

Metal- and solvent-free preparation of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives catalysed by deep eutectic solvents

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Received 20 March 2020; accepted 19 June 2020

Abstract:

A straightforward method for the preparation of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives catalysed by an acidic deep eutectic solvent from choline chloride (ChCl) and phenol via the Biginelli reaction of 2-aminobenzimidazole, ethyl acetoacetate, and aldehydes has been developed under metal- and solvent-free conditions. The desired products were obtained in moderate to good yield (49-79%) and the DESs were known as an economical and environmentally friendly catalyst.

Keywords: Biginelli reaction, deep eutectic solvents, green catalyst, green chemistry.

Classification number: 2.2

Introduction

Deep eutectic solvents (DESs) were first reported by Abbott and co-workers in 2001 and has since been widely applied to electrolytes [1], electrodeposition [2], electropolishing [3], ionothermal synthesis [4], gas adsorption [5], and biotransformation [6]. DESs are classified as a new class of ionic liquids that present many outstanding characteristics such as low vapor pressure, nonflammability, easy preparation, low cost, and large recovery [7]. These characteristics make DESs well-known as green solvents for organic transformations.

The Biginelli reaction, first reported in 1891, played an important role in the synthesis of pyrimidine derivatives [8]. Benzo[4,5]imidazo[1,2-a]pyrimidine and other compounds containing a pyrimidine framework have been since recognized for their significant biological activities. Many different catalysts including silica sulfuric acid [9], ionic liquids [10, 11], $H_3PO_4-Al_2O_3$ [12], and $\alpha-Zr(CH_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$ [13] have been investigated for the efficient synthesis of these compounds. However, the drawbacks of these protocols are toxicity, expensive agents, and environmental harm. Herein, we describe an effective method for the preparation of benzo[4,5]imidazo[1,2-a]pyrimidine using a deep eutectic solvent as an efficient and reusable

catalyst. This is the first time DES has been used as a catalyst for the synthesis of benzo[4,5]imidazo[1,2-a]pyrimidine.

Experimental

All chemicals were purchased from Sigma-Aldrich. Solvents were supplied by ChemSol (Vietnam). 1H and ^{13}C nuclear magnetic resonance (NMR) spectra were performed on a Bruker Advance II 500 MHz NMR spectrometer (Fig. 1).

A typical procedure for the synthesis DES: a mixture of ChCl and phenol with a 1:2 molar ratio was magnetically stirred at 100°C until a colourless liquid was obtained. After cooling the reaction mixture to room temperature, the product was washed with diethyl ether and then dried in vacuum at 60°C for 6 h before use in experiments. The purity of the DES was confirmed by 1H -NMR and ^{13}C -NMR spectroscopy. Further characterization of DES by our group is reported in the previous paper [14].

DES ChCl:phenol (1:2): colorless liquid. 1H -NMR (500 MHz, $DMSO-d_6$) δ 9.49-9.35 (m, 2H), 7.14 (t, $J=7.8$ Hz, 4H), 6.85-6.63 (m, 6H), 5.52-5.45 (m, 1H), 3.82 (td, $J=4.9, 2.4$ Hz, 2H), 3.43 (m, 2H), 3.13 (s, 9H). ^{13}C -NMR (125 MHz, $DMSO-d_6$) δ 157.85 (s), 129.78 (s), 119.20 (s), 115.73 (s), 67.57-67.27 (m), 55.57 (s), 53.77-53.46 (m).

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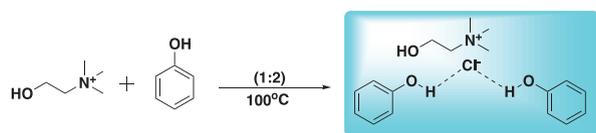


Fig. 1. Preparation of DES from choline chloride and phenol.

A typical procedure for the synthesis of benzo[4,5]imidazo[1,2-a]pyrimidine: 2-aminobenzimidazole (1.0 mmol), ethyl acetoacetate (1.0 mmol), aldehydes (1.0 mmol), and DES [ChCl][Phenol]₂ (10% mmol) were reacted at 100°C for 60-180 min under solvent-free magnetic stirring, then checked for completion by thin-layer chromatography (TLC). The crude products were recrystallized from hot ethanol to afford the desired products. The purity and identity of the products were confirmed by ¹H-NMR and ¹³C-NMR. The catalyst was washed with diethyl ether and activated by heating under reduced vacuum at 80°C for 30 min and then ready for the next recycle.

Results and discussion

Deep eutectic solvent-catalysed Biginelli reactions under green conditions is our ambition for the preparation of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives, which are widely applied in pharmaceuticals. To evaluate the catalytic activity, we investigated DESs as homogeneous catalysts. A good yield was obtained from DES [ChCl][phenol]₂ (Table 1, entry 1). The reaction did not proceed in the absence of DES. The [ChCl][Glucose] provided the desired product in low yield due to high viscosity, which affected the diffusion of starting materials in the reaction mixture. The [Emim]Cl ionic liquid gave an acceptable yield (57%) and the best yield was obtained with [ChCl][Phenol]₂.

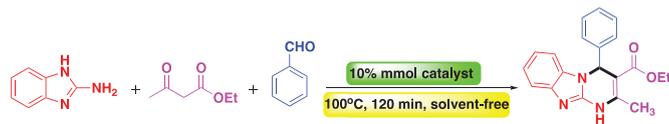


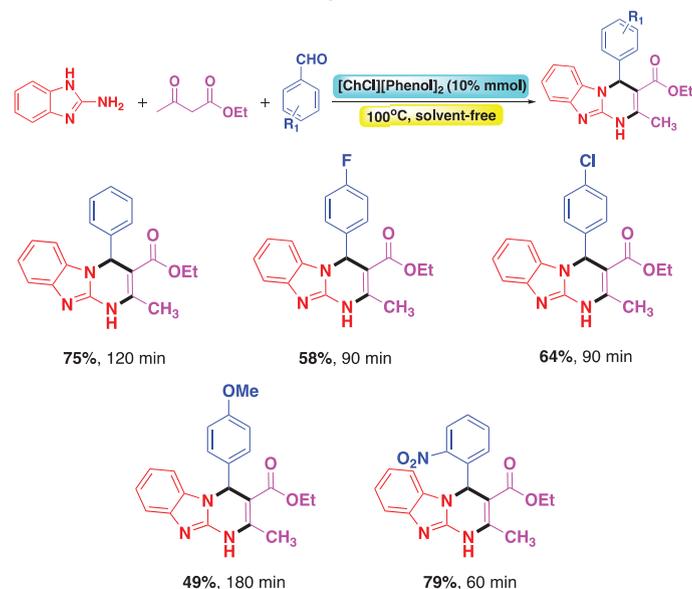
Table 1. Effect of homogeneous catalysts on the condensation reaction.

Entry	Homogeneous catalyst	Isolated yield (%)
1	[ChCl][Phenol] ₂	75
2	-	0
3	[ChCl][Glucose]	39
4	[Emim]Cl	57

Reaction condition: 2-aminobenzimidazole (1 mmol), ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol).

To study the scope of aldehydes on this condensation reaction, aldehydes containing either electron-donating or electron-withdrawing substituents were applied (Table 2). The reaction achieved a higher yield with electron-withdrawing substituents such as -NO₂, -F and -Cl and a lower yield and long reaction time with an electron-donating group like -OMe. At room temperature, this reaction occurred despite a very low yield (~12%).

Table 2. Different substrates of aldehydes on the condensation reaction using DES.



Reaction condition: 2-aminobenzimidazole (1 mmol), ethyl acetoacetate (1 mmol), aldehydes (1 mmol).

To characterize the structure of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives, ¹H-NMR and ¹³C-NMR were recorded on a Bruker Advance II 500 MHz NMR spectrometer using DMSO-*d*₆ as solvent (Table 3).

In the ¹H-NMR spectrum, similar patterns for proton resonance were also observed in five compounds. A triplet at δ 1.05-1.15 ppm (3H) and a multiplet at δ 4.21-3.76 ppm (2H) displayed the protons from the -OC₂H₅ group. Three protons from -CH₃ on the pyrimidine ring had a singlet at δ 2.46-2.42 ppm while the other proton was found as a singlet at δ 6.41-6.37 ppm. The protons from the two phenyl rings gave signals in the aromatic area. Besides, the three protons from the substituent -OMe of compound 4 had a singlet at δ 3.66 ppm. The ¹³C-NMR spectrum given in Table 3 had all signals match to all the carbon atoms.

Table 3. The spectral data of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives.

Compound	R ₁	¹ H-NMR	¹³ C-NMR
1 [15]	H	(500 MHz, DMSO- <i>d</i> ₆) δ 7.35 (m, 3H), 7.25 (m, 3H), 7.17 (t, J=7.3 Hz, 1H), 7.04 (t, J=7.5 Hz, 1H), 6.94 (t, J=7.5 Hz, 1H), 6.41 (s, 1H), 4.07-3.96 (m, 2H), 2.45 (s, 3H), 1.13 (t, J=7.3 Hz, 3H).	(125 MHz, DMSO- <i>d</i> ₆) δ 165.7, 146.9, 146.1, 142.7, 142.5, 132.0, 128.8, 128.2, 128.2, 127.5, 127.5, 122.2, 120.6, 117.2, 110.3, 98.4, 59.8, 56.4, 19.6, 14.5.
2 [15]	F	(500 MHz, DMSO- <i>d</i> ₆) δ 7.40 (m, 2H), 7.34 (d, J=8 Hz, 1H), 7.26 (d, J=8 Hz, 1H), 7.11-7.01 (m, 3H), 6.95 (m, 1H), 6.45 (s, 1H), 4.12-3.90 (m, 2H), 2.45 (s, 3H), 1.14 (t, J=7.0 Hz, 3H).	(125 MHz, DMSO- <i>d</i> ₆) δ 165.6, 162.8 (d, J=244.2 Hz), 160.9, 147.0, 145.9, 142.7, 138.8, 131.9, 129.7, 122.3, 120.7, 117.4, 115.7, 115.5, 110.4, 98.3, 59.8, 55.7, 19.1, 14.5.
3 [15]	Cl	(500 MHz, DMSO- <i>d</i> ₆) δ 7.46 (m, 1H), 7.36 (d, J=8.0 Hz, 1H), 7.32-7.19 (m, 4H), 7.10-7.03 (m, 1H), 7.00-6.93 (m, 1H), 6.46 (s, 1H), 4.21-3.76 (m, 2H), 2.46 (s, 3H), 1.15 (t, J=7.0 Hz, 3H).	(125 MHz, DMSO- <i>d</i> ₆) δ 165.5, 147.5, 145.9, 144.9, 142.7, 133.3, 131.9, 130.9, 128.3, 127.6, 126.1, 122.4, 120.8, 117.4, 110.3, 97.8, 59.9, 55.8, 19.1, 14.5.
4 [15]	OMe	(500 MHz, DMSO- <i>d</i> ₆) δ 7.33 (d, J=7.5 Hz, 1H), 7.25 (m, 3H), 7.06-7.01 (m, 1H), 6.98-6.90 (m, 1H), 6.80 (d, J=8.5 Hz, 2H), 6.37 (s, 1H), 4.14-3.91 (m, 2H), 3.66 (s, 3H), 2.44 (s, 3H), 1.15 (t, J=7.3 Hz, 3H).	(125 MHz, DMSO- <i>d</i> ₆) δ 165.7, 159.1, 146.6, 146.1, 142.8, 134.6, 132.0, 128.7, 128.7, 122.2, 120.6, 117.2, 114.1, 114.1, 110.3, 98.7, 59.8, 55.8, 55.4, 19.0, 14.6.
5 [16]	NO ₂	(500 MHz, DMSO- <i>d</i> ₆) δ 7.91 (dd, J=8.0, 1.0 Hz, 1H), 7.59-7.54 (m, 1H), 7.43 (m, 3H), 7.26 (dd, J=8.0, 1.0 Hz, 1H), 7.11 (s, 1H), 7.10-7.07 (m, 1H), 7.00-6.95 (m, 1H), 4.03-3.97 (m, 1H), 3.94-3.88 (m, 1H), 2.42 (s, 3H), 1.05 (t, J=7.0 Hz, 3H).	(125 MHz, DMSO- <i>d</i> ₆) δ 165.4, 148.3, 147.8, 145.9, 137.3, 134.7, 134.7, 132.2, 129.7, 129.5, 124.5, 122.7, 121.3, 117.6, 110.0, 97.9, 60.1, 51.1, 19.4, 14.5.

Conclusions

In conclusion, we reported an effective and green procedure for the preparation of benzo[4,5]imidazo[1,2-a]pyrimidine via the condensation of 2-aminobenzimidazole, ethyl acetoacetate, and aldehydes under mild reaction conditions, short reaction time, and in environmentally-friendly media.

ACKNOWLEDGEMENTS

This research is funded by Vietnam National University, Ho Chi Minh city (VNU-HCM) under the grant number 562-2020-18-01.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

REFERENCES

- [1] A.P. Abbott, R.C. Harris, K.S. Ryder (2007), "Application of hole theory to define ionic liquids by their transport properties", *J. Phys. Chem. A*, **111(18)**, pp.4910-4913.
- [2] A.P. Abbott, G. Capper, D.L. Davies, R.K. Rasheed (2004), "Ionic liquid analogues formed from hydrated metal salts", *Chem. Eur. J.*, **10(15)**, pp.3769-3774.
- [3] A.P. Abbott, G. Capper, K.S. Ryder (2006), "Electropolishing of stainless steels in a choline chloride based ionic liquid: an electrochemical study with surface characterisation using SEM and atomic force microscopy", *Phys. Chem. Chem. Phys.*, **8(36)**, pp.4214-4221.
- [4] E.R. Cooper, C.D. Andrews, P.S. Wheatley, P.B. Webb, P. Wormald, R.E. Morris (2004), "Ionic liquids and eutectic mixtures as solvent and template in synthesis of zeolite analogues", *Nature*, **430**, pp.1012-1016.
- [5] X. Li, M. Hou, B. Han, X. Wang, L. Zou (2008), "Solubility of CO₂ in a choline chloride + urea eutectic mixture", *J. Chem. Eng. Data*, **53(2)**, pp.548-550.
- [6] J.T. Gorke, F. Sreenc, R. Kazlauskas (2008), "Hydrolase-catalysed biotransformations in deep eutectic solvents", *Chem. Commun.*, **(10)**, pp.1235-1237.
- [7] E.L. Smith, A.P. Abbott, K.S. Ryder (2014), "Deep eutectic solvents (DESs) and their applications", *Chem. Rev.*, **114(21)**, pp.11060-11082.
- [8] P. Biginelli (1891), "Ueber aldehyduramide des acetessigäthers", *Eur. J. Inorg. Chem.*, **24(1)**, pp.1317-1319.
- [9] L. Wu, F. Yan, C. Yang (2010), "Silica sulfuric acid promoted one-pot synthesis of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives under solvent-free conditions", *Bull. Chem. Soc. Ethiop.*, **24(3)**, pp.417-423.
- [10] P.H. Tran, T.P.T. Bui, X.Q.B. Lam, X.T.T. Nguyen (2018), "Synthesis of benzo 4,5 imidazo 1,2-a pyrimidines and 2,3-dihydroquinazolin-4(1H)-ones under metal- free and solvent- free conditions for minimizing waste generation", *RSC Adv.*, **8**, pp.36392-36399.
- [11] M.V. Reddy, K.R. Byeon, S.H. Park, D.W. Kim (2017), "Polyethylene glycol methacrylate-grafted dicationic imidazolium-based ionic liquid: Heterogeneous catalyst for the synthesis of aryl-benzo[4,5]imidazo[1,2-a]pyrimidine amines under solvent-free conditions", *Tetrahedron*, **73**, pp.5289-5296.
- [12] H.R. Shaterian, N. Fahimi, K. Azizi (2014), "New applications of phosphoric acid supported on alumina (H₃PO₄-Al₂O₃) as a reusable heterogeneous catalyst for preparation of 2,3-dihydroquinazolin-4(1H)-ones, 2H-indazolo-[2,1-b]phthalazintriones, and benzo[4,5]imidazo[1,2-a]pyrimidines", *Res. Chem. Intermed.*, **40**, pp.1879-1898.
- [13] O. Rosati, M. Curini, F. Montanari, M. Nocchetti, S. Genovese (2011), "α-zirconium sulfophenylphosphonate as a catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-one derivatives under solvent free conditions", *Catal. Lett.*, **141**, pp.850-853.
- [14] N.T. Phuong, N.T.T. Duy, N.S. Vinh, D.T.D. Thi, L.M. Hung, T.C. Wei, T.H. Phuong (2019), "Application of deep eutectic solvent from phenol and choline chloride in electrolyte to improve stability performance in dye-sensitized solar cells", *J. Mol. Liq.*, **277**, pp.157-162.
- [15] C.-S. Yao, S. Lei, C.-H. Wang, C.-X. Yu, Q.-Q. Shao, S.-J. Tu (2008), "One-pot three-component solvent-free synthesis of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives catalysed by sulfamic acid", *Chin. J. Chem.*, **26(11)**, pp.2107-2111.
- [16] G. Kaur, A. Singh, P. Venugopalan, N. Kaur, N. Singh (2016), "Selective recognition of lithium (i) ions using Biginelli based fluorescent organic nanoparticles in an aqueous medium", *RSC Adv.*, **6(3)**, pp.1792-1799.