Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 3979–3981

Studies on regioselective hydrogenation of thebaine and its conversion to hydrocodone

Hannes Leisch,[a] Robert J. Carroll,[a] Tomas Hudlicky[a,*] and D. Phillip Cox[b]

[a]*Department of Chemistry and Centre for Biotechnology, Brock University, St. Catharines, Ontario, Canada L2S 3A1*
[b]*Noramco, Inc., 409 Silverside Road, Suite 200, Wilmington, DE 19809, United States*

Received 22 February 2007; revised 5 April 2007; accepted 10 April 2007
Available online 14 April 2007

Abstract—Thebaine was subjected to catalytic hydrogenation under a variety of conditions in order to determine the regioselectivity for C-6/C-7 versus C-8/C-14 olefin saturation.

The chemistry of thebaine, usually the minor constituent in crude opium, has been investigated in connection with the production of C-14 hydroxylated derivatives. The addition of singlet oxygen provides an endoperoxide, whose reduction yields 14-hydroxycodeinone **2**.[1] Similarly the treatment of thebaine **1** with formic acid and hydrogen peroxide gives 93% yield of **2**.[2] The dienol ether unit in thebaine has been transformed to neopinone ketal **3** by Rapoport and Barber[3] and by Dauben et al. (Fig. 1).[4] As the diene unit in thebaine is polarised, we reasoned that it may be possible to effect a regioselective reduction of the C-8/C-14 olefin through a directed catalytic hydrogenation of thebaine[5] under various conditions in order to provide for a direct conversion of thebaine to hydrocodone **5** via 8,14-dihydrothebaine **4**, as shown in Scheme 1. Although 8,14-dihydrothebaine can be obtained from thebaine by reduction with diimide (generated from hydrazine and oxygen) in 79% yield without chromatography on a 0.1 mol scale,[6] the need for an environmentally benign catalytic method still exists. A regioselective hydrogenation of thebaine to **4** would provide a more convenient alternative for the conversion of thebaine to hydrocodone.

The use of Crabtree catalyst **8**[7] led to regioselective hydrogenation of the C-8/C-14 olefin to produce enol ether **4** in 45% yield. Improved yields were achieved at lower pressure, as indicated in Table 1, entry 1–4.

The use of rhodium catalyst **9**[9] provided for an interesting contrast in the regioselectivity of hydrogen addition as shown in Table 2. Up to 40% yield of allylic ether **6** was obtained in addition to the fully saturated natural isomer of tetrahydrothebaine **7**, which in our hands were inseparable by column chromatography. Enol ether **6** was isomerised in preliminary experiments using Wilkinsons' catalyst in refluxing ethanol to yield **4** in 20% yield with 80% recovery of unreacted starting material.

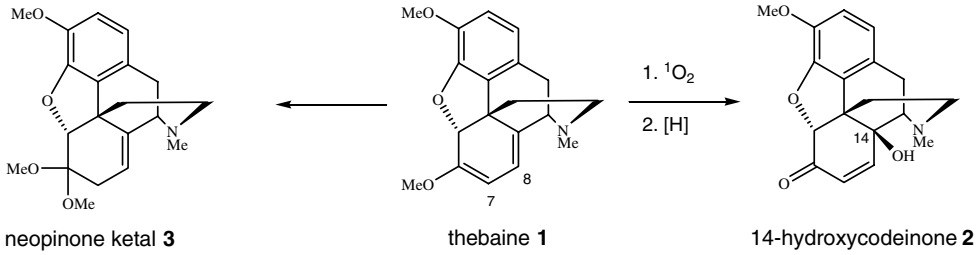
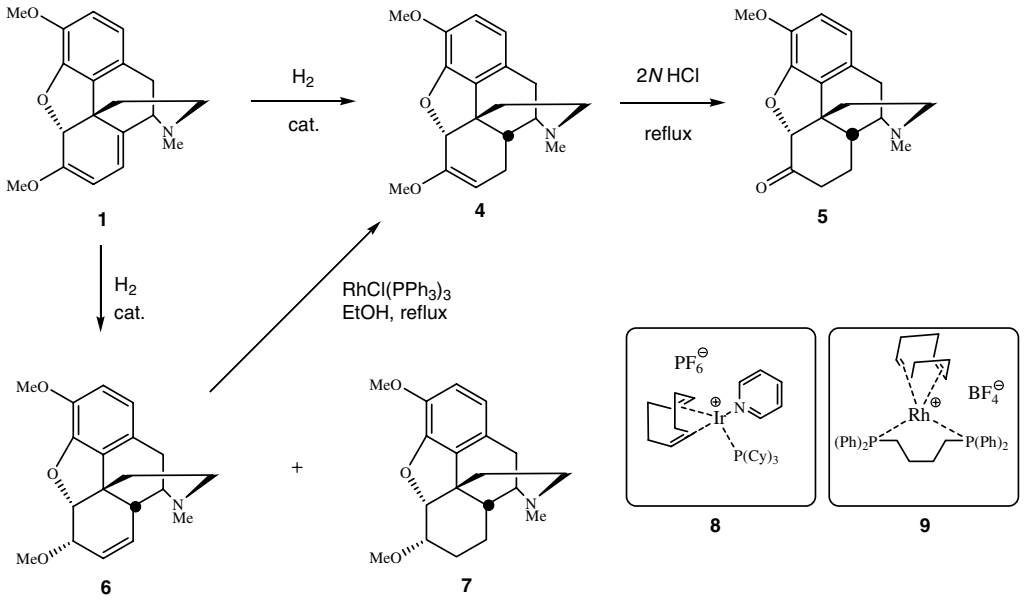


Figure 1.

* Corresponding author. Tel.: +1 905 688 5550; e-mail: thudlicky@brocku.ca

0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.04.051



Scheme 1.

Table 1. Hydrogenation of thebaine with Crabtree catalyst in methanol at room temperature

Entry	mol %	H_2 (psi)	Time (h)	Conversion[a] (%)	Yield of **4**[a] (%)	Yield of **7**[a] (%)
1	5	55	16	19	9	5
2	5	55	96	75	43	25
3	10	55	192	85	44	27
4	**15**	**55**	**288**	**95**	**45**	**27**
5	5	150	16	10	3	2
6	5	400	64	78	24	18

[a] The conversion and the yields were determined by ^{1}H NMR and HPLC.[8]

Table 2. Hydrogenation of thebaine over rhodium catalyst **9**

Entry	H_2 (atm)	Solvent	Time (h)	Conversion[a] (%)	Yield of **6**[a] (%)	Yield of **7**[a] (%)
1	1	EtOH	18	100	0	60
2	**1**	**DCM**	**18**	**100**	**0**	**90**
3	1	$CHCl_3$	18	80	0	0
4	**1**	**MeOH**	**18**	**40**	**38**	**0**
5	1	MeOH	27	85	33	30
6	1	MeOH	36	100	0	85
7	2	MeOH	5	10	8	0
8	1	MeOH, 30 °C	5	9	7	0
9	1	MeOH, 30 °C	18	100	0	60
10	1	MeOH, 0 °C	5	0	0	0

[a] The conversion and the yields were determined by ^{1}H NMR.[8]

A similar method for the isomerisation of codeine to hydrocodone has previously been published.[10] Hydrolysis of **4** using 2 N HCl yielded hydrocodone **5** in 82% isolated yield after flash column chromatography. Tetrahydrothebaine **7** is a significant by-product produced by over-reduction of thebaine under most of the conditions that were tried and is likely to be formed in any process developed in the future that uses catalytic hydrogenation. Rice described a practical method for the conversion of tetrahydrothebaine to dihydromorphine with HBr in AcOH thereby converting this by-product into a valuable compound.[11]

Other catalysts investigated during these studies include $RhCl(PPh_3)_3$ (Wilkinsons' catalyst), $RuCl_2(PPh_3)_3$, $Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$, Lindlars' catalyst and 5% Rh/Al. In the case of Wilkinsons' catalyst and $RuCl_2(PPh_3)_3$, no conversion was obtained in methanol at atmospheric pressure of hydrogen after 18 h. The use of other catalysts under the same conditions led (after 18 h) to complete consumption of starting materials, yielding compounds not structurally related to **4**, **5** or **7**. Tetrahydrothebaine **7** was obtained in 8% yield with $Pd_2(dba)_3$, in 10% yield for $PdCl_2(PPh_3)_3$ and in 26% yield with Rh/Al. With Lindlars' catalyst, dihydrotheba-

ine **4** was obtained in 8% yield along with 10% of tetrahydrothebaine **7**.

In conclusion, some level of regioselectivity in hydrogenation of the C-8/C-14 olefin was demonstrated by using catalysts capable of coordinating to the nitrogen atom of thebaine. Further optimisation studies for this conversion are ongoing.

Acknowledgements

The authors are grateful to Noramco, Inc., TDC Research, Inc. and the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support of this work. We also thank Brian Bullen, Chem Actives, Inc. and Tasmanian Alkaloids, Inc. for the provision of thebaine.[12]

References and notes

1. (a) Lopez, D.; Quinoa, E.; Riguera, R. *Tetrahedron Lett.* **1994**, *35*, 5727; (b) Lopez, D.; Quinoa, E.; Riguera, R. *J.Org. Chem.* **2000**, *65*, 4671.
2. (a) Krassnig, R.; Hederer, C.; Schmidhammer, H. *Arch. Pharm.* **1996**, *329*, 325; (b) Francis, C. A.; Lin, Z.; Kaldahl, C. A.; Antczak, K. G., Kumar, V. US 2005/0038251 A1; (c) Casner, M. L.; Dung, J. S.; Keskeny, E. M.; Luo, J. US 2006/111383.
3. Barber, R. B.; Rapoport, H. *J. Med. Chem.* **1976**, *19*, 1175.
4. Dauben, W. G.; Baskin, C. P.; Van Riel, H. C. H. A. *J. Org. Chem.* **1979**, *44*, 1567.
5. (a) Freund, M.; Speyer, E.; Guttmann, E. *Chem. Ber.* **1920**, *53*, 2250; (b) Skita, A.; Nord, F. F.; Reichert, J.; Stukart, P. *Chem. Ber.* **1921**, *54*, 1560; (c) Wieland, H.; Kotake, M. *Ann.* **1925**, *444*, 69; (d) Schopf, C. *Ann.* **1927**, *452*, 211; (e) Stork, G. *J. Am. Chem. Soc* **1952**, *73*, 504; (f) Birch, A. J. *J. Chem. Soc. (C)* **1966**, 1894; (g) Grew, E. L.; Robertson, A. A. US 1974/3812132.
6. Eppenberger, V.; Warren, H. E.; Rapoport, H. *Helv. Chim. Acta* **1968**, *51*, 381.
7. (a) Crabtree, R. *Acc. Chem. Res.* **1979**, *12*, 331; (b) Crabtree, R. H.; Felkin, H.; Morris, G. E. *J. Organomet. Chem.* **1977**, *141*, 205; (c) Crabtree, R. H.; Demou, P. C.; Eden, D.; Mihelcic, J. M.; Parnell, C. A.; Quirk, J. M.; Morris, G. E. *J. Am. Chem.* **1982**, *104*, 6994.
8. Ratios were determined by ^{1}H NMR in $CDCl_3$ by comparison of the intensities of H-5 protons of the morphine alkaloids (thebaine **1**, 5.29 ppm (s); 8,14-dihydrothebaine **4**, 4.84 ppm (s); codeine methylether **6**, 4.99 ppm (d, $J = 5.8$ Hz); tetrahydrothebaine **7**, 4.68 ppm (d, $J = 5.0$ Hz). Separation by HPLC was performed on a Hitachi L-6000 HPLC using a Hitachi L-4000H UV detector (254 nm) with a Phenomenex primespher 5 C18 HC 250 × 10 mm column; 2 ml/min flow; 5 mM KH_2PO_4, 0.1% NEt_3, pH 2.8 adjusted with 2 N HCl:MeOH (75:25). Retention times are as follows: thebaine **1**, 44.7 min; 8,14-dihydrothebaine **4**, 41.2 min; tetrahydrothebaine **7**, 31.0 min.
9. (a) Anderson, M. P.; Pignolet, L. H. *Inorg. Chem.* **1981**, *20*, 4101; (b) Brown, J. M.; Chaloner, P. A.; Kent, A. G.; Murrer, B. A.; Nicholson, P. N.; Parker, D.; Sidebottom, P. J. *J. Organomet. Chem.* **1981**, *216*, 263.
10. Wang, P. X.; White, C. R. WO 2005/047291 A1.
11. Przybyl, A. K.; Flippen-Anderson, J. L.; Jacobson, A. E.; Rice, K. C. *J. Org. Chem.* **2003**, *68*, 2010.
12. The use of thebaine and other morphinans was carried out in accordance with Health Canada guidelines and procedures. [licence # 2006/7531].