Proceedings of the 10th World Congress on New Technologies (NewTech'24)
Barcelona, Spain - August 25-27, 2024
Paper No. ICBB 109
DOI: 10.11159/icbb24.109

Utilizing Deep Eutectic Solvents for Hydroxide-Catalysed Synthesis of Ellagic Acid from Bio-Based Ethyl Gallate

Miša Mojca Cajnko, Anže Prašnikar, Blaž Likozar
Department of Catalysis and Chemical Reaction Engineering, National Institute of Chemistry, Hajdrihova 19, 1000 Ljubljana, Slovenia
misa.cajnko@ki.si; anze.prasnikar@ki.si; blaz.likozar@ki.si

Extended Abstract

There is a growing recognition among individuals about the significance of embracing a healthy lifestyle and the contributions of natural plant products to it. Among these valuable natural compounds is ellagic acid (EA), a polyphenolic compound which is found in abundance in a variety of fruits, vegetables, and other plant sources. EA boasts a wide array of health benefits including anti-inflammatory [1], antioxidative [2], anti-mutagenic [3] and anticarcinogenic [4], and antimicrobial [5] properties.

In our current study, we aimed to synthesize EA directly from ethyl gallate, a gallic acid derivative. We based our experiments on two simple reaction protocols, one utilizing a hydroxide and aeration [6] and the other utilizing an ionic liquid [7]. We employing an N,N-dimethylammonium N',N'-dimethylcarbamate (DIMCARB) ionic liquid, alongside three different hydroxides (NH_4OH, NaOH and KOH) and aeration, as well as five choline chloride (ChCl)-based deep eutectic solvents (DES) in combination with a hydroxide and aeration. DIMCARB exhibited poor performance, yielding less than 2% EA, despite our attempts at optimization. On the other hand, the reactions with hydroxides yielded better results. We tested reaction times (24 – 72h) and catalyst concentration (0.5 – 5% (w/w)), and afterwards, also the addition of various DES. NaOH and KOH did not perform very well, with 27.8 % yield and 83.9 % purity for 1% KOH, and 19.5 % yield and 82.2 % purity for 1% NaOH after 48h. However, the reactions with a 1% NH_4OH catalyst yielded 50.3% EA with 85% purity after 48h. Afterwards, the 1% NH_4OH system was tested with the addition of 10% (w/w) of selected DES. We used ChCl:glycerol (molar ratio 1:2), ChCl:urea (molar ratio 1:2), ChCl:p-toluenesulfonic acid (molar ratio 1:3), ChCl:acetic acid (molar ratio 1:2) and ChCl:oxalic acid (molar ratio 1:2). While the more acidic mixtures of DES/NH_4OH did not yield any product, the addition of 10% ChCl:glycerol or ChCl:urea DES to 1% NH_4OH increased conversions up to 77.5% yield with 82.9% purity. Two other ChCl:glycerol or ChCl:urea concentrations (5 and 20% (w/w)) were also tested but resulted in lower yields. We also performed a simple scale-up process of the most efficient DES/NH_4OH system. After optimizing the aeration process (air bubbling), we obtained an EA yield of 61.8% EA with purity exceeding 80%. Furthermore, we developed a model for the engineered synthesis process, elucidating pH as the pivotal design factor affecting equilibrium, mechanistic rate kinetics, and product solubility. Notably, DES was found to decrease EA solubility, contributing to the significant yield enhancement. This modeling provided valuable insights for subsequent screening endeavors.

Acknowledgements
This research was funded by the Slovenian Research Agency within the projects L2-3175, P2-0152 and J7-1816.

References

[1] A.P. Rogerio, C. Fontanari, É. Borducchi, A.C. Keller, M. Russo, E.G. Soares, D.A. Albuquerque, L.H. Faccioli, Anti-inflammatory effects of Lafoensia pacari and ellagic acid in a murine model of asthma, Eur. J. Pharmacol. 580 (2008) 262–270. https://doi.org/10.1016/J.EJPHAR.2007.10.034.

[2] M.M. Kannan, S.D. Quine, Ellagic acid ameliorates isoproterenol induced oxidative stress: Evidence from electrocardiological, biochemical and histological study, Eur. J. Pharmacol. 659 (2011) 45–52. https://doi.org/10.1016/J.EJPHAR.2011.02.037.

[3] G. Loarca-Piña, P.A. Kuzmicky, E. González De Mejía, N.Y. Kado, D.P.M. Hsieh, Antimutagenicity of ellagic acid against aflatoxin B1 in the Salmonella microsuspension assay, Mutat. Res. Mutagen. Relat. Subj. 360 (1996) 15–21. https://doi.org/10.1016/S0165-1161(96)90232-0.

[4] S. Umesalma, G. Sudhandiran, Ellagic acid prevents rat colon carcinogenesis induced by 1, 2 dimethyl hydrazine through inhibition of AKT-phosphoinositide-3 kinase pathway, Eur. J. Pharmacol. 660 (2011) 249–258. https://doi.org/10.1016/J.EJPHAR.2011.03.036.

[5] Atta-Ur-Rahman, F.N. Ngounou, M.I. Choudhary, S. Malik, T. Makhmoor, M. Nur-E-Alam, S. Zareen, D. Lontsi, J.F. Ayafor, B.L. Sondengam, New antioxidant and antimicrobial ellagic acid derivatives from Pteleopsis hylodendron, Planta Med. 67 (2001) 335–339. https://doi.org/10.1055/S-2001-14306.

[6] W. Zeng, Y. -H Heur, T.H. Kinstle, G.D. Stoner, Synthesis of [14CO]ellagic acid, J. Label. Compd. Radiopharm. 29 (1991) 657–666. https://doi.org/10.1002/JLCR.2580290607.

[7] S.A. Chowdhury, P.M. Dean, R. Vijayaraghavan, D.R. MacFarlane, S.A. Chowdhury, P.M. Dean, R. Vijayaraghavan, D.R. MacFarlane, Efficient Synthesis of Ellagic Acid Salts Using Distillable Ionic Liquids, Aust. J. Chem. 64 (2011) 1624–1627. https://doi.org/10.1071/CH11236.