Full Paper

Old is Gold? Nefopam Hydrochloride, a Non-opioid and Non-steroidal Analgesic Drug and its Practical One-pot Synthesis in a Single Solvent for Large-Scale Production

Mohan Reddy Bodireddy, Kiran Krishnaiah, Prashanth Kumar Babu, Chaithanya Bitra, Madhusudana Rao Gajula, and Pramod Kumar

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.7b00228 • Publication Date (Web): 19 Oct 2017

Old is Gold? Nefopam Hydrochloride, a Non-opioid and Non-steroidal Analgesic Drug and its Practical One-pot Synthesis in a Single Solvent for Large-Scale Production

Mohan Reddy Bodireddy, **Kiran Krishnaiah**, **Prashanth Kumar Babu**, **Chaithanya Bitra**, **Madhusudana Rao Gajula**,*** and Pramod Kumar ***

Chemical Research Division, API R&D Centre, Micro Labs Ltd., Plot No.43-45, KIADB Industrial Area, 4th phase, Bommasandra-Jigani Link Road, Bommasandra, Bangalore-560 105, Karnataka, India.

Abstract: Nefopam hydrochloride is extensively used in most of the European countries till today as an analgesic, owing to its non-opiate (non-narcotic) and non-steroidal action with fewer side-effects compared with opioid and other analgesics which causes more troublesome side-effects. A multi-kilogram synthesis of Nefopam hydrochloride has been achieved in one-pot using single solvent (toluene). The purity of API was achieved ≥99.9% with excellent overall yield (≥79%). The one-pot multistep (five steps) synthetic process involves formation of acid chloride (**3**) from benzoylbenzoic acid (**2**) followed by amidation (**4**), reduction (**5**), cyclization (**6**) and hydrochloride salt (**1**) formation. The major advantages include i) use of single solvent, ii) >90% conversion in each step, iii) cost-effective and operational friendly process, iv) averting the formation of genotoxic impurities and v) one-pot operation provided improved overall yield (≥79%). For the first time, we report the characterization data of API (**1**), intermediates (**3**, **4** and **5**) and also possible impurity **5a**.

Keywords: Nefopam, one-pot, single solvent, toluene, vitride, analgesic

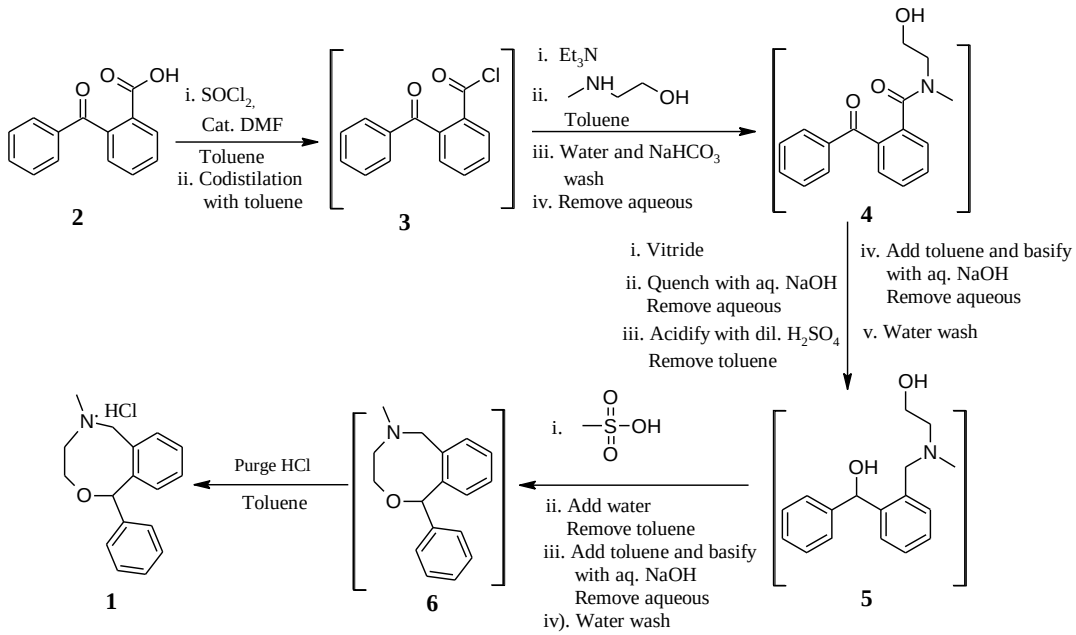
Introduction

Any kind of pain has a significant impact on quality of life.[1] Human being always try to get rid from pain immediately which leads to extensive consumption of analgesic drugs,[2-4] especially easily available opioid and steroidal analgesics which cause troublesome side-effects and increased death rates from overdose. The study is aimed to overcome such troublesome side-effects by focussing attention on use of Nefopam hydrochloride[5] drug as an alternative to opioid and steroidal analgesics because of its superior advantages, for example it is i) central analgesic[6] with non-opiate action,[7] ii) non-steroidal analgesic,[8] iii) effectiveness in post-cardiac operative analgesia,[9] iv) superior than aspirin,[10] v) less side-effects,[11] vi) incompetence of respiratory depression[12] compared with morphine[13] and oxycodone,[14] and v) less probability of common death from overdose compared with opioid analgesic drugs.[15] Interestingly, Nefopam hydrochloride[16] was developed in the early 1960 and its consumption

was limited to European countries where it is widely used for the prevention of post-operative shivering,[17] severe hiccups,[18] post-trauma and post-operative pain,[19] dental pain,[20] and renal colic pain.[21] At the same time practical commercial process with good yield and purity is found to be essential for its quick adoptability throughout the world which is now limited to France, the U. K[22] and few other European countries.

The extensive literature search revealed that the reported processes[23-27] for the synthesis of Nefopam hydrochloride suffer from one or more disadvantages such as i) multi-step synthesis involving isolation, drying and analysis increases cycle time, labour and utility costs and also compromising in yield, ii) cumbersome workup procedure, iii) lack of practicality and viability, and iv) use of industrially undesired solvents such as low boiling and chlorinated solvents. In addition, it was observed that none has been reported about i) characterization and purity of API, intermediates and impurities, ii) comprehensive results and discussion of the reported processes and iii) commercial feasibility to prepare desired quality of API. The above mentioned process problems and metrics to 'green' chemistry[28] encouraged us to develop a practical one-pot multi-step process involving proper selection of synthetic route, reagents, bases, acids, catalysts and use of single solvent for five steps.

Herein, we report a commercially viable process for the multi-kilogram synthesis of Nefopam hydrochloride (**1**). The one-pot synthesis starts from formation of acid chloride (**3**) from benzoylbenzoic acid (**2**) followed by amidation (**4**), reduction (**5**), cyclization (**6**) and hydrochloride salt formation (**1**) in toluene as shown in Scheme 1.



Scheme 1: One-pot Synthesis of Nefopam Hydrochloride (**1**) from Benzoylbenzoic Acid (**2**).

Results and Discussion

The major fundamental components in the optimization of process are i) reducing the number of different operations in the selected synthetic route of synthesis.[29] In the present work, higher yield was achieved (≥79%) with the run of multiple reactions in a single vessel (one-pot), ii) coordinating solvents, in general solvents need to be changed between steps in multi-step process. It was achieved by selection of toluene as a single solvent which is compatible with five steps, thus reducing waste and cost in multi-step sequences[28] iii) selection and use of reagents to run the process safely at production level as plant safety is the most important concern always. It was achieved by the use of vitride[30] instead of $LiAlH_4$ and borane dimethylsulfide ($BH_3.SMe_2$). In some patents, $NaBH_4$ was also reported, however it was unfruitful in our study, iv) impurities control strategy: selection of suitable reagents, temperature, mode of addition, order of reagents addition, and workup procedures play a vital role in control of impurities and overall yield of API with desired quality. The control of impurities in line with ICH guidelines is the major task in the design of efficient process that is capable in removal of carryover or metallic impurities (formed from unreacted substrates, byproducts and reagents) wherever possible during workup. It was accomplished in the present process in each and every stage as discussed in the below sections and v) control or avoid of genotoxic impurities based on dosage of API is one of the key points in design of process. It was accomplished with the use of toluene as solvent instead of alcoholic solvents during hydrochloride salt formation.

Optimum Process Conditions for the Synthesis of 2-Benzoyl-*N*-(2-hydroxyethyl)-*N*-methylbenzamide (**4**): The synthesis of compound **4** involves preparation of compound **3** from compound **2** using $SOCl_2$ followed by reaction of compound **3** with 2-(methylamino)ethanol. The preparation of acid chloride (**3**) is well known process.[31] Initially, the compound **2** was treated with $SOCl_2$ in dichloromethane in presence of catalytic quantity of dimethylformamide at 20-30 °C to prepare compound **3**. The conversion was good (94%), however the removal of unreacted $SOCl_2$ becomes difficult at kilogram scale by codistillation using dichloromethane and it is undesired solvent at commercial level. In the next step, the presence of unreacted $SOCl_2$ affected the formation (88%) of compound **4**. Hence we planned to improve the formation of compound **4** by carrying out a reaction in toluene at 20–30 °C. The reaction was completed in 5 h with 94% conversion (entry 1, Table 1). Hence, it was aimed to reduce the duration of reaction time and improve the conversion. Accordingly, the same reaction was carried out at 30–40 °C, 40–50 °C and 50–60 °C and the reaction was

completed in 3 h, 1 h and 40 min with the conversion of 95%, 98% and 97%, respectively (entries 2–4). The study revealed that 40–50 °C is ideal temperature for maximum formation of compound **3** with in 1 h (entry 3, Table 1, and Figure S6, Supporting Information). The removal of volatiles from the reaction mass by codistillation using toluene under vacuum helped to improve formation (98%) of compound **4**.

The preparation of amide from organic acid using different methods were reported, however the preparation *via* acid chlorides is one of the simple and most economical methods.[32] The major problems associated with acid chlorides during amide formation include racemization, hydrolysis, deprotection, and other side reactions.[33] Hence, we planned to optimize the reaction conditions in a systematic approach. The reaction of compound **3** with 2-(methylamino)ethanol in toluene in presence of Na_2CO_3 at 20–30 °C offered moderate conversion (72%) (entry 5, Table 1). The same reaction with K_2CO_3 and Et_3N offered 76% and 81%, respectively (entries 6 and 7). The same reaction at low temperature offered improved conversion (up to 98%) (entry 9). The effect of order of addition of reagents was also studied. For example, if the order of addition, i) 2-(methylamino)ethanol followed by addition of Et_3N at 0–10 °C offered moderate conversion (77%) (entry 9, conversion in parenthesis, Table 1) and the unreacted substrate (**3**) was more (22%) and ii) addition of Et_3N followed by 2-(methylamino)ethanol at 0–10 °C offered maximum conversion (98%) (entry 9, Table 1 and Figure S12 & S13, Supporting Information). The conformational isomerism (rotamers) was found in compound **4** as per characterization data (Figure S14–S17, Supporting Information).

Table 1: Effect of Reaction Conditions for the Preparation of Compound 4[a]

entry	temp (°C)	time (h)	base	mole ratio	product	Product (% by HPLC)[b]	
						3	**4**
1	20–30	5	-	-	**3**	94	-
2	30–40	3	-	-	**3**	95	-
3	40–50	1	-	-	**3**	98	-
4	50–60	40 min	-	-	**3**	97	-
5	20–30	1	Na_2CO_3	3.0	**4**	-	72
6	20–30	1	K_2CO_3	3.0	**4**	-	76
7	20–30	1	Et_3N	3.0	**4**	-	81

8	10–20	1	Et_3N	3.0	**4**	-	95
9	0–10	1.5	Et_3N	3.0	**4**	-	98 (77)[c]

[a]**Reaction conditions**: compound **2** (10.0 mmol), $SOCl_2$ (12.0 mmol), base, 2-(methylamino)ethanol (11.0 mmol) in toluene at specified temperature.

[b]Order of addition: 2-(methylamino)ethanol followed by Et_3N at 0–10 °C.

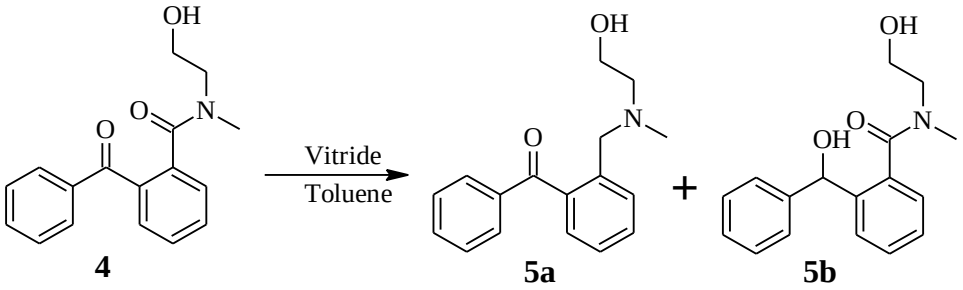
[c]Order of addition: Et_3N followed by 2-(methylamino)ethanol at 0–10 °C.

Optimum Process Conditions for the Synthesis of 2-[{2-[Hydroxy(phenyl)methyl]benzyl}(methyl)amino]ethanol (**5**): Direct conversion of amides to the corresponding amines is not as facile as it seems. Even though many procedures were reported for the reduction of both amide to amine and ketone to 2˚ alcohol of compound **4**, the efficient reagents are Lithium Aluminum Hydride ($LiAlH_4$),[34] diborane or borane complex,[35] and others reducing agents such as DIBAL–H,[36] $NaBH_4$–TFA and $NaBH_4$–TFAA,[37] $NaBH_4$–I_2,[38] LiH_3BNMe_2.[39] Most of the reported reducing agents are good to reduce ketone to 2˚ alcohol, however most of them are not suitable for the reduction of amide to amine of compound **4** at production level because of their i) probability of ignition that cause safety concerns, ii) requirement of more quantity of reducing agent or in combination with other reagents affects cost, handling and isolation, iii) handling and personal safety problems, and iv) less stability at higher temperature.

The reduction of compound **4** was reported in many patents with good yields using $LiAlH_4$.[40] However, $LiAlH_4$ possess major drawbacks. For example i) it is expensive and its handling is very risky compared with other reagents, ii) it reacts violently with water and even a little humidity in the working surroundings or in the solvents can produce hydrogen and it causes ignition.[41] Some patents reported use of borane dimethylsulfide ($BH_3.SMe_2$) to reduce amide to amine[24] of compound **4.** The same reagent was applied in our laboratory, the conversion was low (68%) compared with reported yields even after 24 h with 4.0 equiv of reagent. The drawbacks associated with $BH_3.SMe_2$ reagent is that it is expensive and flammable as it reacts readily with water to produce a flammable hydrogen gas. The reduction of amide functionality of compound **4** was tested with $NaBH_4$ and DIBAL–H, however the reactions were not successful. The literature search revealed that vitride (Red–Al),[30] chemically known as sodium bis(2–methoxyethoxy)aluminumhydride is the best option among the available reagents for reduction of both amide to amine and ketone to 2˚ alcohol of compound **4** at production level. Because vitride i) does not have inconvenient pyrophoric nature and short

shelf-life, ii) reacts with air and moisture exothermically however does not ignite, iii) tolerates higher temperatures, and iv) soluble in aromatic solvents. Interestingly, in one patent, the reduction of amide and ketone functionalities of compound **4** using vitride was reported.[25] The same reaction was carried out in our laboratory using 1.5 eq. of vitride (70% in toluene) and low formation (52%) of compound **5** (entry 1, Table 2) was observed. To improve the conversion and to make the process cost effective, reaction conditions were optimized in a systematic way. Initially, the reduction was carried out using 2.0, 3.0, 4.0, 5.0 and 6.0 equiv of vitride and the conversion was 58%, 64%, 71%, 80% and 92%, respectively (entries 2–6, table 2) at 20–30 °C. To reduce the consumption quantity of vitride and to achieve cost effective process, the same reaction was carried out at higher temperatures as the vitride reagent tolerate high temperatures. For example, 2.0, 2.5, 3.0 equiv of vitride offered 72%, 95% and 94% of compound **5** (entries 7–9, table 2) at 90-100 °C. The study disclosed that 2.5 equiv. of vitride offered excellent formation (95%) of compound **5** at 90–100 °C (entry 8). To study further the effect of temperature on the course of the reaction, the same reaction was carried out at 60–70 °C, 70–80 °C and 80–90 °C and the conversion was 67%, 73% and 78%, respectively (entries 11–13). The study disclosed that the formation of compound **5** from compound **4** was excellent (>90%) both at 20–30 °C with 6.0 equiv. of vitride (entry 6) and at 90–100 °C with 2.5 equiv. of vitride (entry 8).

Interestingly, it is found that the dilution of the reaction mass has significant effect on the course of the reduction. For example, compound **5** (82%) (entry 8, conversion in parenthesis, table 2), impurity **5a** (8%) and impurity **5b** (0.1%) were formed in 5 vol. of toluene solvent using 2.5 equiv. of vitride at 90–100 °C (scheme 2). The same reaction in 2 vol. of toluene provided maximum formation (95%) of compound **5** (entry 8, table 2) and impurities **5a** (0.03%) and **5b** (0.01%) were formed. The same reaction on increase of further dilution (10 vol. of toluene as solvent) the formation of compound **5** was decreased (66%) and impurities **5a** (18%) and **5b** (0.25) were formed more. The study revealed that the reduction of **4** was not effective at high dilution. Further, the same reaction was offered low conversion (52%) (entry 15) without toluene. The study disclosed that 2.5 equiv of vitride reagent (70% in toluene) in 2 vol. of toluene at 90–100 °C provided maximum formation (95%) of compound **5** (entry 8, Table 2 and Figure S23, Supporting Information). The impurity **5b** was not formed at higher level in the present reaction conditions, so it was not isolated. But the impurity **5a** was carried up to API. Hence, impurity **5a** was isolated and characterized (Scheme 2 and Figure S24–S33, Supporting Information).



Scheme 2: Formation of probable impurities during reduction of compound 4.

Table 2: Effect of Reaction Conditions on Reduction of Compound 4.[a]

entry	equiv. of Reducing agent	temp (°C)	volume of toluene	time (h)	product	Product 5 (% by HPLC)[b]
1	1.5	20–30	2	9	**5**	52
2	2.0	20–30	2	7	**5**	58
3	3.0	20–30	2	6	**5**	64
4	4.0	20–30	2	5	**5**	71
5	5.0	20–30	2	3	**5**	80
6	6.0	20–30	2	2	**5**	92
7	2.0	90–100	2	3	**5**	72
8	2.5	90–100	2 (5)[b]	1.5	**5**	95 (82%)[b]
9	3.0	90–100	2	1	**5**	94
10	2.5	100–110	2	30 min	**5**	83
11	2.5	60–70	2	4	**5**	67
12	2.5	70–80	2	3	**5**	73
13	2.5	80–90	2	2.5	**5**	78
14	2.5	90–100	10	6	**5**	66
15[c]	2.5	90–100	-	1	**5**	52

[a]**Reaction conditions**: compound **4** (10.0 mol), Vitride in toluene at specified temperature.

[b]Conversion when 5.0 vol of toluene was applied

[c]Neat reaction

Optimum Process Conditions for the Synthesis of 5-Methyl-1-phenyl-3,4,5,6-tetrahydro-1*H*-2,5-benzoxazocine (6) *via* Intramolecular Cyclization:

The formation of 8-membered ring *via* intramolecular cyclization is a central issue as several methods failed to get high yield with minimum reaction time. The catalysts reported for the

cyclization are not viable at production level, for example in few patents *p*-toluenesulfonic acid was reported for intramolecular cyclization for the formation of compound **6**.[26] But, the major drawbacks associated with this method include i) difficulty to stir the reaction mass as it is in semi-solid form and it leads to unfavorable for production in plant, and ii) the percentage of unreacted substrate (**5**) is also more (25–40%) [entry 1, Table 3).

The drawbacks associated with *p*-toluenesulfonic acid encouraged us to search for catalyst with almost similar chemical features. In this thirst we found that methanesulfonic acid is one of the best options available because of its efficiency in cyclization reactions as reported in literature.[42] As expected, it offered 76% formation of compound **6** in 24 h at 100–110 °C in presence of 1.0 equiv. of methanesulfonic acid (entry 2, Table 3). To increase the conversion further and to reduce the duration of reaction time, the same reaction was carried out azeotropically to remove the water, a byproduct of the reaction, amazingly the reaction completed in 1.5 h with 96% formation of **6** in presence of 2.0 equiv. of methanesulfonic acid (entry 3). The same reaction in presence of 3.0 equiv. of methanesulfonic acid offered 93% of compound **6** (entry 4). The same reaction in presence of polyphosphoric acid, it was observed that the reaction mass was dark in color, moderate conversion (73%) and poor appearance of API even after carbon treatment (entry 5). The same reaction in presence of hydrobromic acid[26] provided low formation (66%) of compound **6** (entry 6).

The study disclosed that 2.0 equiv of methanesulfonic acid offered excellent formation (96%) of 8-membered ring compound **6** (Figure S34, Supporting Information).

Table 3: **Effect of Reaction Conditions on Intramolecular Cyclization to Prepare 8-Membered Ring Compound** (**6**):

entry	Catalyst	equiv.	time (h)	product	Product 6 (% by HPLC)[b]
1	*p*-toluenesulfonic acid	2.0	24	**6**	61
2	methanesulfonic acid	1.0	6	**6**	76
3		2.0	1.5	**6**	96
4		3.0	1	**6**	93
5	polyphosphoric acid	2.0	5	**6**	73
6	hydrobromic acid	2.0	8	**6**	66

[a]**Reaction conditions**: compound **5** (10.0 mol), catalyst, toluene (5 vol) and acidic catalyst at 100–110 °C.

[b]Remaining unreacted substrate

Optimum Process Conditions for the Synthesis of 5-Methyl-1-phenyl-3,4,5,6-tetrahydro-1*H*-2,5-benzoxazocine hydrochloride (1):

The hydrochloride salt formation (**1**) of compound **6** was carried out in different solvents, for example acetone, methanol, ethanol and isopropyl alcohol offered lower yields 71%, 76%, 80% and 85%, respectively with purity ≥98% except in isopropyl alcohol (97%). The formation of genotoxic impurities (alkyl chlorides and alkyl methanesulfonate etc) is the major problem with alcoholic solvents. To avoid the formation of genotoxic impurities, the same reaction was carried out in toluene at 0–10 °C. The formed product **1** was in viscid nature even after 6 h stirring at 0–10 °C. To avoid formation of **1** with viscid nature, the same salt formation was carried out by purging dry HCl gas into reaction mass (compound **6** in toluene) at 0–10 °C and the product was obtained with ≥97% purity.

The HPLC data of crude Nefopam hydrochloride (**1**) revealed that it did not fulfil the specifications of API (Figure S35, Supporting Information). Hence, it was planned to recrystallize in different alcoholic solvent systems, for example, methanol, ethanol and mixture of aqueous alcoholic solvent system (H_2O:methanol in 1:1 ratio) as the compound **1** was practically insoluble in other solvents. The results obtained were presented in Table 4. The study disclosed that the methanol provided excellent purity >99.9% with excellent yield (95%) (entry 1, Table 4 and Figure S46, Supporting Information). Before the finalization of alcoholic solvents for purification of compound **1**, the content of methanesulfonic acid was checked as its presence forms the genotoxic impurities (alkyl methanesulfonates). Interestingly, the analysed crude compound **1** did not have any methanesulfonic acid which helped to avoid the formation of such genotoxic impurities.

Table 4. Selection Suitable Solvent for the Purification of Nefopam Hydrochloride (1)[a]

entry	solvent	yield[b] (%)	product	purity (% by HPLC)					
				1	**2**	**4**	**5**	**5a**	**unknown**
1	methanol	95	**1**	99.96	0.02	0.00	0.00	0.00	0.01
2	ethanol	96	**1**	99.50	0.20	0.10	0.02	0.03	0.15
3	water:methanol (1:1 ratio)	82	**1**	99.41	0.10	0.2	0.06	0.03	0.2

[a]**Reaction conditions**: crude compound **1** (10 g, 0.031 mol) in solvent (100 mL] at 60–65 °C for 1h, cool to 0–10 °C, stir for 2 h and filter the solid.
[b]Isolated yield.

Experimental

The solvents and reagents were obtained from commercial sources and were used without any purification. Nuclear magnetic resonance (NMR) spectra of the synthesized compounds were recorded on Ascend Bruker 400 (Bruker, Fallanden, Switzerland) instrument and operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR using either $CDCl_3$ or DMSO-d_6 solvent and tetramethylsilane (TMS) as internal standard. Spin multiplicities are given as s (singlet), d (doublet), dd (doublet of doublet), t (triplet), and m (multiplet) as well as brs (broad singlet). The ^{1}H chemical shift values were reported on δ scale in ppm, relative to TMS (δ = 0.00 ppm) and in the ^{13}C chemical shift values were reported relative to DMSO-d_6 (δ = 39.5 ppm). The ESI/MS experiments were performed on a Velos Pro Ion Trap mass spectrometer from Thermo Scientific (San Jose, CA, U.S.A.). The CHN analyses were recorded on a Vario EL analyser.

Synthesis of 5-Methyl-1-phenyl-3,4,5,6-tetrahydro-1*H*-2,5-benzoxazocine hydrochloride (**1**).

In a 50 L reactor, benzoylbenzoic acid (**2**) (2.0 kg, 8.841 mol), toluene (10 L), DMF (60 mL) and thionyl chloride (1.26 kg, 10.609 mol) were charged and maintained at 40–50 °C for 1 h. After completion of the reaction, the volatiles were distilled out under vacuum at 40-50 °C and chased out with toluene (4 L). The toluene (20 L) and Et_3N (2.68 kg, 26.523 mol) were charged and 2-(methylamino)ethanol solution (0.730 kg, 9.725 mol, in 4 L toluene) was added slowly at 0–10 °C. The temperature of the reaction mass was increased to 20–30 °C and maintained for 1 h. After completion of the reaction, water (6 L) was added and the product (**4**) was extracted (toluene layer) at 50–60 °C and washed with 5% aq. $NaHCO_3$ solution (6 L) followed by water (6 L). The solvent was evaporated from the organic layer (**4**) until reaction mass became 2–3 vol and vitride (70% in toluene) (6.38 kg, 22.102 mol) was added slowly at 0–15 °C followed by maintenance at 90–100 °C for 1.5 h. After completion of the reaction, toluene (10 L) was charged and quenched the reaction mass using aq. NaOH solution (0.6 kg NaOH, 15.00 mol, in 20 L water) at 0–15 °C. The product toluene layer (**5**) was collected at 40–50 °C and to this added dil. H_2SO_4 (1.0 kg H_2SO_4, 10.167 mol, in 10 L water) at 5–15 °C. The aqueous layer was collected and added fresh toluene (14 L) followed by basification using aq. NaOH solution (0.884 kg NaOH, 22.1 mol, in 6 L water) at 5–15 °C. The organic layer was collected and washed with water (6 L) at 40–50 °C. The solvent was evaporated until reaction mass became 4–5 vol followed by addition of methanesulfonic acid (1.7 kg, 17.682 mol) at 20–30 °C. The reaction was maintained at 100–110 °C for 1.5 h by collecting water azeotropically. After completion of the reaction, water (10 L) was added at

20–30 °C. The aqueous layer was collected and added toluene (10 L) followed by basification using aq. NaOH solution (0.99 kg NaOH, 24.755 mol, in 6 L water) at 5–15 °C. The organic layer (**6**) was collected and washed twice with water (2x4 L). The HCl gas was purged slowly into the reaction mass at 0–10 °C for 30 min and stirred at the same temperature for 1 h. The reaction mass was filtered, washed with toluene (2 L). The obtained solid product (**1**) was dried under vacuum at 50–55 °C. Yield = 2.15 kg. The yield of compound **1** is 84% with purity 98.06% (Before purification).

Purification of 5-Methyl-1-phenyl-3,4,5,6-tetrahydro-*1H*-2,5-benzoxazocine hydrochloride (**1**).

In a 2 L RB flask, compound **1** (2.0 kg) in methanol (20 L) was heated to 60–65 °C and stirred at the same temperature until clear solution was obtained. The activated carbon (100 g) was charged and stirred for 30 minutes. The reaction mass was filtered through hyflo bed and washed with methanol (2 L). The filtrate was collected and the solvent was evaporated under vacuum until the reaction mass became 3–4 vol. The reaction mass was cooled to 0–10 °C and stirred for 2 h at 0–10 °C. The reaction mass was filtered and washed with methanol (1 L).

Yield = 1.9 kg (95%) with HPLC purity 99.96%. The overall yield is 79.8% (after purification).

Characterization data:

2-Benzoylbenzoyl chloride (**3**) [Figure S1–S6, Supporting Information)**:**

^{1}H NMR (400 MHz, $CDCl_3$, *δ/ppm*): 7.91 (d, 1H, arom H, *J* = 7.6 Hz), 7.78 (t, 1H, arom H, *J* = 7.6 Hz), 7.69–7.66 (m, 3H, arom H), 7.60 (t, 1H, arom H, *J* = 7.6 Hz), 7.42-7.38 (m, 3H, arom H).

^{13}C NMR (100 MHz, $CDCl_3$, *δ/ppm*): 167.1, 151.3, 138.2, 135.5, 130.8, 130.0, 129.7, 128.8, 128.5, 125.9, 125.8, 123.6, 123.5, 99.9

MS *m/z* (ESI): 209.06 ($M^{+\cdot}$)

2-Benzoyl-*N*-(2-hydroxyethyl)-*N*-methylbenzamide (**4**) [Figure S7–S13, Supporting Information]**:**

^{1}H NMR (400 MHz, CD_3OD, recorded at 55 °C, *δ/ppm*): 7.77 (d, 2H, arom H, *J* = 7.6 Hz), 7.64 (t, 2H, arom H, *J* = 7.6 Hz), 7.60–7.49 (m, 5H, arom H), 3.69 (t, 2H, –CH_2–O–, *J* = 7.6 Hz), 3.52 (t, 1H, –C**H**(H)–), 3.37 (t, 1H, –CH(**H**)–), 2.99 (s, 3H, –CH_3).

^{13}C NMR (100 MHz, DMSO–d_6, recorded at 90 °C, *δ/ppm*): 195.5, 168.9, 137.1, 136.7, 136.6, 132.4, 130.2, 128.9 (2C), 128.6, 127.9, 127.8 (2C), 126.7, 58.0, 45.5, 32.0

MS *m/z* (ESI): 284.15 $(M+H)^{+\cdot}$

2-[{2-[Hydroxy(phenyl)methyl]benzyl}(methyl)amino]ethanol (**5**) [Figure S18–S23, Supporting Information]**:**

^{1}H NMR (400 MHz, $CDCl_3$, *δ/ppm*): 8.68 (s, 1H, –CH–O–), 7.41–7.33 (m, 4H, arom H), 7.31–7.25 (m, 3H, arom H), 7.21 (t, 2H, arom H, *J* = 7.6 Hz), 3.72–3.62 (m, 2H, $–CH_2–$), 3.44 (d, 1H, –CH(**H**)–, *J* = 12.4 Hz), 3.36 (d, 1H, –C**H**(H)–, *J* = 12.4 Hz), 3.04 (s, 1H, –OH), 2.65–2.51 (m, 2H, $–CH_2–$), 2.21 (s, 3H, $–CH_3$).

^{13}C NMR (100 MHz, $CDCl_3$, *δ/ppm*): 144.1, 143.3, 135.8, 132.0, 130.0, 128.2, 127.9 (2C), 127.5, 126.7, 126.0 (2C), 75.5, 61.4, 59.2, 59.0, 41.5

MS *m/z* (ESI): 272.22 $(M+H)^{+\cdot}$

5-Methyl-1-phenyl-3,4,5,6-tetrahydro-1*H*-2,5-benzoxazocine hydrochloride (1) [Figure S37–S49, Supporting Information]**:**

White crystalline solid, m. p. 248–251 °C, $[\alpha]_D^{20}$= -0.016 (c 1.0, H_2O).

^{1}H NMR (400 MHz, D_2O, *δ/ppm*): 7.36–7.25 (m, 6H, arom H), 7.21–7.18 (m, 2H, arom H), 7.12–7.10 (m, 1H, arom H), 5.89 (s, 1H, Aryl–C**H**–Aryl), 5.45 (d, 1H, Aryl–C**H**(H)–N–, *J* = 12.8 Hz), 4.34–4.27 (m, 1H, –C**H**(H)–O–), 4.21 (d, 1H, Aryl–C**H**(H)–N–, *J* = 13.2 Hz), 4.05–4.00 [m (dt), 1H, –C**H**(H)–O–, *J* = 6.8 Hz and *J* = 3.6 Hz], 3.30-3.23 (m, 1H, –C**H**(H)–N–), 3.08–3.02 [m (dt), 1H, –CH(**H**)–N–, *J* = 7.2 Hz and *J* = 3.6 Hz), 2.87 (s, 3H, $–CH_3$).

^{13}C NMR (100 MHz, D_2O, *δ/ppm*): 142.4, 141.1, 134.3, 130.5, 129.1, 129.0 (2C), 128.7, 128.4, 127.7 (2C), 125.3, 85.3, 64.9, 58.3, 50.5, 41.6

MS *m/z* (ESI): 254.20 $(M+H)^{+\cdot}$

CHN analysis data (%/w): Anal. Calcd. for $C_{17}H_{19}NO.HCl$ or $C_{17}H_{20}NOCl$: C, 70.46; H, 6.96; N, 4.83; Found: C, 70.39; H, 7.25; N, 4.49; S, not found.

Isolation of (2-{[(2-Hydroxyethyl)(methyl)amino]methyl}phenyl)(phenyl)methanone (**5a**): The mother liquor (100 mL) of 5-Methyl-1-phenyl-3,4,5,6-tetrahydro-1*H*-2,5-benzoxazocine hydrochloride (**1**) was taken and concentrated. The crude mass was purified

over column filled with Silica gel using 10% EA in hexane. The obtained impurity **5a** (850 mg) was characterized.

^{1}H NMR (400 MHz, $CDCl_3$, *δ/ppm*): 9.24 (bs, 1H, –OH), 7. 75–7.64 (m, 6H, arom H), 7.61–7.57 (m, 1H, arom H), 7.49 (t, 2H, arom H, *J* = 7.6 Hz)), 4.49 (d, 1H, Aryl–C**H**(H)–N–, *J* = 12.8 Hz), 4.29 (d, Aryl–CH(**H**)–N–, *J* = 12.8 Hz), 4.04–3.91 (m, –N–CH_2–), 3.51–3.45 (m, 1H, –C**H**(H)–O–), 3.33 (d, 1H, –CH(**H**)–O–), 2.94 (s, 3H, –CH_3).

^{13}C NMR (100 MHz, $CDCl_3$, *δ/ppm*): 200.0, 138.0, 136.7, 134.5, 134.4, 133.4, 133.2, 131.0 (2C), 130.3, 129.9, 128.8 (2C), 60.2, 57.4, 55.3, 39.3

MS *m/z* (ESI): 270.15 $(M+H)^{+\cdot}$

Conclusion

A versatile one-pot method using single solvent has been developed for the manufacture of Nefopam hydrochloride (**1**) with excellent purity (≥99.9%) and overall yield (≥79%). The present work addressed several process issues to make the entire mechanism operational friendly for multi-kilogram scale production. The optimization of reaction conditions during reduction of both amide and ketone functionalities using minimum quantity (2.5 equiv) of vitride is one of the key success in the present process. In addition, the process impurity **5a** and carryover impurities (**2**, **4** and **5**) are efficiently removed during purification process. The formation of genotoxic impurities (alkyl chlorides and alkyl methanesulfonates) was eliminated by using toluene as solvent instead of alcoholic solvents during hydrochloride salt (**1**) formation. The concept of green chemistry was also achieved partially by developing one-pot multi-step synthetic strategy (avoided step by step process) using single solvent (toluene). Our team hoping that the present work can help both in focussing and adopting Nefopam hydrochloride as alternative safe analgesic to the rest of the countries which is now limited to United Kingdom, France and few other European countries.

Corresponding author
Dr. Pramod Kumar
Senior Vice-President ,
API R&D Centre, Micro Labs Ltd., Bangalore.
Tel. No. 0811 0415647, *Ext. No.* 245
Mobile No. +91 9008448247
E-mail: pramodkumar@microlabs.in

Notes

The authors declare no competing financial interest.

Acknowledgments

The authors are thankful to the management of Micro Labs Limited for financial support for this research work (No. NEF/2016-17). We are grateful to colleagues in the Analytical Research Division, API R&D Centre, Micro Labs Limited, Bangalore. Our special thanks to Dr. R. V. Jayanth Kasyap and Ridhima Kochar for their support.

Supporting information

Copies of relevant ^{1}H, ^{13}C NMR, DEPT-135, mass spectra, CHN analyses, Powder XRD and also HPLC chromatograms are available in the supporting information.

References

1. American Academy of Pain Medicine. *AAPM facts and figures on pain*. www.painmed.org/patient/facts.html. February 25, **2011**.
2. National Centres for Health Statistics. Health, United States, 2006, *With Chart book on Trends in the Health of Americans.* www.cdc.gov/nchs/data/hus/hus06.pdf. February 25, **2011**.
3. (a). Chou, R.; Qaseem, A.; Snow, V.; Casey, D.; Cross, J. T. Jr.; Shekelle, P.; Owens, D. K. *Ann. Intern. Med.* **2007**, *147*, 478–491.; (b). Richmond, J.; Hunter, D.; and Irrgang, J. *et al. J. Bone Joint Surg. Am.* **2010**, *92*, 990–993.; (c). Agency for Healthcare Research and Quality, US Department of Health and Human Services. *J. Pain & Palliat Care Pharmacother.* **2009**, *23*, 433–457.; (d). American college of Rheumatology subcommittee on osteoarthritis guidelines. *Arthritis Rheum.* **2000**, *43*, 1905–1915.; (e). Snow, V.; Weiss, K.; Wall, E. M.; Mottur-Pilson, C. *Ann. Intern. Med.* **2002**, *137*, 840–849.
4. Munir, M. A.; Enany, N.; Zhang, J. M. *Anesthesiology Clin.* **2007**, *25*, 761–774.
5. Glaser, R.; Cohen, S.; Donnell, D.; Agranat, I. *J. Pharm. Sci.* **1986**, *75*, 772–774.
6. (a). Guirimand, F.; Dupont, X.; Bouhassira, D.; Brasseur, L.; Chauvin, M. *Pain* **1999**, *80*, 399–404.; (b). Heel, R. C.; Brogden, R. N.; Pakes, G. E.; Speight, T. M.; Avery, G. S. *Drugs.* **1980**, *19*, 249–267.; (c). Kapfer, B.; Alfonsi, P.; Guignard, B.; Sessler, D. I.; Chauvin, M. *Anesthesia and Analgesia*. **2005**, *100*, 169–174.
7. (a) Payen J. F.; Genty, C.; Mimoz, O.; Mantz, J.; Bosson, J. L.; Chanques, G. *J. Crit. Care.* **2013**, *28*, 534.e7–534.e12.; (b). Eremenko, A. A.; Sorokina, L. S.; Pavlov, M. V. *Anesteziol. Reanimatol.* **2013**, *5*, 11–15.; (c). Kapfer, B.; Alfonsi, P.; Guignard, B.; Sessler, D. I.; Chauvin, M. (January). *Anesthesia and Analgesia*. **2005**, *100*, 169–174.

8. Balandin V. V., Gorobets, E. S., *Anesteziol. Reanimatol.* **2014**, *1*, 40–43.
9. Eremenko, A. A.; Sorokina, L. S.; Pavlov, M. V. *Anesteziol. Reanimatol*. **2013**, *2*, 78–82.
10. Cohen, A.; Hernandez, C. M. *J. International Med. Res*. **1976**, *4*, 138–143.
11. Glaser, R.; Cohen, S.; Donnell, D.; Agranat, I. *J. Pharm. Sci*. **1986**, *75*, 772–774.
12. Gasser, J. C.; Bellville, J. W. *Clin. Pharmacol. Ther.* **1975**, *18*, 175–179.
13. (a). Pillans, P. I.; Woods, D. J. *N. Z. Med. J.* **1995**,*108*, 382–384.; (b). Sunshine, A.; Laska, E. *Clin. Pharmacol. Ther.* **1975**, *18*, 530–534.; (c). Phillips, G.; Vickers, M. D. *Br. J. Anaesth.* **1979**, *51*, 961–965.
14. Tigerstedt, I.; Tammisto, T.; Leander, P. *Acta Anaesthesiol. Scand*. **1979**, *23*, 555–560.
15. (a). Bismuth, C; Fournier, P. E.; Bavoux, E.; Husson, O.; Lafon, D. *J. Toxicol. Clin. Exp.* **1987**, *7*, 343–346.; (b). Tracqui, A.; Berthelon, L.; Ludes, B. *J. Anal. Toxicol.* **2002**, *26*, 239–243.
16. (a). Klohs, M.; Draper, M.; Petracek, F. *US Patent 3830803*, 20th Aug. **1974**.; (b). Heel, R. C.; Brogden, R. N.; Pakes, G. E.; Speight, T. M.; Avery, G. S. *Drugs*. **1980**, *19*, 249–267.
17. (a). Taniguchi, Y.; Ali, S. Z.; Kimberger, O.; Zmoos, S.; Lauber, R.; Markstaller, M.; Kurz, A. *Anesth. Analg.* **2010**, *111*, 409–41.; (b). Alfonsi, P.; Adam, F.; Passard, A.; Guignard, B.; Sessler, D. I.; Chauvin, M. *Anaesthesiology*. **2004**, *100*, 37–43.
18. Bilotta, F.; Rosa, G. *N. Engl. J. Med.* **2000**, *343*, 1973–1974.
19. (a). McLintock T. T.; Kenny, G. N.; Howie, J. C.; McArdle, C. S.; Lawrie, S.; Aitken, H. *Br. J. Surg.* **1988**, *75*, 779–781.; (b). Mimoz, O.; Incagnoli, P.; Josse, C.; Gillon, M. C.; Kuhlman, L.; Mirand, A.; Soilleux, H.; Fletcher, D. *Anaesthesia* **2001**, *56*, 520–525.; (c). Hwang, B. Y.; Kwon, J. Y.; Lee, D. W.; Kim, E.; Kim, T. K.; Kim, H. K. .*Int. J. Med. Sci.* **2015**, *12*, 644–649.; (d). Hudcova, J.; McNicol, E.; Quah, C.; Lau, J.; Carr, D. B. *Cochrane Database Syst. Rev.* **2006**, CD003348.; (e). Evans, M. S.; Lysakowski, C.; Tramèr, M. R. *Br. J. Anaesth.*, **2008**, *101*, 610–617.; (f). Du Manoir, B.; Aubrun, F.; Langlois.; Le Guern, M. E.; Alquier, C.; Chauvin, M.; Fletcher, D. *Br. J. Anaesth.* **2003**, *91*, 836–841.
20. Debernardi, G.; Bracco, P.; Debernardi, C.; Messina, F. *Minerva Stomatol*. **1985**, *34*, 317–322.
21. Moustafa, F.; Liotier, J.; Mathevon, T.; Pic, D.; Perrier, C.; Schmidt, J. *Emerg. Med. J.* **2013**, *30*, 143–148.
22. Medicines and Healthcare products Regulatory Agency (MHRA) - Apr 2015 Public Assessment Report (UK National procedure) for Nefopam hydrochloride 30 mg film-

coated tablets (PL 41830/0014 and PL 41830/0034): http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con534711.pdf

23. (a). Saxlund, R. A.; Koskenniska, L. A. *EP 0033585*, 9th Jan. **1981**.; (b). Murle, W. K.; Tarzana, M. D. Draper, Francis J. Petracek, Canoga Park Calif, *US 3830803*, 20th Aug. 1974; (c) Baxter, Andrew Douglas, *EP 1950206 A1*, 30th July 2008.; (d) Baxter, Andrew Douglas, Andrea Walmsley and Elena Lasterra, *GB 2413326*, 26th Oct. 2005.
24. Baxter, Andrew Douglas, *CA 2503172*, 8th July 2004; Baxter, Andrew Douglas, Andrea Walmsley, Elena Lasterra, *US20060019940A1*, 26th Jan. 2006.
25. Wiguel Izquierdo Sanjose, Maria Luisa Lucero de Pablo, Ulpiano Martin-Escudero Perez, *ES 8105723*, 20th May 1980.
26. (a) Baxter, A. D.; Walmsley, A.; Lasterra, E. *GB 1148718*, 26th Oct. **2005**.; (b). Baxter, A. D. *CA 2503172*, 8th July **2004**.; (c). Baxter, A. D.; Walmsley, A.; Lasterra, E. *US20060019940A1*, 26th Jan. **2006**.; (d) Calatayud, J.; Luna, M, *ES8605495A1*, 1st Sep. **1986**.; (e). Colls, A. J. *ES 8607261*, 1st Nov. **2006**.; f) Porta, A. L. *ES8100663*, 1st Feb. **1981**.; (g). Lucero de Pablo, M. L.; Martin-Escudero P. U.; Izquierdo, S., M. *ES 8105723*, 1st Sep. **1981**.; (h). Eberlin, J.W. *US 3978085*, 31st Aug. **1976**.
27. (a). Watson, P.G., *US 4208349*, 17th June **1980**.; (b). Watson, P.G., *GB 1586578*, 18th Mar. **1981**.
28. David J. C. C.; Alan D. C.; Virginia L. C. *Green Chem.*, **2002**, *4*, 521–527.
29. Sheldon, R. A. *Chem. Commun.* **2008**, 3352.
30. (a)http://www.dow.com/assets/attachments/business/soa/reducing_agents/vitride/tds/vitride.pdf.; (b). R. Buchi Reddy, U. Sampath Kumar, S. Nilam, K. Mariappan, G. P. M. Syed Ibrahim, S. Susi, WO2011145019 (A1), 2011.; (c). Gugelchuk, M. A. B.; Silva, L. F. III; Vasconcelos, R. S.; Quintiliano, S. A. P. "Sodium Bis(2-methoxyethoxy)aluminum Hydride". Encyclopedia of Reagents for Organic Synthesis. New York: John Wiley & Sons. 2007. (d). Smith, Michael B. Organic Synthesis. Cambridge, Mass.: Academic Press. p. 368, **2011**. ISBN 9780124158849
31. (a). Boyd, R. W.; Morrison, R. *Organic chemistry*. Englewood Cliffs, N.J: Prentice Hall. **1992**, 666–762.; (b). Clayden, J. *Organic chemistry*. Oxford: Oxford University Press. **2001**, pp. 276–296.; (c). Waites, W. B.; Young, R. E.; Devl'oll, P. R. *US 5672749*, 30th Sep. **1997**.
32. Anderson, N. G. In Practical Process Research & Development: A Guide for Organic Chemists, 2nd ed.; Academic Press: New York, 2012; p 109.
33. Montalbetti, C.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852.

34. (a) Brown, H. C.; Weissman, P. M.; Yoon, N.-M. *J. Am. Chem. Soc.* **1966**, *88*, 1458–1463.; (b) Cha, J. S.; Lee, J. C.; Lee, H. S.; Lee, S. E.; Kim, J. M.; Kwon, O. O.; Min, S. J. *Tetrahedron Lett.* **1991**, *32*, 6903–6904.; (c) Uffer, A.; Schlittler, E. *Helv. Chim. Acta* **1948**, *31*, 1397–1400.

35. (a) Kornet, M. J.; Tan, S. I. *J. Org. Chem.* **1968**, *33*, 3637–3639.; (b) Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3566–3567; (c) Brown, H. C.; Bigley, D. B.; Arora, S. K.; Yoon, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 7161–7167.; (d) Godjoian, G.; Singaram, B. *Tetrahedron Lett.* **1997**, *38*, 1717–1720.

36. Winterfeldt, E. *Synthesis* **1975**, *9*, 617–630.

37. Gribble, G. W.; Nataitis, C. F. *Org. Prep. Proced. Int.* **1985**, *17*, 317–384.

38. Mckennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568–3571.

39. Flaniken, J. M.; Collins, C. J.; Lanz, M.; Singaram, B. *Org. Lett.* **1999**, *1*, 799–801.

40. (a). Saxlund, R. A.; Koskenniska, L. A. *EP 0033585*, 9th Jan. **1981**.; (b). Murle, W. K.; Tarzana, Marshall, D. D.; Francis, J. P.; Canoga, P. C. *US 3830803*, 20th Aug. **1974**.; (c) Baxter, A. D. *EP 1950206 A1*, 30th July **2008**.; (d) Baxter, A. D.; Walmsley, A.; Lasterra, E. *GB 2413326*, 26th Oct. 2005.

41. Keese, R.; Brändle, M.; Toube, T. P. *Practical Organic Synthesis: A Student's Guide. John Wiley and Sons.* **2006**. *p. 134.*

42. Premasagar, V.; Palaniswamy, V. A.; Eisenbraun, E. J. *J. Org. Chem.*, **1981**, *46*, 2974–2976.

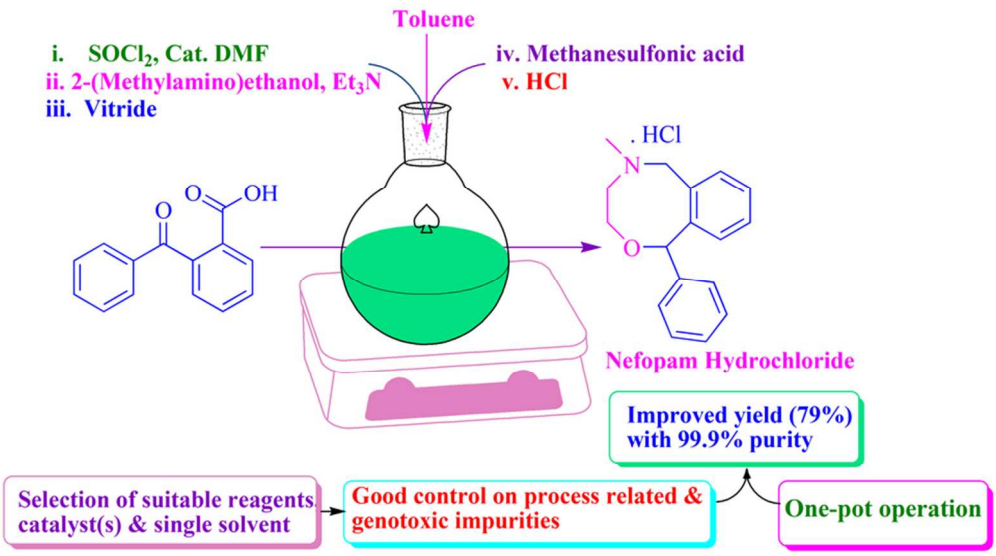


Table of Contents graphic

81x45mm (300 x 300 DPI)