.5 equiv) in a refluxing H_2O–THF (1:1) mixture, in excellent yield. The oxidizing system is inexpensive, stable and environmentally acceptable. The method does not involve any acid and the mild reaction conditions, easy work-up, clean reaction profiles, lower catalyst loading, cost efficiency and excellent yield render this approach an interesting alternative to the existing methods.



Scheme 2 Plausible mechanism for the oxidation of thebaine to 14-hydroxyodeinone by V_2O_5–H_2O_2

Melting points were measured using a Buchi B-540 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on an Avance DPX 300 MHz FT-NMR spectrometer. Chemical shifts are expressed in δ units relative to a TMS signal as internal reference. IR spectra were recorded on an FT-IR-system-2000 Perkin–Elmer spectrometer using KBr pellets. Mass spectra were recorded on an ESQUIRE 3000 mass spectrometer.

14-Hydroxycodeinone (4)

In a 50 mL two-necked round-bottom flask, thebaine **5** (2 mmol) was mixed with V_2O_5 (20 mol%) and 30% H_2O_2 (1.5 equiv) in a mixture of H_2O–THF (1:1, 10 mL). The reaction mixture was then refluxed for 30 min. After the reaction was complete (progress monitored by TLC), the mixture was neutralized through dropwise addition of aq NH_4OH and extracted with EtOAc (3 × 10 mL). The organic layer was washed with brine (1 × 10 mL), dried over Na_2SO_4 and concentrated under vacuum to give the crude product, which was recrystallized (MeOH) to afford pure 14-hydroxycodeinone **4**.

Yield: 0.538 g (86%); off-white crystals; mp 274–275 °C (Lit.[4c] 275 °C); $[\alpha]_D^{31}$ –109.0 (*c* 0.76, 10% AcOH).

FT-IR (KBr): 1674.3, 3423.9 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.67–1.71 (m, 1 H), 2.57 (dd, *J* = 18.4, 4.8 Hz, 1 H), 2.17–2.63 (m, 3 H), 2.44 (s, 3 H), 3.03 (d, *J* = 6.2 Hz, 1 H), 3.13 (d, *J* = 18.4 Hz, 1 H), 3.84 (s, 3 H), 4.71 (s, 1 H), 5.14 (br s, 1 H), 6.17 (d, *J* = 9.96 Hz, 1 H), 6.68 (d, *J* = 8.2 Hz, 1 H), 6.61 (d, *J* = 8.2 Hz, 1 H), 6.63 (d, *J* = 10.1 Hz, 1 H).

ESI-MS: *m*/*z* = 315.0 [M$^+$ + 2].

Anal. Calcd for $C_{18}H_{19}O_4N$: C, 69.00; H, 6.11; N, 4.47. Found: C, 69.08; H, 6.17; N, 4.40.

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