Organic Process Research & Development

Article

pubs.acs.org/OPRD

Selective Olefin Reduction in Thebaine Using Hydrazine Hydrate and O_2 under Intensified Continuous Flow Conditions

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Supporting Information

ABSTRACT: Hydrocodone, a high value active pharmaceutical ingredient (API), is usually produced in a semisynthetic pathway from morphine, codeine or thebaine. The latter alkaloid is an attractive precursor as it is not used as a remedy itself. The key step in this production route is a selective olefin reduction forming 8,14-dihydrothebaine which can be subsequently hydrolyzed to yield hydrocodone. Unfortunately, standard hydrogenation procedures cannot be applied due to severe selectivity problems. A transfer hydrogenation using in situ generated diimide is the only known alternative to achieve a selective transformation. The most (atom) economic generation of this highly unstable reducing agent is by oxidizing hydrazine hydrate ($N_2H_4{\cdot}H_2O$) with O_2. In the past, this route was "forbidden" on an industrial scale due to its enormous explosion potential in batch. A continuous high-temperature/high-pressure methodology allows an efficient, safe, and scalable processing of the hazardous reaction mixture. The industrially relevant reduction was achieved by using four consecutive liquid feeds (of $N_2H_4{\cdot}H_2O$) and residence time units, resulting in a highly selective reduction within less than 1 h.

INTRODUCTION

Hydrocodone (**1**), a non-natural opioid, is one of the most prescribed narcotic drugs with a steadily increasing trend in manufacture and consumption quantities over the past 20 years.[1,2] It is primarily used as an orally administered analgesic and antitussive either formulated with acetaminophen (e.g., Vicodin, Lortab, Norco) or as a pure substance (Zohydro ER).[3] Codeine (**2**) typically serves as precursor for hydrocodone synthesis (Scheme 1). This alkaloid can be found in the opium poppy plant (*Papaver somniferum*), but is mostly obtained via a semisynthetic pathway from morphine (>90%).[1] Transition metal-catalyzed hydrogenation of codeine results in dihydrocodeine (**3**) which can be subsequently transformed into the active pharmaceutical ingredient **1** by an Oppenauer-type oxidation.[4] Alternatively, the same transformation can be carried out in a single isomerization of the allylic alcohol using ruthenium[5] or rhodium[6] based catalysts.

An alternative synthetic precursor also present in the poppy plant is thebaine (**4**) which is not used for therapeutic purposes.[1] The generally low amount of this opiate alkaloid in the opium latex or poppy straw can be significantly enriched by a mutagenized poppy plant,[7] resulting in a remarkable increase of the thebaine production and its conversion to other narcotics during the past decade.[1]

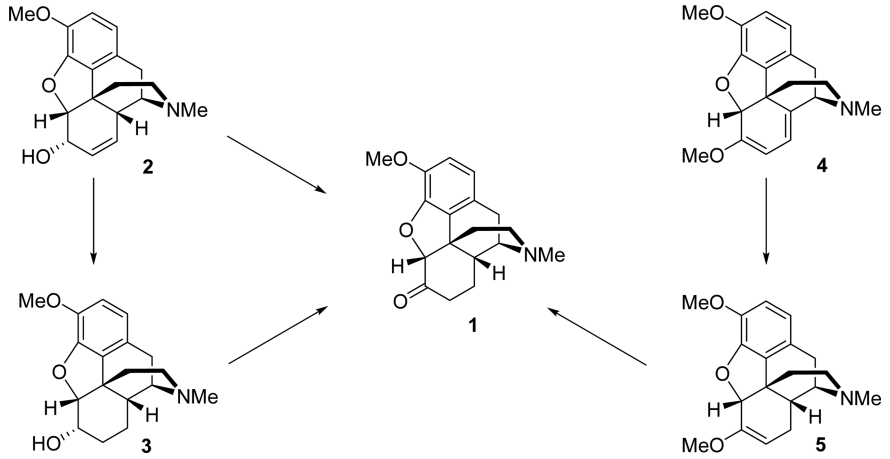
Since a direct transformation of thebaine (**4**) into hydrocodone (**1**) is not feasible, a two-step synthetic strategy toward hydrocodone (**1**) is commonly used. The key transformation in this production route is the selective double bond reduction of thebaine (**4**) resulting in 8,14-dihydrothebaine (**5**). The intermediate can easily be hydrolyzed under acidic conditions providing the title compound **1**. Common hydrogenation procedures using noble metal catalysis suffer from severe selectivity problems due to over-reduction of the diene moiety and hydrogenolysis of the dihydrofuran scaffold.[8,9] A promising alternative is the use of diimide (N_2H_2), a highly unstable compound which is usually generated in situ.[10] This powerful hydrogenation agent predominantly reduces unpolarized carbon−carbon double bonds avoiding the above-mentioned side-reactions, therefore generating the desired intermediate **5** in high selectivity.[11,12] On industrial scale, sulfonyl hydrazides such as *p*-toluenesulfonyl hydrazide (TSH) are currently used in combination with stoichiometric amounts of a weak base to generate the transfer hydrogenation agent enabling a reduction of **4** in high yield and selectivity.[11] A more atom economic and significantly cheaper way is the use of hydrazine which can be oxidized to diimide with e.g. O_2.[10] This strategy was indeed successfully applied toward the selective reduction of thebaine in 1968 providing hydrocodone (**1**) in good isolated yield (79%) after 48 h.[12] However, from an industrial point of view this protocol comes along with severe concerns as reported by Grew and Robertson: "This process involved the use of gaseous oxygen, which is hazardous on an industrial scale since mixtures of hydrazine vapour and oxygen are potentially explosive, and employed a molar ratio of hydrazine to thebaine of 53:1 which is commercially unattractive".[11a] These safety considerations may be true for traditional batch chemistry in which such processes are linked to enormous risks and challenges as the reaction mixture is prone to spontaneous ignition resulting in explosions. One of the rare examples in which this type of diimide generation has been used on a pilot plant scale is therefore accompanied by restrictions of the reaction parameters resulting in a relatively inefficient process.[13] A

Special Issue: Continuous Processing, Microreactors and Flow Chemistry

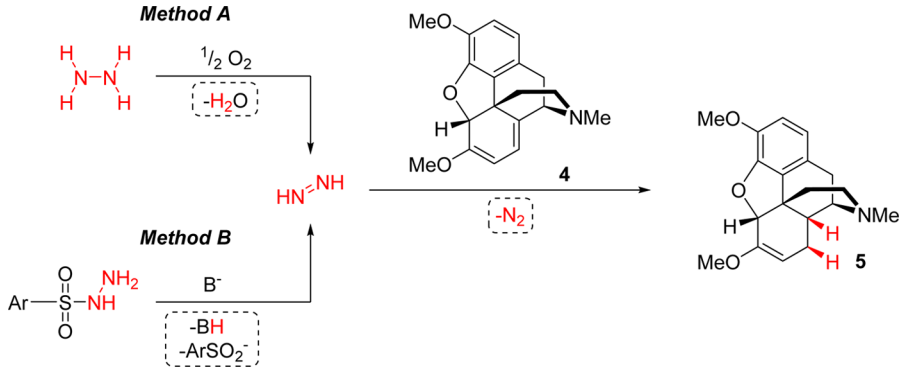
Received: November 6, 2015

DOI: 10.1021/acs.oprd.5b00370
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Scheme 1. Production of Hydrocodone (1) Starting from Codeine (2) or Thebaine (4)



Scheme 2. In Situ Generation of Diimide by Hydrazine Oxidation or Decomposition of TSH and Subsequent Reduction of Thebaine



promising alternative circumventing these boundaries is the use of continuous flow chemistry.[14,15] The small volumes and channel dimensions used by this enabling technology in combination with the reduced headspace minimizes explosion risks in order to safely process such hazardous reaction mixtures.[16]

We have recently shown that a biphasic gas/liquid continuous flow methodology can dramatically enhance the diimide generation from hydrazine hydrate and oxygen to efficiently reduce olefins by operating under high-temperature/high-pressure conditions (high-T/p, Novel Process Windows).[17,18] Consequently, we decided to study the possible application of this synthetic and technological strategy in the selective reduction of thebaine (**4**). Our main focus of attention was the development of a safe and efficient reduction route by generating diimide in situ via the aerobic oxidation of hydrazine. Furthermore, our investigations also cover a translation of the industrial process using TSH into continuous flow mode in order to compare the efficiency and technical feasibility of both synthetic routes.

RESULTS AND DISCUSSION

The oxidation of hydrazine (Scheme 2, Method A) and the decomposition of aryl sulfonyl hydrazides (Method B) can be considered among the most versatile methods to generate the reducing agent in situ for subsequent olefin reductions.[10]

In the former case several metal-[10,19] and organocatalysts[20] and the influence of visible light[21] were studied to enhance the reaction rate of the initial oxidation step which is generally slow under standard batch conditions.[22] Importantly, the use of catalytic species can be totally avoided when working in a continuous high-T/p environment.[17] As a result water and nitrogen are formed as only benign chemical byproducts often allowing for a simple workup strategy. When TSH is used as diimide precursor, the generation of the reactive intermediate is probably more convenient from a technical point of view as no gaseous reagent is involved. On the contrary, a substantially higher amount of chemical waste is generated making this process less sustainable.[23]

Thebaine Reduction Using $N_2H_4 \cdot H_2O$ and O_2. Initial experiments were carried out by a standard gas/liquid continuous flow reactor shown in Figure 1. The liquid stream is pumped via a HPLC pump (P) and mixed with O_2 in a T-piece (T). The gaseous oxidant is delivered by a standard

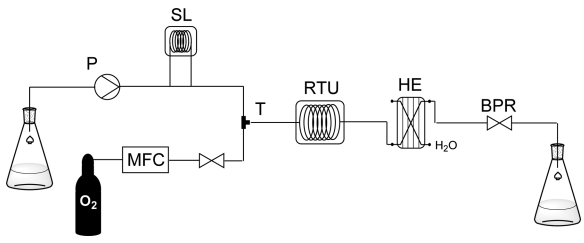


Figure 1. Continuous flow set up for the in situ generation of diimide and subsequent olefin reductions.

DOI: 10.1021/acs.oprd.5b00370
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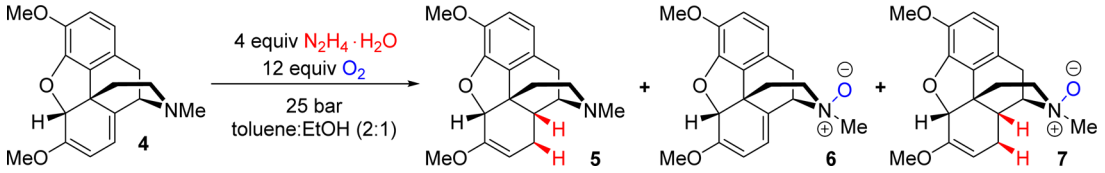
Table 1. Effect of the Coil Material on the Reduction of Thebaine[a]



entry	T (°C)	coil[b] (mL)	t_{res} (min)	4[c] (%)	5[c] (%)	6[c] (%)	7[c] (%)
1	50	PFA (13)	10	81	9	<1	<1
2	100	PFA (13)	12	18	26	32	26
3	120	PFA (13)	14	<1	2	38	58
4	140	PFA (13)	16	<1	<1	23	73
5	120	SS (20)	10	44	49	<1	<1
6	140	SS (20)	10	40	54	<1	<1

[a]Reactions were carried out using 0.5 mmol of **4** and 2 mmol of $N_2H_4 \cdot H_2O$ in 1.5 mL of toluene:EtOH (2:1) at a liquid flow rate of 0.4 mL min^{-1} and an O_2 flow rate of 40 mL_N min^{-1}. [b]PFA = perfluoroakoxy, SS = stainless steel. [c]Determined as HPLC peak area percent at 215 nm.

compressed gas cylinder and the flow controlled by a mass flow controller (MFC). A sample loop (SL) which is connected to the liquid stream via a six-way-valve is utilized for introducing the reaction mixture. The gas/liquid mixture passes a heated residence time unit (RTU) to carry out the desired transformation. Afterward, the reaction mixture is subsequently cooled to room temperature in a heat exchanger (HE) and depressurized by passing a backpressure regulating unit (BPR).

Initial flow experiments were carried out using a liquid flow rate of 400 μL min^{-1} and an oxygen stream of 40 mL_N min^{-1} resulting in a stable segmented flow pattern at a system pressure of 25 bar. The low solubility of thebaine in most organic solvents including alcohols which are usually used for these type of transformations[10,13,17,19−22] caused us to use a toluene/ethanol mixture (2:1) to reach a suitable substrate concentration (0.33 M). Since the solution slowly became biphasic after the addition of hydrazine hydrate (4 equiv), we decided to preheat the sample loop to 70 °C for injecting a totally homogeneous solution into the flow system. A 10 mL coil made out of a perfluoroalkoxy polymer (PFA, 0.8 mm i.d.; 1.6 mm o.d.) was used as residence time unit for the initial set of experiments (Table 1). A first continuous run using 4 equiv of hydrazine hydrate at a reaction temperature of 50 °C resulted in a highly selective reaction, although the conversion was very low (entry 1). When the temperature was increased to 100 °C two additional, unexpected compounds were detected by HPLC analysis (entry 2). LC-MS experiments indicated that these byproducts correspond to *N*-oxides of thebaine (**6**) and the hydrogenated analogue (**7**). Earlier observations using this methodology for molecules with sulfide moieties suffered from an identical side reaction yielding the corresponding sulfoxide.[17] Notably, it has already been demonstrated that in the presence of flavin catalysts a hydrazine hydrate/oxygen combination is able to oxidize a range of sulfides and amines by generating a peroxide intermediate.[24] We therefore believe that the undesired *N*-oxides are more likely a result of H_2O_2 generated during the oxidation of hydrazine hydrate than an aerobic amine oxidation mechanism.[22c]

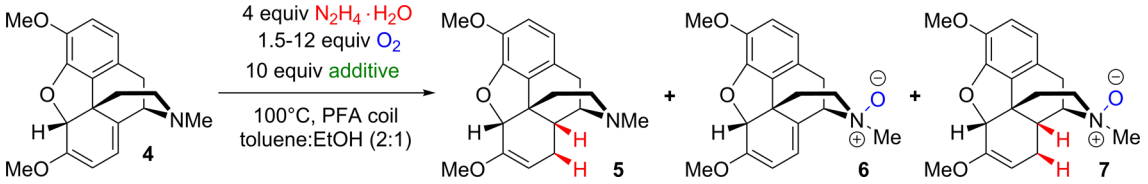
Since *N*-oxides can be easily reduced to amines by standard reagents (e.g., $NaBH_4$, $LiAlH_4$), we tried to intensify this process in order to fully convert thebaine (**4**) to **7**. At temperatures above 120 °C the reaction mixture almost exclusively contained the oxidized compounds **6** and **7**, but the overall amount of double bond reduction did not increase significantly (entry 3). Unfortunately, even at the upper temperature/pressure limit of the PFA coil, an insufficient reduction was observed (entry 4). Experimental as well as computational investigations on the transfer hydrogenation of thebaine *N*-oxide (**6**) additionally indicated that the reduction of **4** is considerably faster than for the oxidized derivative (**6**).[25] It is interesting to note that the residence time got longer at elevated temperatures most likely due to the increasing gas permeability of PFA.[26] Thus, we decided to evaluate the applicability of a stainless steel coil instead of residence time units made out of polymeric material. This would not only allow working at higher temperatures/pressures in a safe manner but also results in a better control of the residence time as gas permeability is not an issue anymore.

We additionally speculated that under the applied corrosive conditions small amounts of Fe^{2+} may be formed on the coil surface which would readily decompose generated H_2O_2 circumventing the above-discussed selectivity issues. Our hypothesis could be immediately proven by a continuous hydrogenation experiment applying a 20 mL stainless steel RTU at 120 °C resulting in a highly selective reduction without detectable amounts of the respective *N*-oxides (entry 5). By increasing the temperature to 140 °C slightly higher conversions were obtained maintaining the high selectivity (entry 6). Interestingly, in both experiments a residence time of ∼10 min was observed which is significantly shorter than experiments using the PFA coil with a smaller volume under otherwise identical conditions. In our hands, this phenomenon can be explained by the gastight coil material and is probably also caused by the decomposition of the assumed hydrogen peroxide intermediate.

The process intensification study was limited by a maximum temperature of 140 °C as a decomposition of thebaine (**4**) was observed at higher temperatures.[25] Keeping this in mind, several dozens of flow experiments varying temperature, back pressure, coil length (= residence time), and $N_2H_4 \cdot H_2O$ amounts were carried out in order to develop a protocol meeting our demands for a quantitative reaction. Unfortunately, all attempts resulted in insufficient conversions (∼50%) of thebaine (**4**). Furthermore, at a certain stage of our optimization study the results turned irreproducible leading to highly diminished substrate consumptions. By systematically changing each component of the continuous flow reactor, we concluded that the residence time unit was the origin of these discrepancies. After trying several washing cycles with various solvents and solvent mixtures we discovered that after a steel

DOI: 10.1021/acs.oprd.5b00370
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

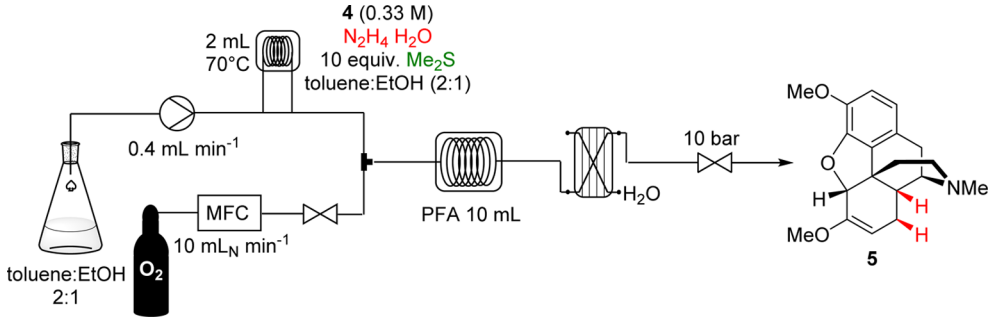
Table 2. Effect of Additives, Pressure, and O_2 Flow Rate in the Continuous Reduction of Thebaine[a]



entry	V_{coil} (mL)	additive	O_2 (mL_N min^{-1})	P (bar)	t_{res} (min)	4[b] (%)	5[b] (%)	6[b] (%)	7[b] (%)
1	13		40	25	12	18	26	32	26
2	13	Et_3N	40	25	12	59	29	6	2
3	13	Me_2S	40	25	12	46	52	2	1
4	10		40	17	11	37	32	16	14
5	10		20	17	25	32	41	12	14
6	10		10	10	10	29	54	6	10
7	10		5	10	17	31	59	4	5

[a]Reactions were carried out using 0.5 mmol thebaine (**4**) and 2 mmol $N_2H_4 \cdot H_2O$ in 1.5 mL toluene−EtOH (2:1) at a liquid flow rate of 0.4 mL min^{-1}. [b]Determined as HPLC peak area percent at 215 nm.

Table 3. Effect of Temperature and $N_2H_4 \cdot H_2O$ Stoichiometry in the Continuous Reduction of Thebaine[a]



entry	$N_2H_4 \cdot H_2O$ (equiv)	T (°C)	t_{res} (min)	4[b] (%)	5[b] (%)
1	4	100	10	37	61
2	4	120	8	26	72
3	3	120	8	27	70
4	2	120	8	42	56
5	4	140	6	25	74
6	3	140	6	23	74
7	2	140	6	41	58

[a]Reactions were carried out using 0.5 mmol thebaine (**4**) in 1.5 mL toluene−EtOH (2:1). [b]Determined as HPLC peak area percent at 215 nm.

passivation procedure using HNO_3 (20% v/v) the original results could be successfully reproduced. We therefore assume that corrosion of the coil surface or reactor fouling is responsible for the observed deviations.[27] Since this implies that the continuous process cannot be carried out in a stable and reproducible fashion on production scale an alternative strategy was required.

It was therefore necessary to switch back to a metal-free coil material trying to develop a method avoiding the formation of unreactive *N*-oxides. We considered that we may be able to trap the formed hydrogen peroxide in a simultaneous oxidation rather than decomposing the oxidation agent by a catalyst. A simple amine (Et_3N) and a sulfide (Me_2S) were tested as suitable additives as those functionalities are known to be oxidized by hydrazine hydrate/oxygen combinations (Table 2).[17,24] When triethylamine was used in excess (10 equiv), very low quantities of the oxidized side products where observed but unfortunately the double bond reduction was less efficient than without an additive (entry 2). Gratifyingly, with dimethyl sulfide as additive, a comparable amount of olefin reduction occurred simultaneously improving the selectivity (entry 3).

In addition, we hoped that we may be able to reduce the amount of *N*-oxide formation by the applied back pressure and O_2 stoichiometry. We decided to study these parameters again in the additive-free reaction system to later combine the improved parameters with the sulfide methodology (entries 4−7). For the first comparison we reduced the back pressure from 25 to 17 bar simultaneously changing the coil length to get a comparable residence time (entry 4). The overall reduction of the unsaturated carbon−carbon bond was not affected, but the amine oxidation could be dramatically reduced indicating a pressure dependency. Lowering the oxygen flow to 20 mL_N min^{-1} (corresponding to 6 equiv of O_2) resulted in slightly higher conversions but also a comparably longer residence time (entry 5). We thus simultaneously decreased the O_2 flow (10 mL_N min^{-1}, 3 equiv) and the back pressure thereby reducing the amount of amine oxidation within a reasonable reaction time (entry 6). Importantly, the reduced amount of oxidation side-products is accompanied by a higher degree of olefin reduction which is in good agreement with the data obtained from the transfer hydrogenation experiments of thebaine *N*-oxide (**6**). Further lowering of the oxygen flow (5 mL_N min^{-1},

DOI: 10.1021/acs.oprd.5b00370
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

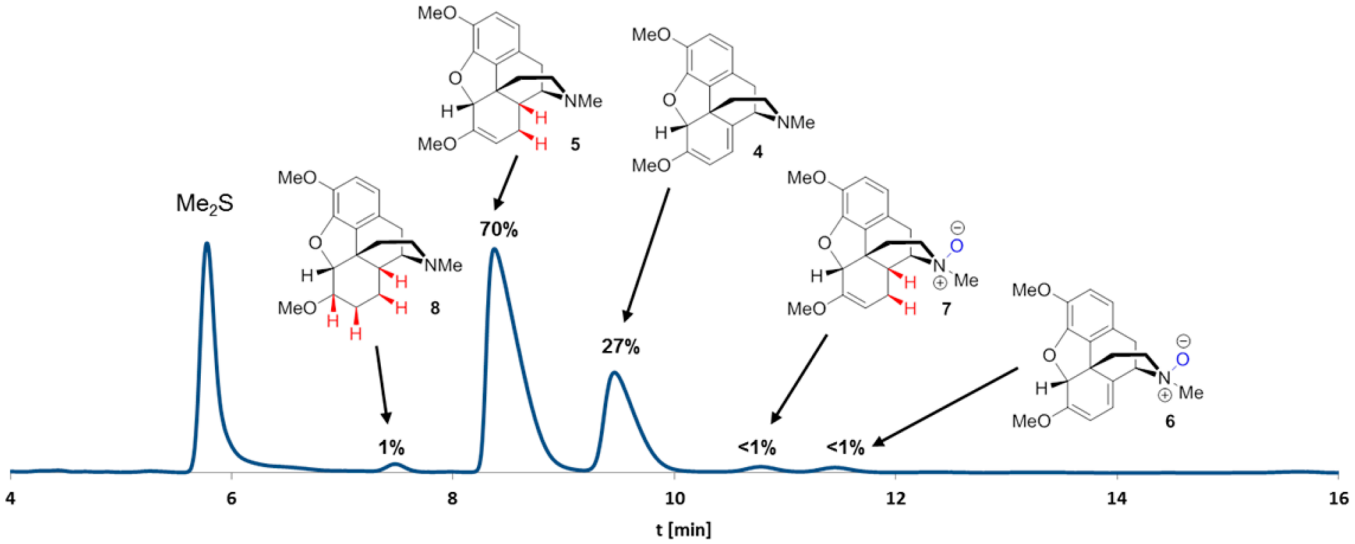


Figure 2. HPLC-UV/vis chromatogram (215 nm) of the thebaine reduction with diimide at 10 bar and 120 °C in the presence of dimethyl sulfide (Table 3, entry 3).

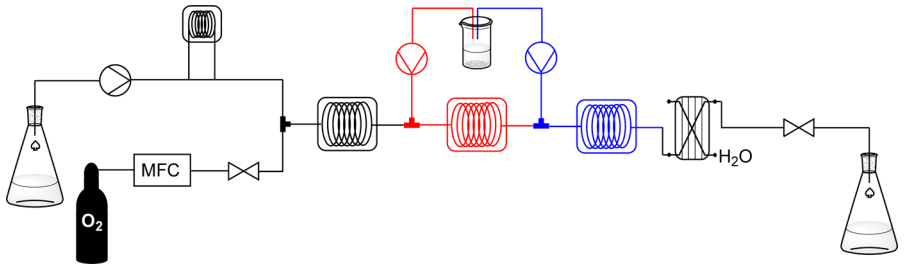


Figure 3. Example of a multi-injection continuous flow set up for the in situ generation of diimide. The basic setup (black) is extended by two additional feeds (red and blue) with the respective residence time units.

1.5 equiv) increased the residence time significantly but had a negligible effect on conversion and selectivity (entry 7).

The subsequent combination of the reduced pressure protocol with the sulfide methodology ultimately provided a clean reduction of thebaine in a PFA coil with moderate conversion (Table 3, entry 1). The double bond reduction could be subsequently improved at 120 °C resulting in ∼70% conversion maintaining the high selectivity (entry 2). In addition the amount of hydrazine hydrate could be reduced to 3 equiv without any influence on the reaction rate. Further improvements were not possible as lower amounts of the diimide precursor resulted in a drop in conversion (entry 4) and reactions at the maximum possible temperature (140 °C) gave similar results as experiments at 120 °C (entry 5−7).

Notably, the amount of undesired *N*-oxides was either below 1% or not detectable at all in each of the reactions discussed above (Table 3). The only other byproduct observed (∼1%) appeared to be the over-reduced tetrahydrothebaine (**8**) (Figure 2).

Since neither a longer residence time nor a higher amount of hydrazine hydrate could drive the reaction to completion, we concluded that the only possibility to achieve quantitative reduction is a multi-injection approach. This strategy is usually applied in continuous processes involving highly exothermic reactions to improve thermal control.[28,29] We could already show during our previous investigations that comparably slow reductions can be driven to completion by continuously adding fresh hydrazine hydrate using this approach.[17b] We hypothesize that the multiple injection reduces the amount of diimide disproportionation due to a reduced hydrazine/diimide concentration along the reactor. In addition, this methodology enables the possibility to increase the effective reaction time since under the continuous high-temperature/high-pressure conditions most of the $N_2H_4{\cdot}H_2O$ is consumed within less than 10 min.[17] From a technical point of view this reactor can be viewed as an extended version of the setup shown above (Figure 1 or Table 3). We simply installed additional feeds and coils in an alternating way between the already installed RTU and the heat exchanger (Figure 3).[30]

The first multi-injection experiment using the optimized temperature and pressure settings described above (Table 3, entry 3) was carried out by installing one supplementary hydrazine hydrate feed delivering an additional 3 equiv of the diimide precursor before passing a second 10 mL RTU (Table 4, entry 1). Gratifyingly, the conversion could be increased from ∼70% to >80% indicating that the multi-injection strategy can lead to a successful reduction. In order to verify that the improved conversion is not simply a result of the extended residence time, we repeated the experiment adding pure EtOH instead of a $N_2H_4{\cdot}H_2O$ solution (entry 2). As expected, the prolonged reaction time alone does not increase the conversion at all. However, a lower oxygen flow (1.5 equiv) also gave less olefin reduction albeit the reaction time was significantly longer (entry 3). We therefore stepwise expanded the continuous flow multiaddition reactor resulting in ≥95% conversion using four liquid feeds, four residence times, and 12 equiv of the diimide

DOI: 10.1021/acs.oprd.5b00370
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Table 4. Reduction of Thebaine Using Multi-injection of Hydrazine Hydrate[a]

entry	$N_2H_4{\cdot}H_2O$ (equiv)	RTU (mL)	t (min)	4[b] (%)	5[b] (%)
1	3 + 3	2 × 10	17	14	83
2	3 + 0	2 × 10	17	29	69
3[c]	3 + 3	2 × 10	30	28	70
4	3 + 3 + 3	3 × 10	26	7	90
5	3 + 3 + 3 + 3	4 × 10	37	4	94
6[d]	3 + 1 + 1 + 1	4 × 10	35	9	87
7	3 + 3 + 3 + 3 + 3	5 × 10	50	5	94

[a]Reactions were carried out using 0.5 mmol of thebaine (**4**) in 1.5 mL of toluene–EtOH (2:1) at 120 °C at O_2 flow of 10 mL_N min^{-1} and liquid flow rate of 0.4 mL min. For the additional feeds a 3.2 M $N_2H_4{\cdot}H_2O$ solution in EtOH was pumped with 0.1 mL min^{-1}. [b]Determined as HPLC peak area percent at 215 nm. [c]A O_2 flow of 5 mL_N min^{-1} was used. [d]A 1 M $N_2H_4{\cdot}H_2O$ solution was used.

precursor in total (entry 5). Reducing the amount of hydrazine hydrate resulted in a conversion drop below 90%. The installation of a fifth liquid feed did not further improve the continuous reaction (entry 6). It is again interesting to note that at an increasing overall reactor volume a nonlinear evolution of the residence time was observed. The amount of gas decreases constantly along the reactor coil, and the segmented pattern disappeared completely at a certain point. In the case of the optimized setup (entry 5) the reaction mixture passed the first coil within ~6, the second after ~8, the third after ~10, and the last coil after ~13 min. At first sight this appears to be related to the consumption of O_2, but since an equimolar amount of N_2 is generated the gas-permeability of PFA must also play a certain role. The additional feeds also increase the amount of solvent within the system which may contribute to this phenomenon as more O_2/N_2 can be dissolved reducing the influence of the gas on the overall flow rate.

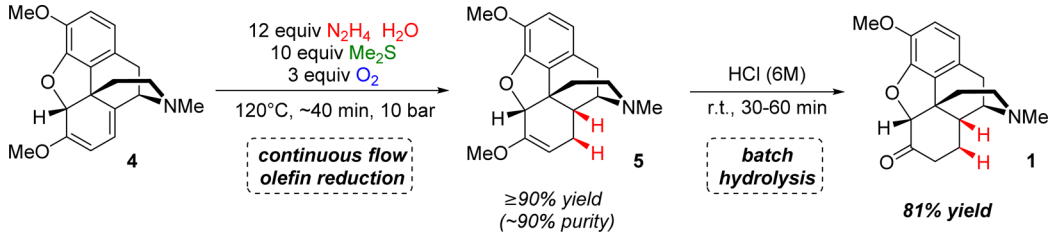
Due to the malodorous nature of the antioxidant, we also investigated several alternatives, such as ethanolamine, morpholine, pyridine, DMSO, *N,N′*-dimethylthiourea, or diphenylsulfide. Unfortunately, all experiments resulted in lower conversions or unselective reductions.[25] Other alternatives like, e.g., didodecyl sulfide, were accompanied by severe solubility problems and therefore not further studied.

In our hands, a complete reduction was inaccessible within a reasonable residence time and a justifiable amount of $N_2H_4{\cdot}H_2O$, so we decided to stop our process intensification study at a conversion of ≥95%. We could isolate the crude material containing ~8% thebaine (**4**) by evaporation of the solvent and precipitation in water in ~90% yield.[25]

As we were neither able to separate 8,14-dihydrothebaine (**5**) from the starting material (**4**) by chromatography nor by recrystallization, we decided to directly hydrolyze the crude material in order to obtain hydrocodone **1**. Therefore, the compound mixture was stirred at room temperature in 6 N HCl.[11b] Analysis by HPLC indicated that **5** is quantitatively hydrolyzed within 30–60 min, whereas thebaine (**4**) and the over-reduced side product (**8**) were not affected. A crucial point was to remove unreacted hydrazine after the continuous flow experiment either by extraction or by crystallization of the crude material as it otherwise reacts with the resulting ketone (**1**) forming the corresponding hydrazone or azine. However, workup after hydrolysis by neutralization, extraction, and column chromatography yielded hydrocodone in up to 81% overall isolated yield as pale-yellow solid (Scheme 3).

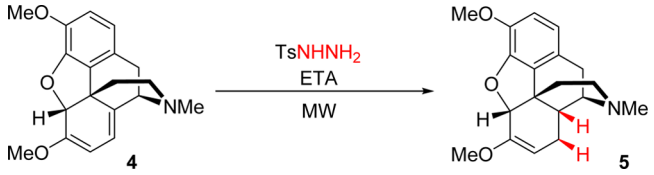
Thebaine Reduction Using p-TSH. Since the above-described olefin reduction necessitates a high excess of hydrazine hydrate in combination with large amounts of dimethyl sulfide, we also considered a translation of the existing batch protocols using *p*-toluenesulfonyl hydrazide (TSH) as diimide precursor into a continuous procedure.[11] Since this reaction does not involve any gaseous reagents, we could conveniently optimize several reaction parameters in batch using a dedicated microwave reactor (Table 5).[31,32] As a starting point we adapted the protocol developed by Orr and Dummitt.[11b] The authors used 2.2 equiv of TSH and ethanolamine (ETA) to carry out the title reaction in ethanol within 11 h at 70 °C resulting in 91% isolated yield. In our modified protocol, we initially mixed thebaine with 2 equiv of the base and the diimide precursor before heating the inhomogeneous mixture for 20 min at 70 °C. Using this significantly reduced reaction time, a totally selective transfer hydrogenation was observed at a reasonable conversion (entry 1). Stepwise increasing the reaction temperature showed an optimum at 120 °C identical to the experiments using hydrazine hydrate described above (entries 2–3). It has to be noted that small amounts of tetrahydrothebaine (**8**, < 1%) were detected as the only byproduct. As already mentioned, the solubility of thebaine in ethanol is very low causing us to again use toluene as cosolvent albeit in a different ratio and concentration than above due to the limited solubility of TSH in unpolar environments (entries 4–10). However, these adaptions did not influence the reaction at all showing identical results to the reaction in ethanol. In general, the reduction proceeds very fast within the first 20 min resulting in 93% conversion (Entry 4). Further processing converts the remaining thebaine comparably slowly into hydrocodone precursor **5** (entries 6–7). Orr and Dummitt made a similar observation in a kinetic study showing that the reaction proceeds relatively fast until a conversion of ~80% is reached followed by a significantly slower reaction rate using their conditions.[11b] This is also in good agreement with the experimental data in the optimization study using the hydrazine hydrate/O_2 system. However, increasing the amount of TSH,

Scheme 3. Continuous Transfer Hydrogenation and Batch Hydrolysis for the Synthesis of Hydrocodone from Thebaine



DOI: 10.1021/acs.oprd.5b00370
Org. Process Res. Dev. XXXX, XXX, XXX–XXX

Table 5. Batch Experiments for the Reduction of Thebaine Using *p*-Toluenesulfonyl Hydrazide[a]



entry	solvent	*c* (M)	TSH (equiv)	ETA (equiv)	*T* (°C)	*t* (min)	conversion[b] (%)
1[c]	EtOH	0.4	2	2	100	20	75
2[c]	EtOH	0.4	2	2	120	20	94
3[c]	EtOH	0.4	2	2	130	20	92
4	toluene−EtOH (1:1)	0.2	2	2	120	20	93
5	toluene−EtOH (1:1)	0.2	2	2	120	10	73
6	toluene−EtOH (1:1)	0.2	2	2	120	30	96
7	toluene−EtOH (1:1)	0.2	2	2	120	120	97
8	toluene−EtOH (1:1)	0.2	2	3	120	20	95
9	toluene−EtOH (1:1)	0.2	2.5	2	120	20	97
10	toluene−EtOH (1:1)	0.2	3	3	120	20	98

[a]Reactions were carried out using 0.2 mmol thebaine (**4**). [b]Determined as HPLC peak area percent at 215 nm. [c]Thebaine is not totally soluble in EtOH causing a inhomogeneous reaction mixture.

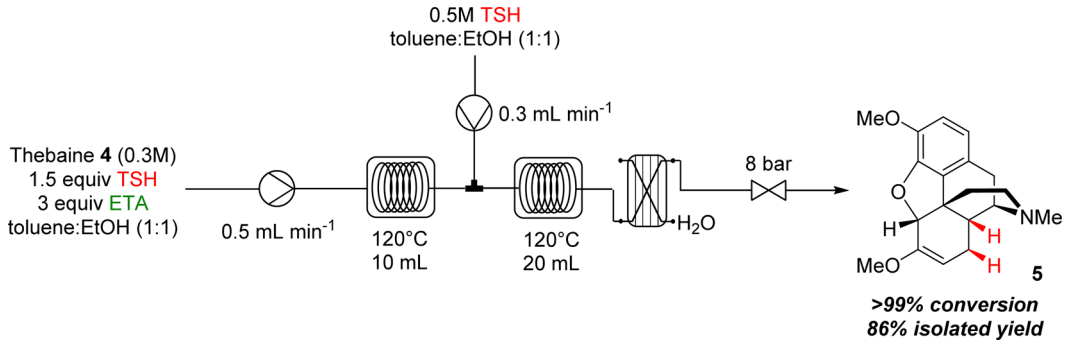


Figure 4. Continuous transfer hydrogenation of thebaine using TSH.

the base equivalents, or both compounds simultaneously did not result in a complete reduction of thebaine (entries 8—10).

Nevertheless, we ultimately moved to a simple continuous flow system pumping the reaction mixture through a heated residence time unit (PFA) using a single feed. Similar to the setup described above, the reaction mixture is subsequently cooled in a heat exchanger (HE) and depressurized by passing a backpressure regulating unit (BPR). The results obtained slightly differed from the batch results, and after a few adaptions we could obtain 94% conversion within 40 min at 120 °C. Since a further improvement was not possible, we again followed the multi-injection strategy installing a second TSH feed. After a short optimization study we could finally show that by adding two times 1.5 equiv of TSH a quantitative reaction can be carried out within 45 min.[25] Crystallization allowed us to isolate pure 8,14-dihydrothebaine (**5**) in 86% as a colorless solid (Figure 4).

By comparing both routes for the diimide generation, it is obvious that the latter approach is characterized by a much simpler setup using less pumps and residence time units. In both cases similar solvent mixtures, reaction times, and identical temperature regimes were required in order to successfully reduce thebaine (**4**). The TSH route provides a quantitative conversion and a high purity profile allowing for isolating the intermediate **5** in good yield. The hydrazine hydrate pathway on the other hand results in a crude mixture contaminated with unreacted starting material which cannot be separated.

However, this was not viewed as crucial since the mixture can be subsequently transformed into hydrocodone (**1**). From a chemical point of view, significantly higher amounts of the diimide precursor are necessary following the hydrazine route to reduce thebaine in satisfying conversions. Furthermore, while the TSH methodology requires stoichiometric amounts of a base (e.g., ETA), a suitable antioxidant (e.g., Me_2S) and oxygen is required when generating N_2H_2 from hydrazine hydrate. The main difference from a cost point of view is the diimide precursor itself, TSH being significantly more expensive than $N_2H_4{\cdot}H_2O$. From a sustainable point of view, the hydrazine hydrate route generates benign chemical byproducts (H_2O, N_2) as well as oxidized organosulfur species thus may being an interesting alternative to the existing process.

In general, both discussed methodologies can be potentially scaled to larger quantities by either numbering-up of flow devices or scaling-up of the reactor volume.[14,15] In the latter case the performance of the reactor can be largely conserved by keeping certain characteristics of the system constant ("smart dimensioning"). Alternatively, simply running a reactor for extended periods of time to generate the desired quantities of pharmaceutical intermediates or final products is often an acceptable strategy.[14,15]

CONCLUSION

In summary, we have developed a scalable methodology for the reduction of thebaine by in situ generating diimide from

DOI: 10.1021/acs.oprd.5b00370
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hydrazine hydrate and oxygen. This simple route to the transfer hydrogenation agent was previously categorized as a "forbidden" process on industrial scale due to safety concerns in batch mode. The described continuous process may break this limitation allowing to fully exploiting the potential of this atom economic reduction process. Key to the success was a multi-injection strategy applying periodic additions of fresh hydrazine hydrate enabling an increased effective residence time. Furthermore, the formation of undesired *N*-oxides could be avoided by addition of dimethyl sulfide as antioxidant.

In addition the standard reduction procedure using *p*-toluenesulfonyl hydrazide as diimide precursor was intensified and translated into continuous flow mode. Both methodologies allow for a highly selective reduction in less than 1 h. The resulting 8,14-dihydrothebaine (**5**) can be readily converted into the high value API hydrocodone by subsequent hydrolysis.

EXPERIMENTAL SECTION

General Remarks. For continuous flow experiments, a commercially available reactor system (FlowSyn, Uniqsis Ltd.) and additional syringe pumps (Asia pumping module, Syrris) were used. The back pressure was either controlled using static or adjustable regulation units.[30] Microwave-assisted reactions were carried out in a Biotage Initiator 2.5 instrument in Pyrex vessels (2−5 mL) controlling the reaction temperature by an external IR sensor. ^{1}H NMR and ^{13}C spectra were recorded on a 300 MHz instrument using $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q, qt, and m are used to indicate a singlet, doublet, triplet, quadruplet, quintuplet, and multiplet, respectively. Analytical HPLC analysis was carried out on a C-18 reversed-phase (RP) analytical column (150 × 4.6 mm, particle size 5 μm) at 37 °C using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (MeCN + 0.1% TFA) at a flow rate of 1.0 mL min^{-1} at an isocratic flow using 5% solvent B for 21 min. Afterward the amount of solvent B was increased to 100% within 1 min and kept at this ratio for 4 min. Column chromatography was carried out using an automated flash chromatography system (Isolera, Biotage) using dichloromethane/methanol mixtures as eluent.

General Procedure for the Synthesis of Hydrocodone from Thebaine Using the Hydrazine Hydrate Route. *Continuous Reduction.* The continuous flow process is based on a liquid feed (toluene/ethanol (2:1)) and a gaseous feed (O_2 purity 5.0). Thebaine (2.00 mmol, 622.9 mg), dimethyl sulfide (20.0 mmol, 1.47 mL), and hydrazine hydrate (6.00 mmol, 291.7 μL) were dissolved in toluene/ethanol (2:1) to a total volume of 6 mL. The resulting mixture was stirred at 70 °C until it became homogeneous. The solution was injected in a preheated sample loop (70 °C) which was connected to the liquid via a six-way valve. The liquid stream (400 μL min^{-1}) and the gaseous stream (10 mL$_N$ min^{-1}) were mixed together in a T-mixer (0.8 mm channel size). The resulting segmented flow stream was passed through a PFA reactor coil (0.8 mm inner diameter, 10 mL reactor volume) at 120 °C. After coil 1, a T-mixer (0.8 mm channel size) connected another feed adding hydrazine hydrate in EtOH (3.2 M) at a flow rate of 100 μL min^{-1}. The combined stream passes an additional 10 mL PFA tubing at 120 °C. This addition principle is repeated two times resulting in three additional hydrazine hydrate feeds and an overall reactor volume of 40 mL. Subsequently, the mixture was cooled in a heat exchanger with water as cooling agent. After passing a back pressure regulator (10 bar) the solution was collected. The reaction mixture was concentrated under reduced pressure resulting in a light brown solid which was dissolved in 20 mL of $CHCl_3$. The solution was extracted twice with slightly basic water (2 × 20 mL; pH = 8−9) to remove residual hydrazine hydrate. The organic phase was dried over Na_2SO_4, and the solvent was removed resulting in 609 mg of a brown solid containing >90% 8,14-dihydrothebaine according to ^{1}H NMR.

Hydrolysis. The crude mixture was dissolved in 6 M HCl (5 mL), and the resulting dark orange solution was stirred until HPLC analysis showed that the 8,14-dihydrothebaine was totally consumed (30−60 min). The acidic solution was diluted with H_2O (10 mL) and extracted with Et_2O (30 mL) to remove organic impurities. Afterward, 3 M NaOH was added until the pH of the aqueous solution was >10. Extraction with $CHCl_3$ (3 × 20 mL) resulted in an orange solution. After solvent evaporation a yellowish solid with a HPLC purity of ∼93% (1−2% THT, 5−6% THE) was obtained. Purification by flash column chromatography using a dichloromethane/methanol gradient (containing 1% v/v Et_3N) finally resulted in 81% (484.2 mg, 1.62 mmol) of hydrocodone as a pale-yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 4.68 (s, 1H), 3.92 (s, 3H), 3.20 (m, 1H), 3.04 (d, J = 18.5 Hz, 1H), 2.59 (m, 2H), 2.49−2.27 (m, 6H), 2.21 (td, J = 11.9, 3.3 Hz, 1H), 2.08 (td, J = 12.0, 4.5 Hz, 1H), 1.86−1.79 (m, 2H), 1.35−1.19 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.89, 145.39, 142.82, 127.24, 126.28, 119.76, 114.47, 91.39, 59.19, 56.75, 56.71, 46.89, 46.83, 42.88, 42.70, 40.23, 35.52, 25.57, 19.95.

General Procedure for the Reduction of Thebaine with *p*-Toluenesulfonyl Hydrazide and Ethanolamine in a Multi-Injection Flow Reactor. A liquid feed (500 μL min^{-1}) consisting of thebaine (623.4 mg, 2.00 mmol), *p*-toluenesulfonyl hydrazide (559.26 mg, 3.00 mmol), and ethanolamine (363 μL, 6.00 mmol) dissolved in toluene−ethanol (1:1) to give a total volume of 6.6 mL was passed through a PFA reactor coil (0.8 mm inner diameter, 10 mL reactor volume) at 120 °C. After coil 1, a T-mixer (0.8 mm channel size) connected another feed adding *p*-toluenesulfonyl hydrazide in toluene:ethanol (1:1. 0.5 M) at a flow rate of 300 μL min^{-1}. The combined stream passes a 20 mL PFA tubing at 120 °C (coil 2). Subsequently, the mixture was cooled in a heat exchanger with water as cooling agent. After passing a back pressure regulator (10 bar) the solution was collected, concentrated under reduced pressure, and the residue dissolved in a minimum of EtOH. Deionized water (15 mL) was added and the pH adjusted to >9 with concentrated ammonium hydroxide. The resulting precipitate was isolated by filtration, washed with H_2O, and dried in a desiccator resulting in 86% (536.3 mg, 1.71 mmol) of 8,14-dihydrothebaine as colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (d, J = 8.2 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 4.86 (s, 1H), 4.75 (m, 1H), 3.87 (s, 3H), 3.51 (s, 3H), 3.16 (m, 1H), 3.04 (d, J = 18.6 Hz, 1H), 2.56 (m, 1H), 2.48−2.23 (m, 6H), 2.06−1.90 (m, 2H), 1.84 (m, 1H), 1.59 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.27, 145.17, 143.09, 129.27, 126.92, 118.54, 113.56, 98.04, 88.56, 59.04, 56.49, 54.35, 46.51, 43.07, 42.48, 39.78, 35.72, 23.61, 20.24.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00370.

DOI: 10.1021/acs.oprd.5b00370
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Additional experimental information, supplementary figures, and copies of ^{1}H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors gratefully thank Dr. David Cantillo for providing computational calculations. We thank NAWI Graz financial support.

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