

A GREEN SYNTHETIC PROTOCOL FOR THE PREPARATION OF 2-HYDROXY-N-PHENYLPROPANAMIDE FROM BIOMASS-DERIVED LACTIC ACID WITH ANILINE

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ABSTRACT

We report a green and efficient synthetic protocol for the formation of 2-hydroxy-N-phenylpropanamide (an α -hydroxy amide) from lactic acid derived from biomass and aniline. The reaction occurs under neat, solvent-free and catalyst-free conditions, produces water as the only by-product and gives an isolated yield of 84% at optimised thermal conditions (1:1 molar ratio, 100 °C, 3 h). Microwave irradiation significantly decreases the reaction time to 15 minutes at 150 °C (91% aniline conversion). The protocol was translated from 1 g to 15 g while maintaining strong amide selectivity (>95%) and ensuring >80% conversion of aniline after 24 h. ^1H and ^{13}C NMR fully characterised the product. This method shows that biomass-derived platform chemicals are renewable feedstocks capable of amide bond formation.

Keywords: Lactic Acid, Amide Synthesis, Green Chemistry, Biomass Valorization, Solvent-Free, Microwave Synthesis, A-Hydroxy Amide

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INTRODUCTION

The increasing natural gas prices and a growing concern about greenhouse gas (GHG) emissions have led to an urgent demand for sustainable chemical feedstock. Biomass represents the sole renewable feedstock¹ that can substitute for petroleum and neutralise the CO_2 in the atmosphere, and thus potentially realises large reductions in lifecycle GHG emissions.²⁻⁴ In fact, chemical and biological conversions of biomass-derived carbohydrates result in three major platform chemicals (furans, carboxylic acids, and alcohols). Lactic acid (2-hydroxypropanoic acid) is particularly interesting because its structure provides rich oxygen functionality, such as hydroxyl and carboxylic groups. Fermentable carbohydrates are the direct precursor of lactic acid.⁵⁻⁷ The structural versatility of α -amino acids has many synthetic applications, such as the synthesis of agrochemicals, pharmaceutical intermediates, and biodegradable polymers like polylactic acid.⁶⁻⁹ Lactic acid is currently produced industrially mainly through microbial fermentation, a pathway fraught with the necessity to neutralise to enable bacterial activity and with challenges in product purification and separation.^{10,11} Heterogeneous Lewis-acid catalysts, especially Sn-beta and Sn-MWW zeolites, have been reported as an effective alternative to convert sugars directly to lactic acid and its ester derivatives, to overcome the existing limitations (Fig.-1).¹²⁻¹⁴ Lactic acid is a precursor for many valued industrial chemicals, such as acrylic acid, pyruvic acid, 2,3-pentanedione, 1,2-propanediol and various lactate esters. Self-condensation gives dilactide, which is an important monomer for poly-lactic acid (PLA).¹⁵⁻¹⁷ Lactic acid contains a carboxylic acid functionality; it is also an attractive building block for forming amide bonds with amines. The resultant α -hydroxy amides possess a free hydroxyl group, allowing them to be modified into desired products such as diols, β -amino alcohols, and other useful relevant structures.

EXPERIMENTAL

Materials

Lactic acid (99%) was obtained from Sigma-Aldrich. Aniline (99%) and ethyl acetate (>99%), hexane (99%) were procured from S.D. Fine Chemicals, Mumbai. The chemicals are analytical reagent grade and used as is without further purification. Thin-layer chromatography (TLC) on silica gel 60 F254 plates was used to monitor all reactions.

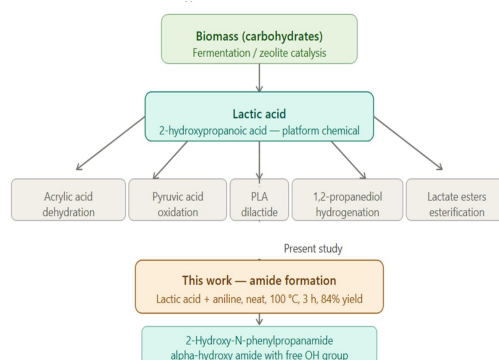


Fig.-1: Production of Lactic Acid from Biomass-Derived Carbohydrates and its Applications

General Reaction Procedure

Lactic acid (1.2 g, 99% purity, ~11.11 mmol) and aniline (1.04 g, 99% purity, 11.11 mmol) were directly mixed in a round-bottom flask under open atmosphere at a molar ratio of 1:1 without using any catalyst or solvent. Heating was performed under thermal conditions (oil bath) according to the temperatures and times given in Table-1. For microwave experiments, the mixture was transferred to a sealed microwave vial and irradiated in a microwave reactor at the specified temperature and power. Reaction progress was monitored by TLC (30% EtOAc/hexane). GC (Shimadzu GC-2010) analysis was used to determine conversion and selectivity.

Product Isolation and Characterisation

The crude mixture of products (Table-1, entry 4) was subjected to column chromatography over silica gel (100–200 mesh) using 30% EtOAc/hexane as eluent to afford 2-hydroxy-N-phenylpropanamide as a light-yellow liquid (isolated yield: 84%). ^1H and ^{13}C NMR spectroscopy was used to characterise the product (Bruker Avance, 500 MHz, CDCl_3).

RESULTS AND DISCUSSION

Optimisation of Reaction Conditions

Lactic acid was condensed with aniline by applying thermal conditions at 100 °C in a 1:1 molar ratio, without using any solvent or catalyst (Table 1). With a kinetic study (Table-1, entries 2–4), we found a gradual increase in aniline conversion (64% to 94%) under prolonged reaction time (e.g., 1 h to 3 h), with the amide selectivity remaining. Column chromatography purification of the 3 h reaction mixture provided access to the desired amide in 84% isolated yield (Table-1, entry 4).

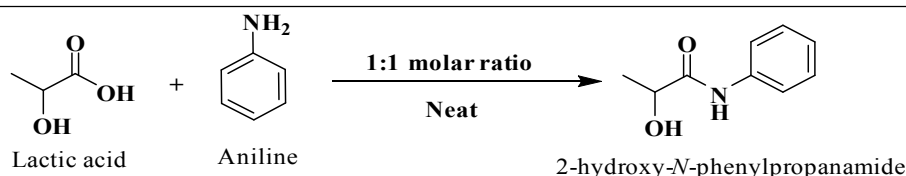


Table-1: Optimisation of Reaction Conditions for Amide Formation from Lactic Acid (1.2 g, 99% purity) with aniline (99% purity) in a 1:1 molar ratio under neat (open atmosphere) Conditions. Conversions determined by GC; *Optimal Conditions; †Isolated Yield After Column Chromatography (30% EtOAc/hexane)

S. No.	Time	Temp (°C)	Heating source	Aniline conv. (%)	Amide sel. (%)
1	1 h	100	Thermal	64	100
2	2 h	100	Thermal	87	100
3*	3 h	100	Thermal	94	100
4†	3 h	100	Thermal	84 (isolated)	100
5	15 min	100	Microwave	80	98-99
6	15 min	50	Microwave	17	98-99
7*	15 min	150	Microwave	91	98-99
8	30 min	100	Microwave	83 (87)	98-99

We then turned our attention toward microwave irradiation to enhance the efficiency of the reaction. An aniline conversion of 80% was achieved at 100 °C for 15 min, which reflects the notable enhancement gained through microwave heating over traditional thermal activation. On increasing the microwave reaction temperature from 50 °C to 150 °C, aniline conversion gradually increased from 17% to 91% in a time scale of minutes (Table-1, entries 5–7), confirming that the rate of this reaction is temperature dependent under microwave heating conditions. Microwave treatment for a longer period of 30 min, on the other hand, did not significantly improve conversion overall but returned to the starting value at 15 min, suggesting under these conditions that a kinetic plateau has been reached.

Product Characterization

The structure of the isolated product (Table-1, entry 4), 2-hydroxy-N-phenylpropanamide, was confirmed by use of both ^1H and ^{13}C NMR spectroscopy (Fig.-3 and Fig.-4). The ^1H NMR spectrum shows the following relevant signal: aromatic protons at δ 7.53 (d, J = 8.5 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H) and also at δ 7.13 (t, J = 7.5 Hz, 1H) characteristic of a monosubstituted phenyl ring; one methine proton at δ 4.32 (m, 1H), adjacent the hydroxyl group; an exchangeable hydroxyl proton at δ 3.98 (s, 1H); and finally a methyl doublet at δ 1.48 (d, 3H). The ^{13}C NMR spectrum confirms the amide carbonyl at δ 172.3 ppm, along with aromatic carbons at δ 135.9 (*ipso*, C-N), 128.0 (*meta*), 123.7 (*para*) and 119.0 (*ortho*) ppm. The carbon attached to C–OH appears at δ 67.7 ppm and the methyl carbon, at δ 20.0 ppm. Comprehensive spectral information is shown in Table-2.

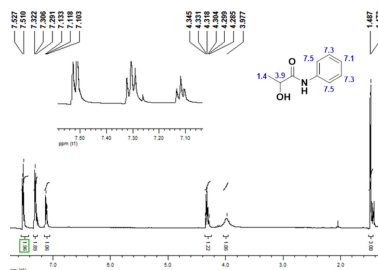


Fig.-2: ^1H NMR of Synthesised 2-hydroxy-N-phenylpropanamide

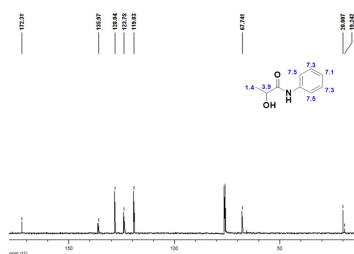


Fig.-3: ^{13}C NMR of Synthesised 2-hydroxy-N-phenylpropanamide

Table-2: Complete ^1H and ^{13}C NMR Spectral Assignments for 2-hydroxy-N-phenylpropanamide (Bruker Avance, 500 MHz, CDCl_3)

Nucleus	δ (ppm)	Multiplicity / J (Hz)	Assignment
^1H	7.53	d, J = 8.5	Aromatic H (ortho, 2H)
^1H	7.32	t, J = 8.0	Aromatic H (meta, 2H)
^1H	7.13	t, J = 7.5	Aromatic H (para, 1H)
^1H	4.32	m	Methine H adjacent to OH (1H)
^1H	3.98	s	Hydroxyl H (1H, exchangeable)
^1H	1.48	d	Methyl H (3H)
^{13}C	172.3	—	Amide carbonyl carbon (C=O)
^{13}C	135.9	—	Ipsso aromatic carbon (C–N)
^{13}C	128.0	—	Meta aromatic carbons
^{13}C	123.7	—	Para aromatic carbon
^{13}C	119.0	—	Ortho aromatic carbons
^{13}C	67.7	—	Methine carbon (C–OH)
^{13}C	20.0	—	Methyl carbon (CH ₃)

Scale-Up Study

The scalability of the optimised amide synthesis protocol was systematically explored, with a total mass of reactants varying from 1 g (laboratory proof-of-concept scale) to 15 g (preparative scale), maintaining identical molar ratios of lactic acid and aniline in a 1:1 ratio under neat, solvent-free, catalyst-free conditions at 100 °C. Aniline conversion was measured at regular intervals of ~4 h over a total reaction period lasting for 24 h by withdrawing small aliquots to analyse by GC chromatography. Under the optimised thermal conditions and on a 1 g scale, aniline conversion of 94% was reached in 3 h at maximum amide selectivity; at 15 g scale, the conversion profile exhibited a broadly similar trend but showed an observable kinetic retardation at early time points attributed mainly to reduced heat transfer efficiency in a larger reaction vessel. Conversion of 38% was observed at the 4 h time point, which steadily increased to 57% (8 h), progressed to 68% (12 h), continued to increase to 76% (16 h) and reached a plateau of about ~80% by 24 h, with amide selectivity consistently greater than >95 % throughout the entire reaction course (Fig.-4). A plateau is observed at ~80% conversion in the 15 g scale reaction rather than attaining 94% at 1 g, which reflects a well-documented side effect of scaling an experiment into greater volume vessels, where a reduced surface-area-to-volume ratio limits the efficiency of conductive heat transfer from the oil bath to the core of the reaction mixture. Finally, at larger scale, the viscosity of the neat reaction mixture increases with reaction progression, thus further retarding convective mass transfer between acid and amine reactants. These elements are inherent to conventional batch thermal processing and do not correspond to any intrinsic limitation of the chemistry itself. Importantly, the amide selectivity remained at >95% across all time points and at both scales, confirming that scale-up does not introduce competing side reactions or lactic acid oligomerisation, which are known to occur under prolonged heating of lactic acid in the presence of trace water. From a green chemistry perspective, this scale-up was achieved without change to the reaction protocol; neither solvent nor co-solvent nor catalyst. This is a notable improvement compared to many existing literature routes for amide synthesis that require very large volumes of solvent to ensure homogeneity at larger scales. Reactor engineering strategies to address the heat transfer limitation indicated at 15 g scale will be explored in future work. In particular, continuous flow reactor designs such as the tubular microreactors employed herein with increased surface-area-to-volume ratios should replace the faster kinetics observed at small scale while preserving the solvent-free and catalyst-free nature of this protocol. It is hypothesised that, with design improvements such as heat exchange jackets adapted from mechanical agitation batch reactor technology, production and research using mechanically agitated batch reactors will allow for hectogram- to kilogram-scale manufacturing in the nearer term.

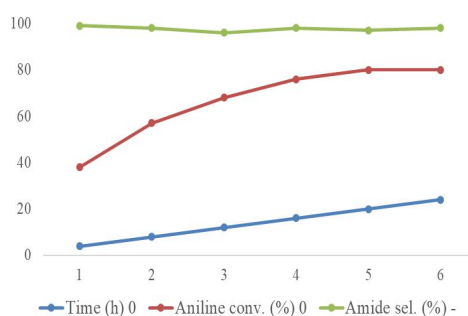


Fig.-4: Reaction Progress in Synthesis of 2-hydroxy-N-phenylpropanamide at 15 g Scale

CONCLUSION

Herein, we develop and optimise a green, solvent-free and catalyst-free protocol for the synthesis of 2-hydroxy-N-phenylpropanamide from biomass-derived lactic acid and aniline. Under optimal thermal conditions (1:1 molar ratio, 100 °C for 3 h), the isolated yield of 2-hydroxy-N-phenylpropanamide was obtained in a total of 84% with complete selectivity (100 %). Under microwave irradiation, the reaction rate was greatly accelerated: at 150 °C, 91% aniline conversion was achieved within 15 min, and the reaction could be scaled from gram to decagram scale (1 g-15 g) with 80% conversion and high amide selectivity retained.

Reaction Highlights

Good atom economy (~93%); water is the only waste product
 Open-atmosphere reaction conditions under mild conditions
 Short reaction time (3 h thermal; 15 min microwave)
 Solvent-free and catalyst-free synthesis
 Easily scalable from 1 g to 15 g while maintaining selectivity

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

The present work is related to *SDG-9: Industry, Innovation, and Infrastructure*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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REFERENCES

1. S. Gundekari, K. Srinivasan, *ChemCatChem*, **11**(3), 1102(2019), <https://doi.org/10.1002/cctc.201801782>
2. R. Kajaste, *Journal of Cleaner Production*, **75**, 1(2014), <https://doi.org/10.1016/j.jclepro.2014.03.070>
3. Y. Kikuchi, N. Torizaki, L. Tähkämö, A. Enström, S. Kuusisto, *Process Safety and Environmental Protection*, **166**, 693(2022), <https://doi.org/10.1016/j.psep.2022.08.054>
4. S. Gundekari, R. Kalusulingam, B. Dakhara, M. Mani, J. Mitra, K. Srinivasan, *Catalysis for Clean Energy and Environmental Sustainability: Biomass Conversion and Green Chemistry*, Volume 1, in: K. K. Pant, S. K. Gupta, E. Ahmad (eds), *Catalysis for Clean Energy and Environmental Sustainability*, pp. 291-343(2021), https://doi.org/10.1007/978-3-030-65017-9_11
5. J. Iglesias, I. Martínez-Salazar, P. Maireles-Torres, D. Martín Alonso, R. Mariscal, M. López Granados, *Chemical Society Reviews*, **49**(16), 5704(2020), <https://doi.org/10.1039/d0cs00177e>
6. R. Lai, F. Qu, M. Ju, C. Xie, H. Qian, T. Xia, C. Wang, G. Yu, Y. Tang, X. Bai, Q. Hou, *Bioresource Technology*, **419**, 132031(2025), <https://doi.org/10.1016/j.biortech.2024.132031>
7. A. Primo, P. Concepción, A. Corma, *Chemical Communications*, **47**(12), 3613(2011), <https://doi.org/10.1039/c0cc05206j>
8. P. Gallezot, *Chemical Society Reviews*, **41**(4), 1538(2012), <https://doi.org/10.1039/c1cs15147a>
9. A.O. Ojo, O. de Smidt, *Processes*, **11**(3), 1(2023), <https://doi.org/10.3390/pr11030688>
10. Y. Huang, Y. Wang, N. Shang, P. Li, *Foods*, **12**(22), 4097(2023), <https://doi.org/10.3390/foods12122311>
11. M. S. Holm, S. Saravanamurugan, E. Taarning, *Science*, **328**(5978), 602(2010), <https://doi.org/10.1126/science.1183990>
12. J. Zhang, L. Wang, G. Wang, F. Chen, J. Zhu, C. Wang, C. Bian, S. Pan, F.S. Xiao, *ACS Sustainable Chemistry & Engineering*, **5**(4), 3123(2017), <https://doi.org/10.1021/acssuschemeng.6b02881>

13. F. F. Wang, C. L. Liu, W. S. Dong, *Green Chemistry*, **15(8)**, 2091(2013), <https://doi.org/10.1039/c3gc40836a>
14. H. Ramezani Dana, F. Ebrahimi, *Polymer Engineering & Science*, **63(1)**, 22(2023), <https://doi.org/10.1002/pen.26193>
15. K. Kohli, R. Prajapati, B.K. Sharma, *Energies*, **12(2)**, 1(2019), <https://doi.org/10.3390/en12020233>
16. N.G. Khouri, J.O. Bahú, C. Blanco-Llamero, P. Severino, V.O.C. Concha, E.B. Souto, *Journal of Molecular Structure*, **1309**, 138243(2024), <https://doi.org/10.1016/j.molstruc.2024.138243>
17. J. Bai, B.K. Zambroñ, P. Vogel, *Organic Letters*, **16(2)**, 604(2014), <https://doi.org/10.1021/ol403508j>
18. Q.L. Luo, L. Lv, Y. Li, J.P. Tan, W. Nan, Q. Hui, *European Journal of Organic Chemistry*, **Vol. 2011(34)**, 6916(2011), <https://doi.org/10.1002/ejoc.201101030>
19. R.M. Lanigan, P. Starkov, T.D. Sheppard, *Journal of Organic Chemistry*, **78(9)**, 4512(2013), <https://doi.org/10.1021/jo400509n>
20. C. Deiana, Y. Sakhno, M. Fabbiani, M. Pazzi, M. Vincenti, G. Martra, *ChemCatChem*, **5(10)**, 2832(2013), <https://doi.org/10.1002/cctc.201300164>
21. C.L. Allen, A.R. Chhatwal, J.M.J. Williams, *Chemical Communications*, **48(5)**, 666(2012), <https://doi.org/10.1039/c1cc15210f>
22. R. S. Vardanyan, V. J. Hruby, *Future Medicinal Chemistry*, **6(4)**, 385(2014), <https://doi.org/10.4155/fmc.13.215>
23. Z. X. Wang, Y. C. Zhu, W. Q. Jin, X. J. Chen, J. Chen, R.Y. Ji, Z.Q. Chi, *Journal of Medicinal Chemistry*, **38(18)**, 3652(1995), <https://doi.org/10.1021/jm00018a026>
24. M.B.M. Reddy, V.P. Jayashankara, M.A. Pasha, *Green Chemistry Letters and Reviews*, **6(1)**, 107(2013), <https://doi.org/10.1080/17518253.2012.710650>
25. O. Kitagawa, M. Takahashi, M. Kohriyama, T. Taguchi, *Journal of Organic Chemistry*, **68(25)**, 9851(2003), <https://doi.org/10.1021/jo035305l>
26. W.F.M. Van Bever, C.J.E. Niemegeers, P.A.J. Janssen, *Journal of Medicinal Chemistry*, **17(10)**, 1047(1974), <https://doi.org/10.1021/jm00256a003>

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