EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201700824

Link to VoR: http://dx.doi.org/10.1002/ejoc.201700824

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Full Paper

Synthesis of Mepivacaine and its Analogues by a Continuous Flow Tandem Hydrogenation−Reductive Amination Strategy

Nícolas S. Suveges,[a,b] Rodrigo O. M. A. de Souza,[a] Bernhard Gutmann,*[b,c] and C. Oliver Kappe*[b,c]

Abstract Herein we report a convenient, fast and high-yielding method for the generation of the racemic amide anaesthetics mepivacaine, ropivacaine and bupivacaine. Coupling of α-picolinic acid and 2,6-xylidine under sealed vessel microwave conditions generates the intermediate amide after a reaction time of only 5 minutes at 150 °C. Subsequent reaction in a continuous flow high-pressure hydrogenator (H-Cube Pro™) in the presence of the respective aldehyde directly converts the intermediate to the final amide anaesthetics in a continuous, integrated, multi-step ring-hydrogenation/reductive amination protocol. Merits and limitations of the protocol are discussed.

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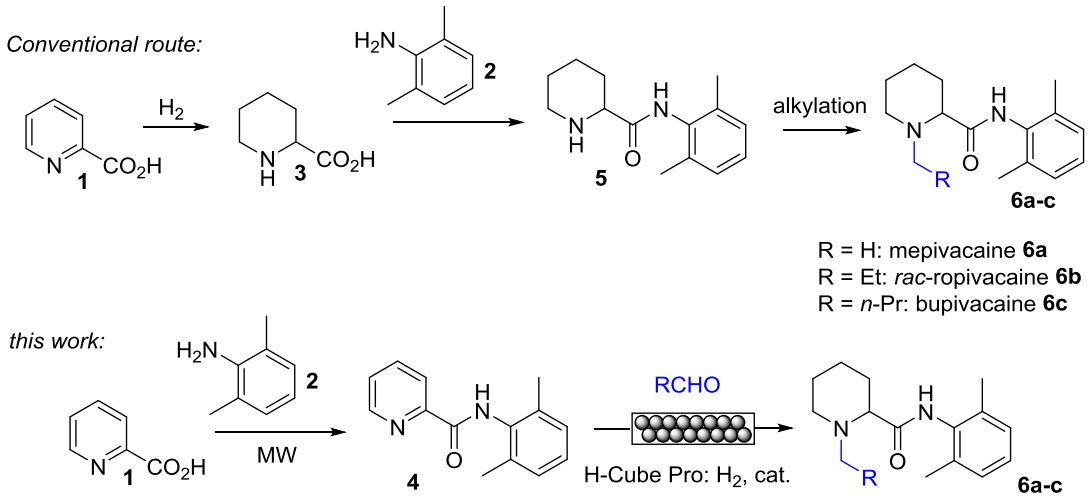
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under http://dx.doi.org/10.1002/ejoc.2017xxxxxx.

Introduction

Mepivacaine, ropivacaine and bupivacaine are potent local anesthetics of the amino amide family.[1] This class of local anesthetics consists of a lipophilic group (*i.e.*, an aromatic ring) connected through an amide linker to an ionizable moiety (*i.e.*, a tertiary amine). For mepivacaine, ropivacaine and bupivacaine, the terminal amino group is part of a piperidine ring (Scheme 1). Mepivacaine and bupivacaine have been in clinical use for more than 30 years. Both compounds are administered as racemic mixtures. In contrast, the more recent amide anesthetics ropivacaine and levobupivacaine (the *S*-(−)-form of bupivacaine) are used in enantiomerically pure form.[1] Bupivacaine is one of the most widely used, long acting local anaesthetic agent in surgery and obstetrics.[1b] It is on the World Health Organization's List of Essential Medicines.



Scheme 1. Synthetic strategies for the synthesis of mepivacaine and its analogues.

A straightforward approach towards the synthesis of racemic mepivacaine and its analogues starts from α-picolinic acid (**1**). α-Picolinic acid (**1**) is produced on an industrial scale by oxidation of 2-methylpyridine and is available at very low cost.[2] Hydrogenation of the α-picolinic acid affords the non-proteinogenic α-amino acid pipecolic acid (**3**) (Scheme 1). Coupling of pipecolic acid (**3**) with 2,6-xylidine (**2**) (2,6-dimethylaniline) provides the intermediate amide (2',6'-pipecoloxylidide **5**).[3-6] Alternatively, direct coupling of α-picolinic acid (**1**) with 2,6-xylidine (**2**) and subsequent selective reduction of the pyridine ring to deliver 2',6'-pipecoloxylidide (**5**) has been reported.[7] 2',6'-Pipecoloxylidide (**5**) then serves as the starting material for the preparation of the racemic anaesthetics mepivacaine (**6a**), *rac*-ropivacaine (**6b**) and bupivacaine (**6c**) by *N*-alkylation. In general the introduction of the *N*-alkyl group can be accomplished by one of three strategies: (i) direct S_N2 alkylation using alkyl-X species (X = Br, I, $MeSO_3$, etc.), (ii) acylation with subsequent reduction of the carbonyl,

(iii) reductive amination with aldehydes. Even though S_N2 alkylation with alkyl-X species is still widely used, the need to handle toxic and carcinogenic reagents and stringent requirements to remove residuals of the alkyl-X species down to vanishingly small levels in the final drug candidate discourages from its use, particularly in a late stage of API (active pharmaceutical ingredient) synthesis. Reductive amination is in many respects the superior approach. Reductive amination is typically performed with stoichiometric reductants, such as sodium cyanoborohydride ($NaBH_3CN$) and sodium triacetoxyborohydride ($NaBH(OAc)_3$).[4,8] For instance, the attachment of the methyl group to the 2',6'-pipecoloxylidide (**5**) with formaldehyde and sodium cyanoborohydride, to generate mepivacaine (**6a**), has been reported in the scientific literature.[4] Furthermore, reductive amination of propanal in the presence of sodium triacetoxyborohydride to generate ropivacaine (**6b**) has been accomplished.[8] The mayor drawbacks of reductive amination protocols based on sodium triacetoxyborohydride or sodium cyanoborohydride are poor atom-economy, cumbersome work-up procedures and formation of high levels of waste material. Catalytic reductive amination with H_2 as reagent is strongly preferred, particularly for large scale reactions. Indeed, generation of mepivacaine and bupivacaine by reductive amination has been demonstrated.[5,9] A reaction of 2',6'-pipecoloxylidide **5** with formaldehyde in the presence of Pd/C (10% catalyst loading) yielded mepivacaine (**6a**) after 3 h under a hydrogen pressure of 3 bar.[5] Similarly, generation of bupivacaine (**6c**) was accomplished on a 2 mmol scale by reductive amination of butanal with stoichiometric amounts of Pd/C (reaction time of 4 h).[9] The corresponding reactions with propanal to produce racemic ropivacaine (**6b**) is, to the best of our knowledge, currently unreported.

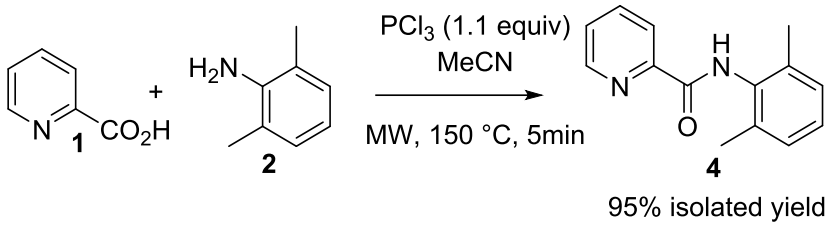
Our goal in this project was to establish a simple, fast and high-yielding lab-scale method for the generation of the racemic amide anaesthetics mepivacaine (**6a**), *rac*-ropivacaine (**6b**) and bupivacaine (**6c**). Herein we disclose the coupling of picolinic acid (**1**) with 2,6-xylidine (**2**) in a sealed vessel microwave reactor in superheated acetonitrile and the subsequent tandem ring-hydrogenation/reductive amination in a high-pressure continuous flow hydrogenator. The combination of both intensified protocols yield the desired products in excellent purity from simple starting materials after an extractive work-up.

Results and Discussion

Amide Coupling: The most common approach for the synthesis of the amide anaesthetics **6a** to **6c** commences with coupling of pipecolic acid (**3**) with 2,6-xylidine (**2**) to form 2',6'-pipecoloxylidide (**5**) (Scheme 1).[3-6] Various coupling procedures are described in the scientific

and patent literature, including reactions with standard coupling reagents such as EDC/HOBt,[4] or reactions with the preformed acid chloride.[6] For instance, WO8500599A1 discloses the synthesis of *L*-2',6'-pipecoloxylidide (*L*-**5**) by condensation of *L*-2-pipecolic acid chloride with 2,6-xylidine (**2**).[6] *L*-2-pipecolic acid chloride, in turn, was generated from *L*-2-pipecolic acid (*L*-**3**) with PCl_5 in acetyl chloride as the solvent. Obvious drawbacks of this route include the requirement for acetyl chloride as solvent and the need to isolate the pipecolic acid chloride hydrochloride intermediate. Furthermore, the use of PCl_5 on large scale is problematic and produces large amounts of phosphate waste.

We chose to first perform the coupling of α-picolinic acid (**1**) with 2,6-xylidine (**3**) before proceeding with selective hydrogenation of the pyridine ring and final alkylation (Scheme 1). Initial attempts to directly couple picolinic acid (**1**) or ethyl α-picolinate with 2,6-xylidine (**3**) in a microwave reactor at elevated temperatures failed. In contrast, following a standard two-step, one-pot procedure for the coupling, consisting of (i) converting the α-picolinic acid to the corresponding acid chloride with an excess of thionyl chloride ($SOCl_2$) (2 h at reflux temperature), (ii) evaporation of excess of $SOCl_2$ and (iii) final coupling of the acid chloride with 2,6-xylidine (**2**) in dicloromethane as solvent, yielded 70% of the desired product.[10] Even though this procedure afforded the desired product in good purity after simple extraction, the handling of $SOCl_2$ is problematic, and the reaction generates toxic gaseous sulfur dioxide. Thus, with the aim to simplify and intensify the coupling procedure we turned to a microwave-assisted amidation protocol developed by NiKem Research in 2009.[11] This very straightforward protocol involves heating of the aromatic amine and carboxylic acid in the presence of phosphorus trichloride in acetonitrile as solvent. Gratifyingly, sealed vessel microwave heating in superheated acetonitrile as solvent on a 1.6 mmol scale (150 °C, ~6 bar) provided complete conversion in a very clean reaction after a reaction time of 5 min. Only a 10% excess of phosphorus trichloride and a 10% excess of α-picolinic acid (**1**) were used in these reactions. After the reaction the small excess of PCl_3 was immediately quenched with 1 M NaOH and the product was isolated by extraction in 95% isolated yield. Scale-up in a 30 mL microwave vessel yielded 344 mg of 2',6'-picolinoxylidide (**4**) in excellent purity and yields identical to those obtained on small scales (Scheme 2). It should be mentioned that various intensified continuous flow coupling protocols have been developed in recent years.[12] However, even though only small amounts of precipitate were formed with the present protocol, adaption of the protocol to continuous flow processing was not attempted at this stage.

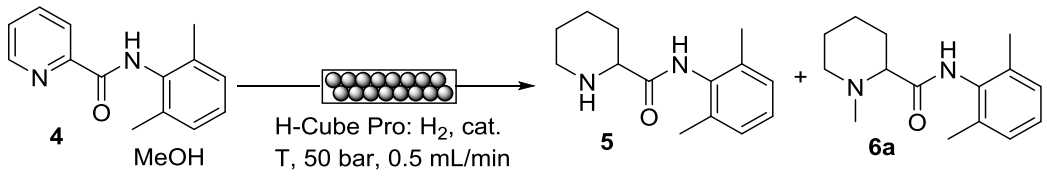


Scheme 2. Amide coupling under sealed vessel microwave conditions.

Selective Hydrogenation: Selective hydrogenation of the pyridine ring of 2',6'-picolinoxylidide (**4**) with H_2 over Raney Nickel as catalyst has been reported by chemists at Pharmathen S.A.[7] After 24 h at a reaction temperature of 90 °C and a hydrogen pressure of ~5 bar, a conversion of 84% was obtained. In addition to the desired product (73%) the methylated analogue was also formed (8%) when MeOH was used as the solvent.[7] We performed the hydrogenation reactions using a continuous flow high pressure hydrogenator (H-Cube Pro™).[13,14] The reactor generates H_2 *in-situ* by electrolysis of water, eliminating the need to store and handle the flammable gas. Hydrogenation occurs in a 70 mm long catalyst cartridge filled with metal catalysts immobilized on a solid support (column volume of about 0.8 mL).[13] High-pressure hydrogenation in continuous flow fixed-bed reactors has attained considerable attention in recent years.[14] Since the catalyst is immobilized in the reactor bed, no catalyst separation is required. Furthermore, the very large interfacial areas and short diffusion paths in the flow reactor ensure a particularly effective contact between the gas, liquid and solid. Extraordinarily high catalyst-to-substrate ratios, and correspondingly short reaction times, can be realized since the substrate flows continuously through the catalyst bed.[14] Using 10% palladium on charcoal (Pd/C) as catalyst and MeOH as solvent allowed complete reduction of the starting material after a single pass through the cartridge at a reaction temperature of 50 °C. As described by Pharmathen S.A. for the reduction of 2',6'-picolinoxylidide (**4**) over Raney Nickel, methylation of the freshly formed piperidine ring to produce mepivacaine was observed to a certain extend (for selected results see Table 1; for further results see Table S1 in the Supporting Information).[7] This side-product is probably formed by a palladium catalyzed dehydrogenation of MeOH and a subsequent palladium catalyzed reductive amination of the generated formaldehyde with 2',6'-pipecoloxylidide (**5**). This reaction amounts to a direct methylation of 2',6'-pipecoloxylidide (**5**) with MeOH as reagent and with water as the only stoichiometric by-product. Unfortunately, attempts to drive the reaction to higher conversion for mepivacaine were mostly fruitless (Table 1 and Table S1 in the Supporting Information). Full hydrogenation of the pyridine ring was observed in all cases.[15] Methylation of the intermediate 2',6'-pipecoloxylidide (**5**) to generate mepivacaine (**6a**) generally increased with

increasing temperature and decreasing flow rate (Table 1 and Table S1 in the Supporting Information). However, even at a reaction temperature of 110 °C only 37% of mepivacaine (**6a**) was formed. Complete reduction of both aromatic rings was not observed under these conditions (HPLC-UV/VIS and HPLC-MS analysis).

Table 1. Hydrogenation of pyridine **4** in MeOH at different temperatures.[a]



	temperature (°C)	conversion (%)[b]	**5** (%)[c]	mepivacaine (**6a**) (%)[c]
1	70	100	77	23
2	80	100	77	23
3	110	100	63	37

[a] Conditions: 0.01 M solution of 2',6'-picolinoxylidide (**4**) in MeOH; H-Cube Pro™: 10% Pd/C, 0.5 mL/min, 50 bar H_2. [b] Conversion of 2',6'-picolinoxylidide (**4**). [c] Selectivity for mepivacaine (**6a**) and 2',6'-pipecoloxylidide (**5**). HPLC peak area integration at 190 nm.

Hydrogenation with Concomitant Reductive Amination: Generation of mepivacaine by catalytic reductive amination with H_2 as the reducing agent would offer significant advantages compared to other alkylation protocols. Reductive amination is extensively used for the generation of simple amines on commodity scale.[16] Reactions with secondary amines are generally more challenging. Nevertheless, reductive amination is increasingly employed also for the production of complex pharmaceutical targets, and the advantages of continuous flow processing to accomplish this transformation are well documented.[17-20] An early pioneering study was the hydrogenation of preformed imines over Pd/C in a continuous flow high pressure hydrogenator (H-Cube™) by Ley and co-workers.[17] The application of a continuous flow fixed-bed high pressure hydrogenator for reductive amination during API synthesis has been demonstrated by chemists from Genzyme Corporation,[18] and chemists from Janssen Research & Development.[19] Researchers of Eli Lilly and Company, on the other hand, recently employed a homogeneous iridium catalyst for a continuous flow reductive amination on a multi ton scale.[20] In view of the available literature, we decided to further explore the possibility to accomplish selective reduction of the pyridine ring and concomitant reductive amination in one step. For these experiments, 4 equiv of formaldehyde (formaldehyde solution 37 wt. % in H_2O) were added to a solution of 2',6'-picolinoxylidide (**4**) in MeOH and the mixture was then

pumped through the H-Cube Pro™. The first experiments were performed in MeOH as solvent at a temperature of 70 °C and a pressure of 30 bar. Only 2 mL of a 0.1 M solution of 2',6'-picolinoxylidide (**4**) were injected into the reactor. With a flow rate of 1 mL/min, a conversion of 50% with a selectivity of 87% for mepivacaine (**6a**) was obtained. The remainder in the crude reaction mixture were 2',6'-pipecoloxylidide (**5**) (5%) and two unidentified side-products (8% in total). Decreasing the flow rate to 0.5 mL/min increased the conversion to 98% at a selectivity for mepivacaine of 77%. Unfortunately, large amounts of product adsorbed on the catalyst cartridges and extensive washing with MeOH was necessary for a complete recovery. To decrease interaction of the product with the catalyst support, acetic acid was added to the solution as a co-solvent (MeOH/AcOH 3:1). Furthermore, the concentration was reduced to 0.01 M. For the next experiments, 80 mL of the reaction solution were processed through the catalyst cartridge. Every 15 min samples were taken and analyzed by HPLC-UV/VIS to trace the activity of the catalyst. As can be seen in Figure 1, full conversion with perfect selectivity was obtained for the first 45 min. The catalyst activity then decreased rapidly and increasing amounts of starting material were detected. The activity for reductive amination, on the other hand, remained comparatively high so that the generated intermediate pipecoloxylidide (**5**) was mostly converted to mepivacaine (**6a**). Attempts to recover catalyst activity by washing the cartridge with MeOH for 2 h at 70 °C under a H_2 pressure of 50 bar failed. Reactions with THF as solvent yielded only 2% conversion under otherwise identical reaction conditions (THF/AcOH 3:1), while reactions with other heterogeneous catalysts, such as Pd/Al_2O_3, Raney Nickel or PtO_2 resulted in low conversions (Table S2 in the Supporting Information).

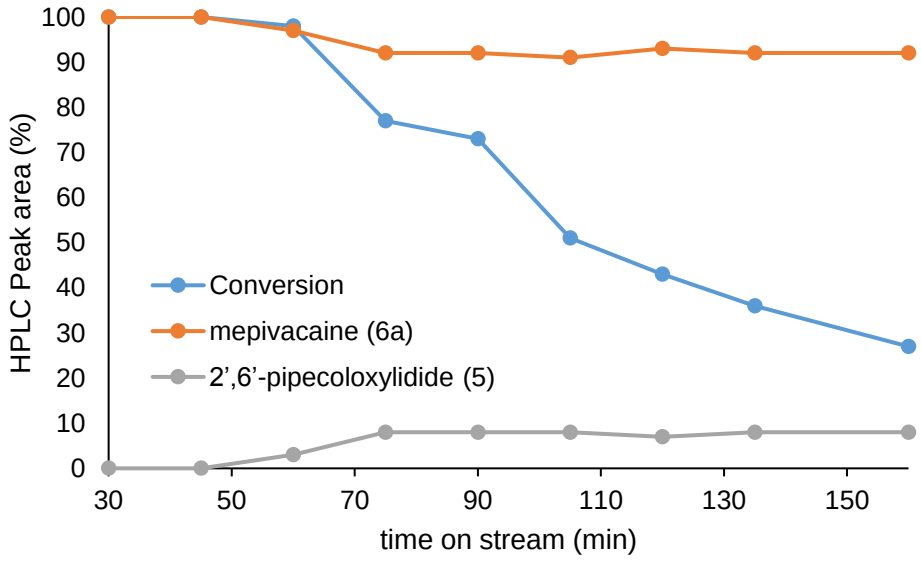


Figure 1. Stability of catalyst. Conditions: 0.01 M solution of 2',6'-picolinoxylidide (**4**) in MeOH/AcOH (3:1) + 4 equiv of formaldehyde (37 wt. % in H_2O); H-Cube Pro™: 10% Pd/C,

70 °C, 30 bar, 0.5 mL/min. Conversion of 2',6'-picolinoxylidide (**4**) and selectivity for **5** and **6a**. HPLC peak area integration at 190 nm.

Decreasing the reaction temperature increased the stability of the catalyst considerably (Figure S1 in the Supporting Information). Indeed, no deterioration in catalyst performance was observed over the explored reaction period (160 min) at temperatures below ca. 40 °C (Figure S1 in the Supporting Information). Full hydrogenation of the pyridine ring was observed at all temperatures. However, the reaction rate for the reductive amination decreased significantly at reduced temperatures (Figure 2). Increasing the amounts of formaldehyde at a reaction temperature of 50 °C did not improve the conversion to mepivacaine (**6a**).

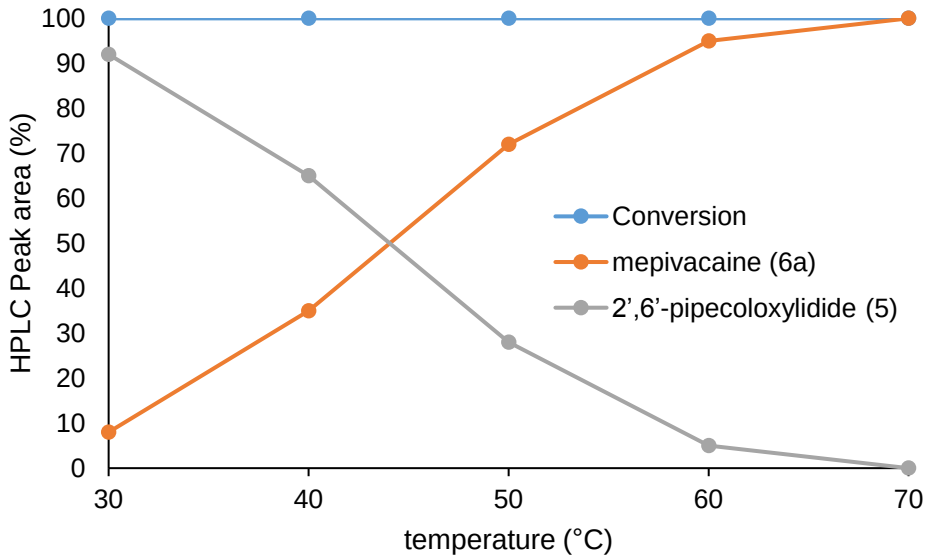


Figure 2. Formation of 2',6'-pipecoloxylidide (**5**) and mepivacaine (**6a**) at different temperatures. Conditions: 0.01 M solution of 2',6'-picolinoxylidide (**4**) in MeOH/AcOH (3:1) + 4 equiv of formaldehyde (37 wt. % in H_2O); H-Cube Pro™: 10% Pd/C, 30 bar, 0.5 mL/min. Conversion of 2',6'-picolinoxylidide (**4**) and selectivity for **5** and **6a**. HPLC peak area integration at 190 nm.

Further optimization revealed that decreasing the amount of AcOH to 1 M at a reaction temperature of 50 °C increased both conversion to mepivacaine (**6a**) and catalyst stability. Ultimately, 80 mL of a 0.01 M solution of 2',6'-picolinoxylidide (**4**) was processed over a period of 160 min to provide mepivacaine (**6a**) with a selectivity of 97%. This amounts to a throughput of 71 mg/h in the H-Cube Pro™ benchtop hydrogenator. After the continuous flow hydrogenation/reductive amination, the solvent was removed in a rotary evaporator and the crude mixture was extracted with ethyl acetate/aq NaOH (1 M) to provide mepivacaine (**6a**) with excellent purity in 83% yield (for spectra see the Supporting Information).

Applying the same conditions, but using either propanal or butanal instead of formaldehyde, generated *rac*-ropivacaine (**6b**) and bupivacaine (**6c**), respectively. No methyl side-product was observed under these conditions. The reaction with propanal to form *rac*-ropivacaine (**6b**) proceeded to 92% selectivity at the first attempt (Figure S2 in the Supporting Information). The corresponding reaction with butanal was slower and produced only around 75% bupivacaine (**6c**) (Figure S3 in the Supporting Information). The remainder consisted of intermediate 2',6'-pipecoloxylidide (**5**) and small amounts of unidentified side-products (typically < 5%). Importantly, in a continuous run for 8 h, processing 240 mL of the reaction solution, a loss of catalytic performance of only 5% was observed (Figure S4 in the Supporting Information). ICPMS analysis of the processed reaction mixture confirmed that leaching of palladium from the catalyst bed does not occur to a significant extend. Merely 5.1 µg of palladium were detected in the processed reaction mixture (Table S3 in the Supporting Information). This amount can be considered insignificant compared to the total amount of palladium contained in the catalyst cartridge (palladium content: ~27.5 mg; leaching: ~0.02%). Upon increasing the amount of propanal to 8 equiv, complete conversion to *rac*-ropivacine (**6a**) in a selectivity of 97% was obtained. For the corresponding reaction with butanal, still 2% of 2',6'-pipecoloxylidide (**5**) could be detected in the crude reaction mixture. Increasing the temperature to 55 °C finally yielded bupivacaine (**6c**) in 95% selectivity (Figure 3). Racemic *rac*-ropivacaine (**6b**) and bupivacaine (**6c**) were isolated as described above in respectively 80 and 89% yield (Figure 4). Coupling of α-picolinic acid (**1**) with aniline under microwave conditions as described above afforded *N*-phenylpicolinamide in 85 % isolated yield. Subsequent ring hydrogenation and reductive aminination with formaldehyde provided the mepivacaine derivative (**6d**) in 76% yield (Figure 4).

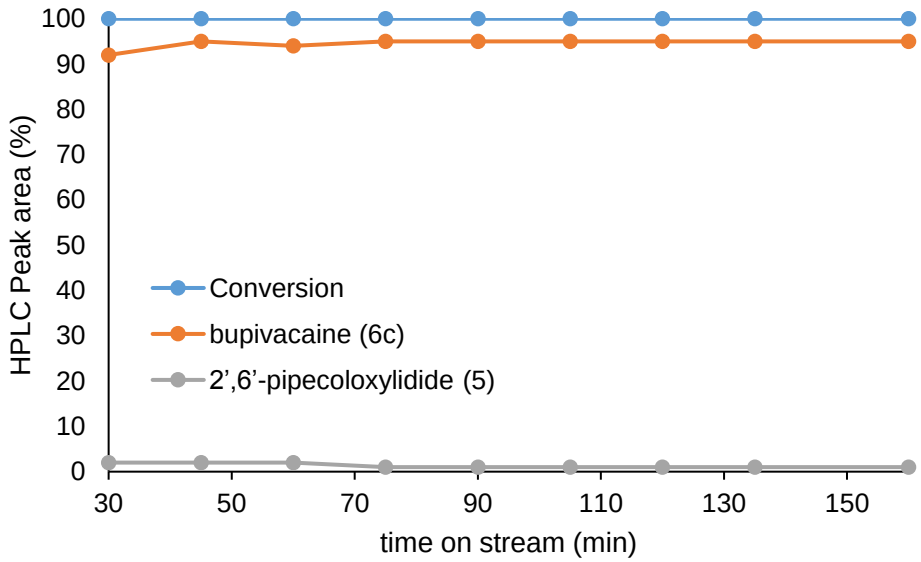


Figure 3. Synthesis of bupivacaine (**6c**) by ring hydrogenation and concomitant reductive amination. Conditions: 0.01 M solution of 2',6'-picolinoxylidide (**4**) in MeOH/AcOH (1 M AcOH) + 8 equiv of butanal; H-Cube Pro™: 10% Pd/C, 55 °C, 30 bar, 0.5 mL/min. Conversion of 2',6'-picolinoxylidide (**4**) and selectivity for **5** and **6c**. HPLC peak area integration at 190 nm.

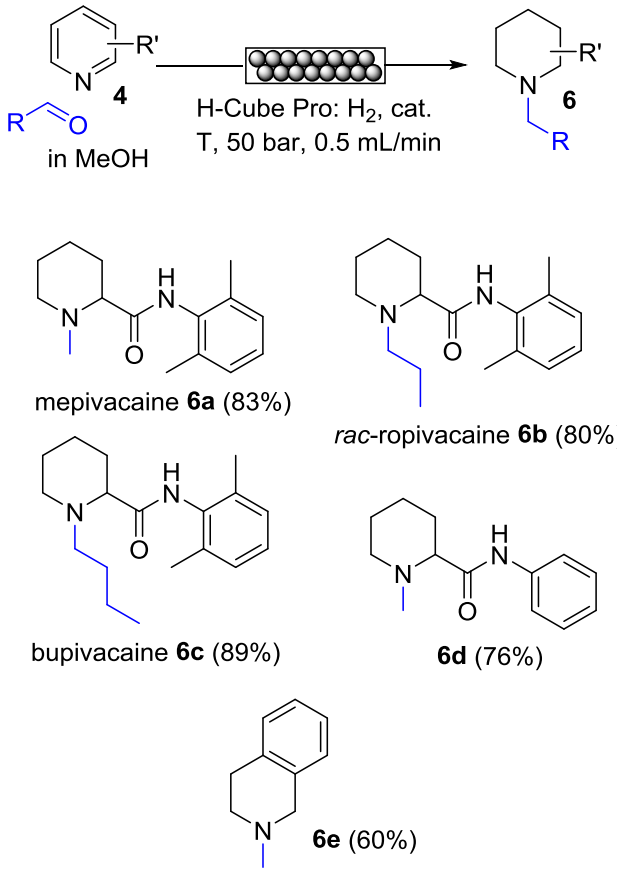
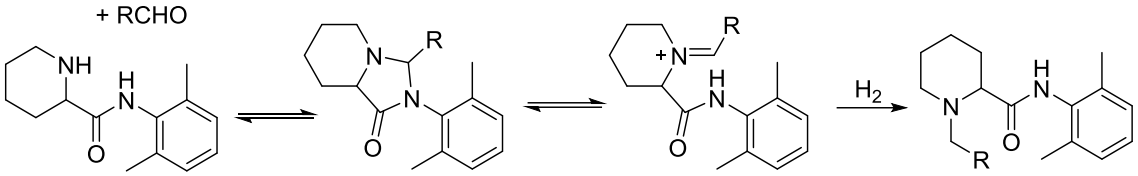


Figure 4. Hydrogenation and concurrent reductive amination. Conditions: 8 equiv aldehyde (**6a**: 4 equiv); 50 °C (**6c**: 55 °C). For details see Experimental Section.

There is experimental evidence for the condensation of 2',6'-pipecoloxylidide (**5**) with aldehydes to form cyclic aminals (Scheme 3).[8] It was previously reported that formation of the cyclic aminal impedes reductive hydrogenation and reduces reaction rates for reductive amination.[8] However, reactions under our reaction conditions suggested that the reductive amination proceeds with essentially the same reaction rate regardless of presence or absence of an amide functionality. For instance, isoquinoline was cleanly converted to *N*-methyl-tetrahydroisoquinoline (**6e**) under our standard reaction conditions using 8 equiv of formaldehyde with the product being isolated in acceptable yield and purity (Figure 4). Reducing the amount of formaldehyde to 4 equiv reduced the reaction rate slightly. It should be mentioned that the *N*-methyl-tetrahydroisoquinoline skeleton is encountered in a number of drugs, including the norepinephrine–dopamine reuptake inhibitors nomifensine and

diclofensine, making the introduced tandem protocol very attractive for future application in continuous API synthesis.



Scheme 3. Mechanism for reductive amination (see ref [8]).

Conclusions

The majority of pharmaceutical ingredients contain nitrogen. It is therefore not surprising that a cross-industry survey by GSK, AZ and Pfizer, analyzing 128 drug candidates with molecular weight below 550, revealed that *N*-acylation and *N*-alkylation are among the most common transformations in API synthesis.[21] Nevertheless, common amidation protocols are atom inefficient and require toxic reagents and chromatographic separation methods. There is a strong need for the development of environmentally more benign amidation procedures. Similarly, even though conventional alkylating agents are still in heavy use for *N*-alkylation, the toxicity and the requirement to reduce residues of these alkylating agents to vanishingly small levels in the final product urges the development of cheap and atom-economic alkylation methods with alternative reagents.

Herein we have described a convenient, fast and high-yielding method for the generation of the racemic amide anaesthetics mepivacaine, *rac*-ropivacaine and bupivacaine. Coupling α-picolinic and 2,6-xylidine in the presence of 1.1 equiv of PCl_3 was completed within 5 minutes at 150 °C under microwave conditions. The coupling product was isolated in excellent purity after a simple extraction procedure. Subsequent selective reduction of the electron-poor pyridine moiety and reductive amination in a benchtop, high-pressure continuous flow hydrogenator over Pd/C as catalyst produces the desired amide anaesthetics in a tandem process. The reaction produces water as the only byproduct, and the final product was isolated in high purity without the need of chromatography.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz instrument. Chemical shifts (δ) are expressed in ppm downfield from TMS as an internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. Analytical HPLC analysis were carried out on a Shimadzu LC20-AD chromatograph equipped with a C18 reversed-phase (RP) analytical column (150 x 4.6mm, particle size 5 μm) at 37 °C

using a mobile phase A (water/acetonitrile 90:10 (v/v) + 0.1% TFA) and B (acetonitrile + 0.1% TFA) at a flow rate of 1.5 mL/min. The following gradient was applied: linear increase from solution 3% B to 25% in 9 minutes, 25% B to 80% in 7 min hold at 80% B for 1 minute. Low resolution mass spectra were obtained on a LC-MS instrument using electrospray ionization (ESI) in positive or negative mode (Shimadzu LCMS-2020). All chemicals, solvents, catalysts, and ligands were obtained from known commercial suppliers and were used without any further purification. Microwave reactions were carried out in a Biotage Initiator+ single-mode microwave instrument. Reaction times refer to hold times at the temperatures indicated, not to total irradiation times. The temperature was measured with an IR sensor on the outside of the reaction vessel.

Experimental Procedure for Amide Coupling under Microwave Conditions: Into a 30 mL microwave vial equipped with a magnetic stir bar were added picolinic acid (221.6 mg, 1.8 mmol) in acetonitrile (20 mL) and, subsequently, 2,6-dimethylaniline (198 µL, 1.6 mmol) and phosphorus trichloride (157 µL, 1.8 mmol). The reaction vial was sealed and the suspension was subjected to microwave heating for 5 min (hold time) at 150 °C. After the reaction time has elapsed, the mixtures were cooled to 50 °C by compressed air. The content of the vial was transferred to a separatory funnel, 1 M sodium hydroxide (25 mL) was added and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The organic layers were combined and dried over magnesium sulfate. After filtration, the solvent was evaporated to afford the product. The product was used without further purification for the continuous flow hydrogenations. For the generation of *N*-phenylpicolinamide, aniline was used as the substrate (1.6 mmol). Otherwise the reaction conditions were the same.

2',6'-Picolinoxylidide (4) mp 102-103 °C (lit.[22] mp 104 °C); Light yellow solid (isolated yield = 95%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.66 (ddd, *J* = 4.8, 1.6, 0.9 Hz, 1H), 8.32 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.93 (td, *J* = 7.7, 1.7 Hz, 1H), 7.51 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.15 (s, 3H), 2.32 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4, 149.8, 148.2, 137.5, 135.4, 133.8, 128.2, 127.2, 126.4, 122.6, 18.6.

Picolinanilide: mp 76 °C (lit.[23] mp 74-75 °C); Light yellow solid (isolated yield = 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.62 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 8.31 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.90 (td, *J* = 7.7, 1.7 Hz, 1H), 7.80 (dt, *J* = 8.8, 1.7 Hz, 2H), 7.48 (ddd, *J* = 7.6, 4.8, 1.2 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.16 (ddd, *J* = 8.5, 2.2, 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 149.8, 148.0, 137.7, 137.7, 129.1, 126.5, 124.3, 122.4, 119.7.

General Experimental Procedure for Hydrogenation with Concomitant Reductive Amination: A mixture of a 0.01 M solution of the substrate in MeOH containing AcOH (100

equiv) and aldehyde (8 equiv; 4 equiv for product **6a**) was pumped through the H-Cube Pro™ flow hydrogenator using 10% Pd/C cartridges. Instrument settings: 30 bar of H_2, 50 °C (55 °C for product **6c**) and a flow rate of 0.5 mL/min. The conversion was monitored by HPLC-UV/VIS analysis at 190 nm. After the continuous flow hydrogenation/reductive amination, the solvent was removed in a rotary evaporator and the crude mixture was extracted with ethyl acetate/aq NaOH (1 M) to yield the desired products with excellent purity.

N-(2, 6-Dimethylphenyl)-1-methylpiperidine-2-carboxamide (Mepivacaine 6a): mp 153-154 °C (lit.[24] mp 149-151 °C); Colorless prisms (isolated yield = 83%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.17 – 7.08 (m, 3H), 3.09 – 2.99 (m, 1H), 2.68 (dd, *J* = 11.3, 3.4 Hz, 1H), 2.44 (s, 3H), 2.27 (s, 6H), 2.20 – 2.11 (m, 2H), 1.83 – 1.56 (m, 4H), 1.36 – 1.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 135.2, 133.5, 128.3, 127.0, 70.2, 55.6, 45.4, 31.5, 25.5, 23.4, 18.9.

N-(2,6-Dimethylphenyl)-1-propylpiperidine-2-carboxamide (rac-Ropivacaine 6b): mp 118-119 °C (lit.[25] mp 121 °C); White solid (isolated yield = 80%); ^{1}H NMR (300 MHz, DMSO) δ 9.08 (s, 1H), 7.06 (s, 3H), 3.11 (dt, *J* = 11.1, 3.6 Hz, 1H), 2.86 (dd, *J* = 9.6, 3.4 Hz, 1H), 2.60 (ddd, *J* = 12.3, 10.4, 6.1 Hz, 1H), 2.14 (s, 6H), 2.02 (td, *J* = 11.0, 3.1 Hz, 1H), 1.93 – 1.78 (m, 1H), 1.72 (dd, *J* = 9.7, 7.0 Hz, 2H), 1.62 – 1.45 (m, 4H), 1.26 (d, *J* = 8.4 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 172.4, 135.8, 135.6, 128.1, 126.8, 68.1, 58.6, 51.6, 30.6, 25.4, 23.6, 19.7, 18.6, 18.6, 12.2.

1-Butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide (Bupivacaine 6c): mp 104-105 °C (lit.[25] mp 107-108 °C); White solid (isolated yield = 89%); ^{1}H NMR (300 MHz, DMSO) δ 9.09 (s, 1H), 7.06 (s, 3H), 3.11 (dt, *J* = 7.2, 3.4 Hz, 1H), 2.86 (dd, *J* = 9.5, 3.3 Hz, 1H), 2.65 (ddd, *J* = 12.2, 10.0, 6.4 Hz, 1H), 2.21 (ddd, *J* = 17.6, 10.0, 5.9 Hz, 1H), 2.14 (s, 6H), 2.00 (tt, *J* = 16.2, 8.0 Hz, 1H), 1.90 – 1.57 (m, 4H), 1.57 – 1.39 (m, 3H), 1.38 – 1.19 (m, 3H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO) δ 172.3, 135.8, 135.6, 128.1, 126.8, 68.0, 56.4, 51.5, 30.7, 28.8, 25.4, 23.6, 20.7, 18.6, 14.5.

1-Methyl-N-phenylpiperidine-2-carboxamide (6d): Light yellow oil (isolated yield = 76%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.63 – 7.57 (m, 2H), 7.37 – 7.30 (m, 2H), 7.10 (ddd, *J* = 8.5, 2.2, 1.1 Hz, 1H), 3.03 – 2.94 (m, 1H), 2.60 (dd, *J* = 11.2, 3.5 Hz, 1H), 2.29 (s, 3H), 2.18 – 2.02 (m, 2H), 1.85 – 1.66 (m, 2H), 1.65 – 1.45 (m, 2H), 1.33 – 1.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 138.0, 129.0, 123.9, 119.4, 70.2, 55.2, 44.9, 30.7, 25.2, 23.3.

2-Methyl-1,2,3,4-tetrahydroisoquinoline (6e): Colorless oil (isolated yield = 60%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 – 7.02 (m, 3H), 6.97 – 6.91 (m, 1H), 3.50 (d, *J* = 5.6 Hz, 2H), 2.88 –

2.81 (m, 2H), 2.66 – 2.56 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7, 133.8, 128.6, 126.4, 126.1, 125.6, 58.0, 52.9, 46.1, 29.2.

Acknowledgements

We thank ThalesNano Inc. for technical support and for providing CatCart® catalyst cartridges. C.O.K acknowledges the Science without Borders program (CNPq, CAPES) for a "Special Visiting Researcher" fellowship. We thank Prof. W. Goessler (University of Graz) for performing ICPMS analysis. N.S.S. thanks CAPES for a scholarship (PGCI 99999.000307/2016-05).

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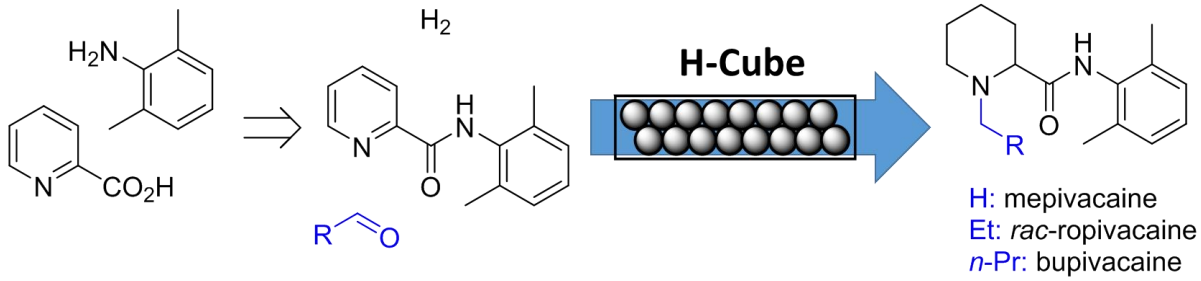
TOC Graphic



Key Topic: Amide Anaesthetics

A tandem, multi-step hydrogenation/reductive amination in a benchtop, continuous flow hydrogenator affords local amide anaesthetics, such as mepivacaine, *rac*-ropivacaine and bupivacaine, in good yields.

Keywords: mepivacaine; ropivacaine; bupivacaine; local anesthetics; reductive hydrogenation; flow chemistry; process integration