E-ISSN: 2664-6773
P-ISSN: 2664-6765
Impact Factor: RJIF 5.6
IJCBS 2024; 6(1): 38-42
www.chemicaljournal.org
Received: 08-12-2023
Accepted: 12-01-2024

Lokesh Ravilla
Anugraha Chemicals, Bangalore, Karnataka, India

Parimala Hanumesh
Adichunchanagiri Institute for Molecular Medicine, Adichunchanagiri Institute of Medical Science, Adichunchanagiri University, BG Nagara, Karnataka, India

Thammanna Gowda SS,
Adichunchanagiri Institute for Molecular Medicine, Adichunchanagiri Institute of Medical Science, Adichunchanagiri University, BG Nagara, Karnataka, India

Manjunath V Shinnur
MS Ramaiah Institute of Technology, Bangalore, Karnataka, India

Ajay Prabu B
MS Ramaiah Institute of Technology, Bangalore, Karnataka, India

Jayapraksh G
MS Ramaiah Institute of Technology, Bangalore, Karnataka, India

Sourabh SH
MS Ramaiah Institute of Technology, Bangalore, Karnataka, India

Shobith Rangappa
Adichunchanagiri Institute for Molecular Medicine, Adichunchanagiri Institute of Medical Science, Adichunchanagiri University, BG Nagara, Karnataka, India

Corresponding Author:
Parimala Hanumesh
Adichunchanagiri Institute for Molecular Medicine, Adichunchanagiri Institute of Medical Science, Adichunchanagiri University, BG Nagara, Karnataka, India

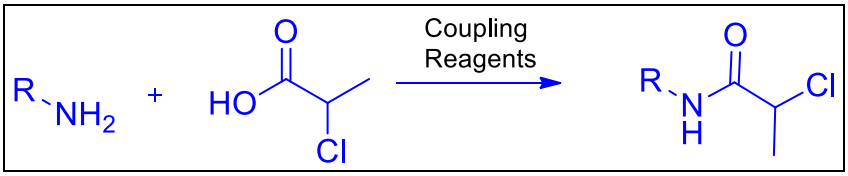
Efficient method for the synthesis of prilocaine precursor amide using 2-chloropropanoic acid by skipping the use of thionyl chloride

Lokesh Ravilla, Parimala Hanumesh, Thammanna Gowda SS, Manjunath V Shinnur, Ajay Prabu B, Jayapraksh G, Sourabh SH and Shobith Rangappa

DOI: https://doi.org/10.33545/26646765.2024.v6.i1a.78

Abstract
A streamlined approach for generating a precursor for prilocaine is presented. Revisiting the conversion of 2-chloropropanoic acid to 2-chloropanoyl chloride using thionyl chloride, the synthesis of the prilocaine derivative precursor has been explored using various coupling reagents and reaction conditions to improve yield. Optimal results were attained by utilizing 1.5 equivalents of HATU as the coupling reagent, in conjunction with 2 equivalents of 2-chloropropanoic acid, at a temperature of 35 °C. The synthesis of prilocaine amide required 14 hours under these conditions.

Graphical Abstract



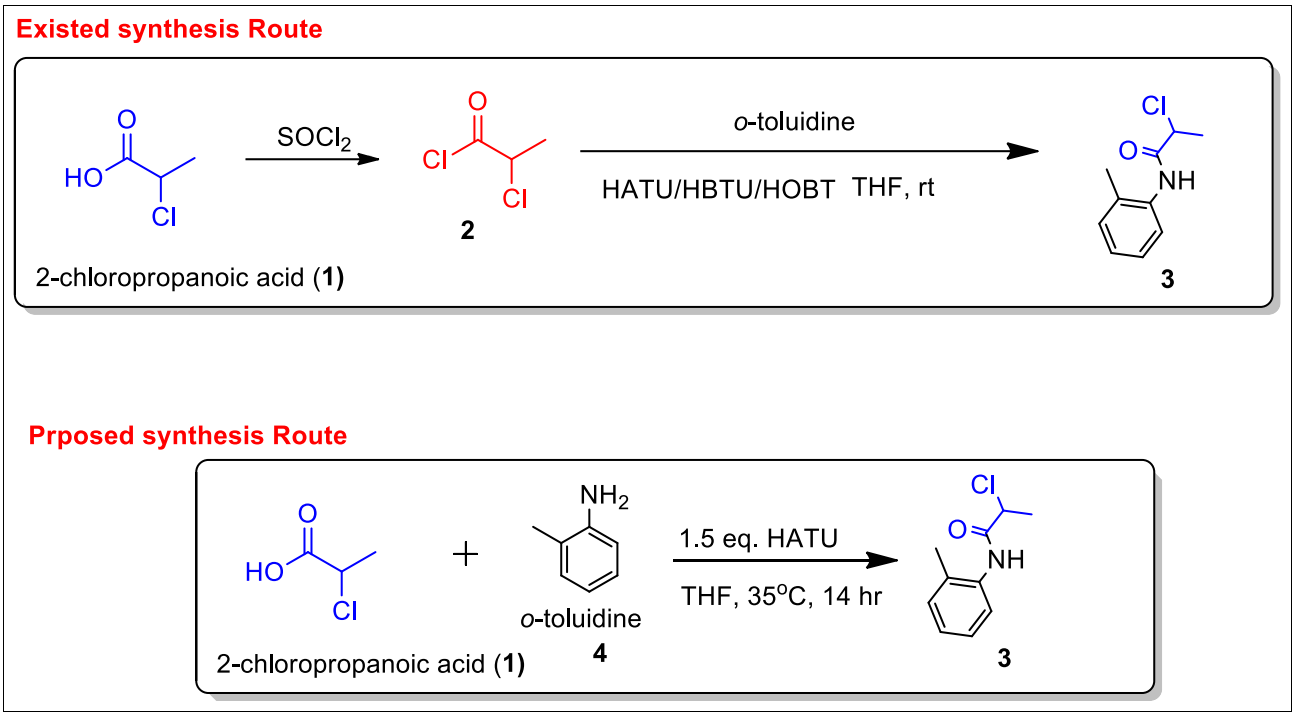
Keywords: Amides, prilocaine, coupling reagents, 2-chloropropanoic acid, thionyl chloride

Introduction

Despite advancements in dentistry, dental procedure-related pain remains a significant source of fear and anxiety for patients, regardless of gender or age. While various local anesthetics are available, dental practitioners seek agents that are both highly effective and pose minimal toxicity risks to patients [1]. Many local anesthetics are vasodilators, leading to increased absorption and shorter duration of action. To tackle these challenges, dental practitioners are increasingly turning to articaine and prilocaine amides as local anesthetic agents [2].

Prilocaine, categorized as an aminoamide and known as the weakest potent vasodilator among local anesthetics, exerts therapeutic effects on the nervous system. Its mechanism involves stabilizing neuronal membranes by preferential binding and inhibiting sodium channel activity [3, 4]. The rapid tissue uptake by plasma and efficient metabolism make prilocaine an optimal anesthetic agent, particularly in dentistry [5]. Prilocaine, primarily used for maxillary infiltration or nerve block anesthesia, proves valuable for patients who cannot tolerate local anesthetics containing adrenaline [5, 6]. Administration methods include subcutaneous (fast-acting, 1-2 hours duration), intravenous (fast-acting, 0.5-1 hour duration), peripheral block (fast-acting, 0.5-3 hours duration), and epidural (fast-acting, 1-3 hours duration) [7, 8, 14].

Prilocaine metabolism occurs in two stages, first in the lungs and then in the kidneys, resulting in metabolite production [9, 13]. Therefore, synthesizing local anesthetic molecules is vital in dentistry. The conventional synthesis route (General Scheme 1) involves thionyl chloride [10]. However, in this study, we aim to revisit the synthesis of prilocaine anesthetic amides using various coupling agents to optimize reaction conditions, increase yield percentage, and reduce costs by eliminating the use of thionyl chloride, which poses hazards to human health [11, 12]. This method holds promise for process development in synthesizing industrial-scale prilocaine amides, contributing to environmental preservation by avoiding thionyl group compounds.



General Scheme 1: Existed and proposed route of prilocaine synthesis

Material and Methods

Chemicals used in the synthesis of amides are 2-chloropropionic acid from Merck, 2-chloropropionyl chloride from Alfaeasar, and O-toluidineandmethyl 3-amino-4-methylthiophene-2-carboxylate from Alfraeasar. Propyl amine, Solvents, different coupling reagents and TLC plates are obtained from Merck.

Instruments used-Rotavaporator from Heidolph, Melting point apparatus from Campbell Electronics, UV chamber for thin layered chromatography from Metro electronics labs were utilized.

Synthesis of 2-chloro-N-(o-tolyl)propanamide

In a 150 mL three neck RB flask equipped with overhead stirrer, 15mL of DMF was taken and added 2-chloropropanoic acid (0.39g, 3.6mmol) methyl 3-amino-4-methylthiophene-2-carboxylate (0.25g, 1.46mmol), HATU (0.832g, 2.18mmol). The contents were stirred for 5 minutes. After clear solution formation DIPEA (0.472, 3.6mmol) was added [18]. The reaction was conducted initially at 0-5 °C and after addition of all ingredients increased to particular temperature to optimize the reaction time and temperature [11, 12]. After completion, the reaction was confirmed by TLC, arrested reaction by adding 50mL of ethyl acetate. The reaction mixture was subjected to concentrate to remove the THF before taking the reaction mass to extraction. The product which is dissolved in ethyl acetate was extracted with demineralized water (100mL) followed with 5% sodium bicarbonate and 1% HCl solution wash. The ethyl acetate layer was dried over anhydrous sodium sulfate and distilled off the volatiles under reduced pressure to get the crude product. This crude material was subjected to purification using silica. The pure material thus obtained yielded 0.42g and 91.80% yield of the product of desired purity,^{1}HNMR (500 MHz, CDCL3) δ ppm: 1.86 (3H, d, J1=7.1Hz), 2.30 (3H, s), 4.6 (1H, q), 7.11 (1H, t, J1=7.5), 7.22 (2H, t, J=8.7), 7.88 (1H, d, J=7.9), 8.26 (1H, s), Mass m/z: 198.62 (M+1), Melting point 115±5 ^{0}C.

Results and Discussion

The conventional method for synthesizing Prilocaine amides (3) typically entails a two-step process using thionyl chloride. However, the widespread industrial application of thionyl chloride may escalate health and environmental risks. Therefore, we propose a cost-effective single-step synthesis approach (General Scheme 1) for producing Prilocaine amides with enhanced yields. In this investigation, we fine-tuned coupling agents [17, 18], equivalence ratios, temperature, and reaction time to improve efficiency while mitigating potential risks.

Yield percentage of amides

The synthesis of prilocaine amide in a single step, utilizing 2-chloropropanoic acid (1) while avoiding the use of thionyl chloride, was explored. To select the most suitable coupling reagents, various options were studied, including combinations of two coupling reagents such as Hydroxybenzotriazole (HOBt) with dicyclohexylcarbodiimide (DCC), HOBt with ethyl (dimethylaminopropyl) carbodiimide (EDC), Hexafluorophosphate Benzotriazole Tetramethyl Uronium (HBTU), TBTU, and Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium (HATU). Surprisingly, HATU yielded a higher percentage of 90.30% compared to other coupling reagents (Table 1). The intermediate amide underwent column purification using a mixture of 4% ethyl acetate and hexanes. Further optimization studies, including determination of equivalence ratios, reaction temperature, and reaction time, were conducted to confirm the economic feasibility of using HATU.

Optimization of equivalence

Multiple batch reactions were conducted with different equivalence of 2-chloropropanoic acid with respect to the moles of amine added in the reaction for synthesis of prilocaine amide. Different equivalent assumed with respect to amine are the ratios of 1:1.2, 1:1.5 and 1:2 and 1:2.5.

The Fig.1 states that, as we increases the equivalence of amine, the percentage of reaction completion is also increasing but at 2.5 completion reactions was not showing any effect compared to 1:2 and stays plateau. Therefore we have opted 1:2 as the best equivalence with respect to good yield of amide. The reaction completion was monitored using TLC.

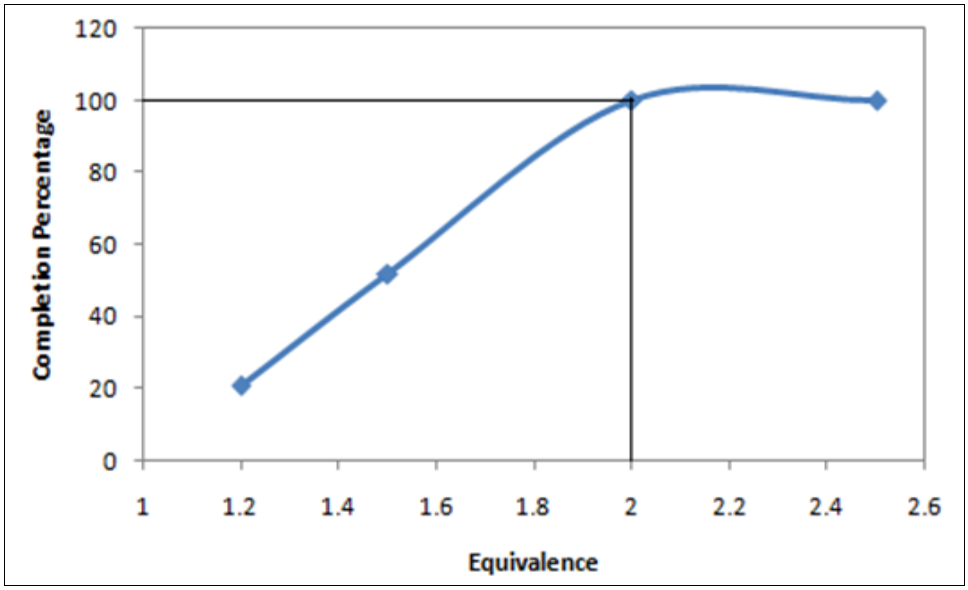


Fig 1: Graph of yield percentage v/s Equivalence for Prilocaine amide

Optimization of reaction temperature

Various reaction temperatures were studied to optimize the percentage yield with minimal impurities in the synthesis of prilocaine. The reactions were conducted at different temperatures while keeping other parameters constant. The percentage yield at different temperatures is depicted in Fig. 2. As the reaction temperature increased from 25 °C to 35 °C, the percentage yield rose from 90% to 92%. However, further elevation in temperature led to a decrease in yield. At 35 °C, the maximum yield was observed, and the resulting products were free from impurities. Conversely, at the other two temperatures, an increase in impurity formation was noted with the rise in reaction temperature during the synthesis of prilocaine amide. The completion of the reaction was monitored using TLC.

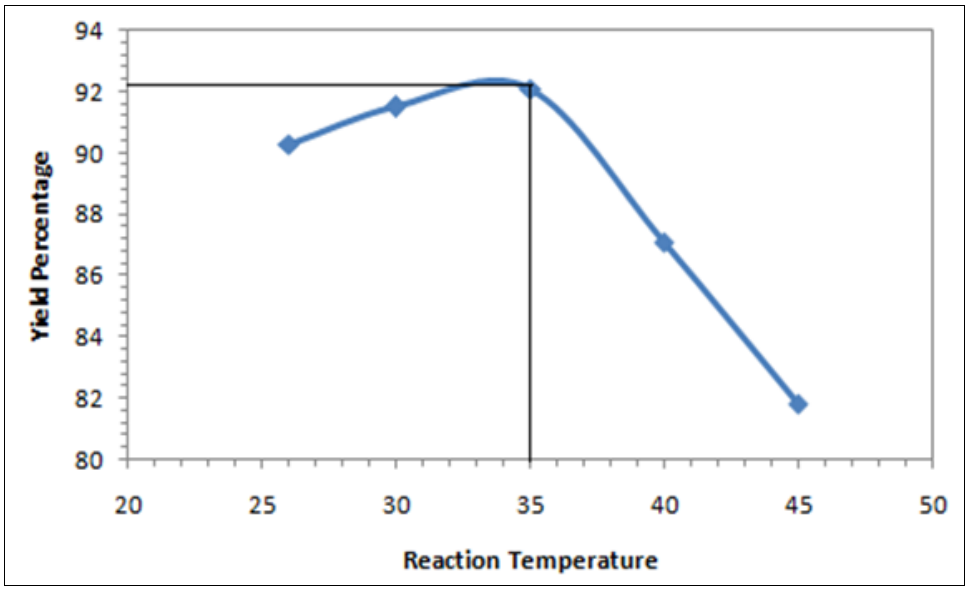


Fig 2: Graph of yield percentage v/s reaction temperature (ºC) for Prilocaine amide

Optimization of reaction time

The reaction time was fine-tuned to achieve maximum conversion of reactants to prilocaine amide. Various reaction times ranging from 1 to 28 hours were studied to optimize the reaction completion. It was found that 14 hours resulted in complete conversion to prilocaine amide, with the product being free from impurities. As shown in Fig. 3, increasing or decreasing the reaction time inhibited product conversion and led to the observation of impurities in both amides. The progress of the reaction was monitored using TLC.

Table 1: Coupling of 2-chloropropanoic acid with o-toluidine

Entry	Reagents(equiv.)	Solvent	Temp(°C)	Time (hrs)	Yield (%)
1	HOBT (1.3), DCC(1.6), Et3N(4.26)	THF	35	14	28.30
2	HOBT (1.5), EDC(1.5), Et3N (2.5)	THF	35	14	67.21
3	HBTU (1.5), DIPEA (2.5)	DMF	35	14	65.05
4	TBTU (1.5), DIPEA (2.5)	DMF	35	14	80.24
5	HATU (1.5), DIPEA (2.5)	DMF	35	14	90.30

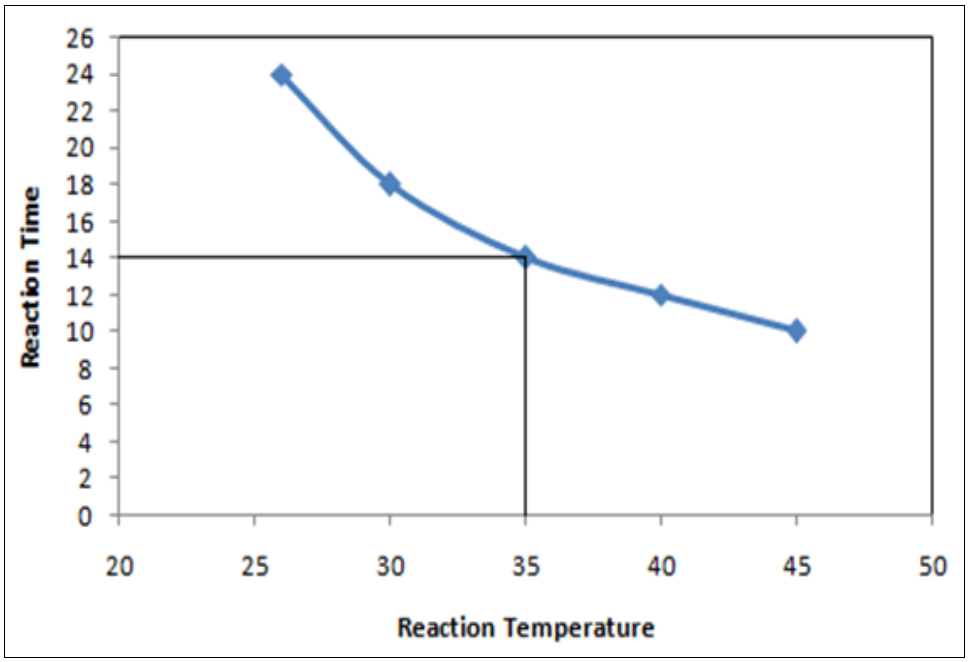


Fig 3: Graph of reaction time (hr) v/s reaction temperature (°C) for Prilocaine amide

Conclusion

In brief, this research addresses the synthesis of 2-chloro-N-(o-tolyl) propanamide for prilocaine production in industries, addressing issues of low yield and lengthy reaction times. In the present study, amides for prilocaine were synthesized using various coupling reagents, including HOBT, DCC, EDC, HBTU, TBTU, and HATU, which are non-hazardous and easy to handle. Notably, employing HATU (entry 5, table 1) yielded a high percentage (90.3%) of prilocaine amide. To render the process suitable for industrial-scale production, parameters such as equivalence, reaction time, and temperature were optimized. Characterization of the synthesized amide product via NMR analysis, Mass, and melting point determination yielded optimized values: equivalence ratio of 1:2, reaction time of 14 hours, and an optimum reaction temperature of 35°C (table 1). This method's applicability extends to industries, with potential for procaine amide production as a prilocaine intermediate. Ongoing research includes impurity characterization and addressing challenges encountered during industrial-scale production.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests.

Acknowledgments: We thank Anugraha chemicals, who helped in analysis and synthesis.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abbreviations

Hydroxybenzotriazole (HOBt), dicyclohexylcarbodiimide (DCC), ethyl (dimethylaminopropyl) carbodiimide (EDC), Hexafluorophosphate Benzotriazole Tetramethyl Uronium (HBTU), Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium (HATU). Dimethyl Formamide (DMF), Tetrahydrofuran (THF), Ethyl acetate (EtoAc).

Reference

1. Katari NK, Jonnalagadda SB. Treatments, Mechanisms, and Adverse Reactions of Anaesthetics and Analgesics. In: Prilocaine: Mechanisms and application. Science Direct, Academic Press; c2022. p. 151-164.
2. Haas DA, Harper DG, Saso MA, Young ER. Comparison of articaine and prilocaine anesthesia by infiltration in maxillary and mandibular arches. Anesth Prog. 1990 Sep-Oct;37(5):230-7.
PMID: 2096746; PMCID: PMC2148603.
3. Suzuki S. Local Anesthetics. In: Pharmacology and Physiology for Anesthesia. Elsevier; c2019. p. 390-411. doi:10.1016/B978-0-323-48110-6.00020-X
4. Shafaifard S, Khan RH. The Use of Lidocaine and Prilocaine in Dental Surgery. A Review. Arch Anesth & Crit Care. 2016;2(2):197-199.
5. Jeffcoat MK, Geurs NC, Magnusson I, *et al*. Intra pocket Anesthesia for Scaling and Root Planning: Results of a Double-Blind Multicenter Trial Using Lidocaine Prilocaine Dental Gel. J Periodontol. 2001;72:895-900. https://doi.org/10.1902/jop.2001.72.7.895
6. Deupree J. Pharma: The Comprehensive Pharmacology Reference. Elsevier; c2007.
DOI: doi.org/10.1016/B978-008055232-3.62457-2
7. Gazal G. Is prilocaine safe and potent enough for use in the oral surgery of medically compromised patients. Saudi Med J. 2019 Jan;40(1):97-100. PMID: 30617388; DOI: 10.15537/smj.2019.01.23475. PMCID: PMC6452603.
8. Tran AN, Koo JY. Risk of systemic toxicity with topical lidocaine/prilocaine: A review. J Drugs Dermatol. 2014 Sep;13(9):1118-1122. PMID: 25226014.
9. Salonen M, Forssell H, Scheinin M. Local dental anaesthesia with prilocaine and articaine. Effects on plasma catecholamines, heart rate and blood pressure. Int J Oral Maxillofac Surg. 1988;17:392-394.
10. Hu Y, *et al*. Process for preparation of prilocaine hydrochloride. Faming Zhuanli Shenqing; c2011 Jun 15.
11. Valeur R, Bradley M. Amide formation: beyond the myth of coupling reagents. Chem Soc Rev. 2009;38:606-631.

12. Shen W, *et al*. Preparation method for prilocaine base. Faming Zhuanli Shenqing; c2016 Mar 30.
13. Malamed SF. Local anesthetics: Dentistry's most important drugs, clinical update 2006. J Calif Dent Assoc. 2006 Dec;34(12):971-6.
14. Katyal V. The efficacy and safety of articaine versus prilocaine in dental treatments: A meta-analysis. J Dent. 2010;38:307-317.
15. Prilocaine Hydrochloride (local). The American society of health-system pharmacists. Retrieved Aug 26, 2015.
16. Valeur R, Bradley M. Amide formation: Beyond the myth of coupling reagents. Chem Soc Rev. 2009;38:606-631.
17. Demare P, Regla I. Synthesis of two local anesthetics from Toluene: An organic multistep synthesis in a project-oriented laboratory course. J Chem Educ. 2012;89(1):147-149.