Organic Chemistry Research

Article

Organic Chemistry Research
www.orgchemres.org

Cite this: *Org. Chem. Res.* **2022**, *Vol. 8,* 95-98.
DOI: 10.22036/org.chem.2024.435241.1316

Choline Chloride-urea as a Solvent/catalyst for the Synthesis of 2-Aminoimidazopyridines *via* Strecker Reaction

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Received: January 11, 2024; Accepted: February 2, 2024

Abstract: The three-component Strecker reaction between 2-aminopyridine, aldehyde, and KCN in choline chloride-urea deep eutectic solvent (DES) was used for the synthesis of 2-aminoimidazopyridines. This reaction was carried out in simple conditions, and the reaction yields were very favorable. The use of the choline chloride-urea as an environmentally friendly solvent/catalyst is the main advantage of the presented synthesis method.

Keywords: Deep eutectic solvent, 2-Aminoimidazopyridine, Choline chloride-urea, Green chemistry, Strecker reaction

1. Introduction

Solvents occupy a strategic place in chemistry, and in order to qualify as green mediums, they must meet different criteria such as availability, non-toxicity, biodegradability, recyclability, flammability, and low price among others.[1a] According to green chemistry, the goal of a solvent is to enhance performance in chemical and engineering processes, minimize energy consumption, and avoid adverse impact on the environment, health, and safety (Figure 1).[1b]

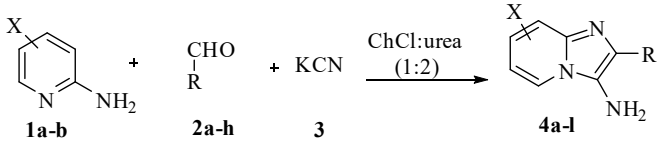
Figure 1. The goal of using the solvent in reactions.

In recent years, organic solvents have been replaced with easily recyclable systems such as supercritical CO_2 ($scCO_2$), fluorinated solvents, solvent-free conditions, non-volatile systems such as ionic liquids (ILs), deep eutectic solvents (DESs), and low-melting mixtures (LMMs).[2-3]

The first research on DES was reported in 2001.[4] DES are composed of eutectic mixtures of Lewis-Brønsted acids and bases. These solvents can be prepared by using natural raw materials such as amino acids, urea, organic acids, sugars, or choline derivatives. They are biodegradable, biocompatible, and meet the principles of green chemistry. The two main applications of DESs are in metal processing,[2,5] the food sector,[6] and synthesis media.[8-10]

Choline chloride (ChCl) is an organic salt that forms a DES with urea with a molar ratio of 1 to 2 with a freezing point of 12 °C.[7] This DES is liquid at room temperature and has the ability to form hydrogen bonds with susceptible compounds. According to the scientific reports, DES are used as both solvent and catalyst with an acidic role.[4]

In the last century, multicomponent reactions (MCRs) have been widely used in the synthesis of heterocyclic compounds, leading to the creation of new diverse heterocyclic compounds.[11-14] In addition, MCRs and DESs adhere to the principles of green chemistry.[8-11] So, ChCl-urea was investigated as a solvent and catalyst in a three-component reaction between 2-aminopyridines (**1a-b**), aldehyde (**2a-h**), and KCN (**3**), as shown in Scheme 1.



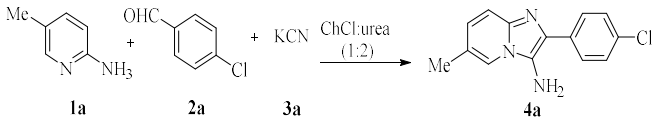
1a-b **2a-h** **3** **4a-l**

Scheme 1. ChCl-urea as a solvent and catalyst for the three-component reaction

2. Results and Discussion

Initially, the ChCl:urea DES was prepared using ChCl and

urea with molar ratio of 1:2 at 100 °C.[7] After preparing the DES, the reaction of 5-methyl-2-aminopyridine (**1a**), *para*-chlorobenzaldehyde (**2a**), and KCN with a molar ratio 1:1:1 in ChCl-urea (1 mL) at room temperature was performed.



Scheme 2. The model reaction in ChCl-urea

The progress of the reaction was monitored by TLC, and it was found that room temperature (r.t.) was not suitable and the reaction was not performed. In order to improve this preliminary finding, the reaction was carried out at 80 °C. The reaction progressed with the adjusted temperature for 3 h. In order to separate the product, two drops of 37% hydrogen chloride were added to the reaction mixture, followed by the addition of 6 mL of distilled water in two steps. The formed precipitate was separated from the solvent and dissolved in chloroform. The reaction product, which was a dark green compound, was obtained once the chloroform was evaporated. The results of spectroscopic methods showed that the intended product was formed. After it was ensured that the reaction was carried out in ChCl-urea, the optimization of the reaction was carried out to obtain suitable conditions, including amount of solvent, reaction temperature, and molar ratio of the reactant materials (Table 1). Optimizing of the reaction conditions showed that the presence of choline chloride-urea solvent is necessary for this reaction and the reaction cannot proceed without it (Table 1, entry 5). In addition, the reaction product has an amine functional group that, once formed in the reaction container, can react with the unreacted aldehydes in the container and create the corresponding imine. [16-19] To prevent this, the molar excess amount of 2-aminopyridine and cyanide (1.2 eq. instead of 1 eq.) was used and a higher yield was obtained (Table 1, entry 8-10). Using TMSCN as a cyanide source creates a higher yield (Table 1, entry 11), but due to its high cost and the availability and cheapness of KCN, the latter was used in the reactions. Finally, the best reaction conditions were identified as: molar ratio 1.2 (**1a**): 1 (**2a**): 1.2 (**3**) in ChCl-urea (1 mL) at 80 °C (Table 1, entry 10).

After the reaction was complete, the reaction mixture was dissolved in water and the crude product was extracted with EtOAc. The aqueous phase was placed under vacuum at 80 °C until its water evaporated and DES was recovered. The recovered DES was used again and had the same yield as the first time (Table 1, entry 12).

The scope and limitations of the presented methodology were investigated by changing the aldehydes and 2-aminopyridines, and the results are summarized in Figure 2.

The mechanism of the synthesis of imidazo[1,2-a]pyridine was presented in Figure 3. First, aldehyde carbonyl (**2a-k**) was activated with DES as an acidic catalyst. Then, the activated aldehyde was attacked by the 2-aminopyridine amino group (**1a-b**), and after proton exchange and the loss of one mole of water, the imine intermediate **A** was formed. Then, [4+1] cyclization reaction between intermediate **A** and cyanide was carried out with the presence of DES. Finally, during imine-enamine tautomerization, imidazo[1,2-a]pyridine derivatives (**4a-k**) were obtained.[6-12]

Table 1. Optimization of the reaction conditions for the synthesis of **4a**[a]

Entry	ChCl-urea (mL)	T (°C)	Time (h)	Yield (%)[b]
1	1	r.t.	24	-
2	1	50	24	23
3	1	80	3	57
4	1	100	3	60
5	-	80	24	-
6	0.5	80	3	42
7	1.5	80	3	58
8[c]	1	80	3	62
9[d]	1	80	3	63
10[e]	1	80	3	75
11[f]	1	80	3	83
12[g]	1	80	3	74

[a]Reaction condition: **1a** (0.25 mmol), **2b** (0.25 mmol), **3** (0.25 mmol); [b]Isolated yield; [c]**1a** (0.3 mmol); [d]**3** (0.3 mmol); [e]**1a** (0.3 mmol), **3** (0.3 mmol); [f]**1a** (0.3 mmol) and TMSCN (0.3 mmol) as a cyanide source; [g] recovered DES, **1a** (0.3 mmol), and **3** (0.3 mmol).

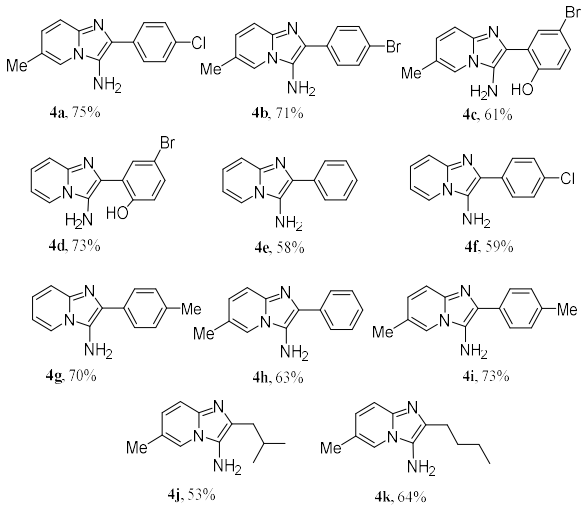


Figure 2. Structure of synthesized derivatives.

3. Experimental

All commercial materials were used without further purification. Reactions were followed by Thin-Layer

Chromatography (TLC) performed using precoated plates of

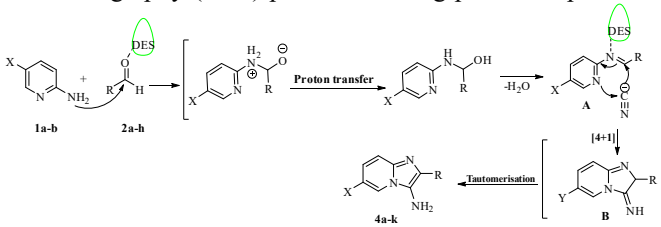


Figure 2. Mechanism of synthesis imidazo[1,2-a]pyridine.

silica 60 F254, with U.V light as a visualizing agent. NMR spectra were recorded at 298 K on a Brucker Avance 300 MHz spectrometer, using DMSO-*d6* as solvent. Melting points were determined on an Electro- thermal 9200 apparatus and were left uncorrected.

Considering the compounds **4a** and **4e-k** were synthesized and identified previously,[19-22] their identification was done by comparing the reported melting points. The structures of imidazo[1,2-a]pyridines **4b-d** were identified by ^{1}H and ^{13}C NMR (see Supporting Information).

General procedure for the synthesis of imidazo[1,2-a]pyridin-3-amines 4a-k: A mixture of aldehydes (0.25 mmol), KCN (0.3 mmol), and 2-aminopyridines (0.3 mmol) in 1 mL of the DES was stirred for 3 h at 80 °C. The reaction was cooled to room temperature, and 2 drops of HCl (37%) was added to the reaction vessel. Then, the reaction mixture was washed with water (2 × 3 mL) and the solid residue recrystallized from $CHCl_3$/*n*-hexane to obtain the products.

2-(4-Chlorophenyl)-6-methylimidazo[1,2-a]pyridin-3-amine (4a): White powder (48 mg, 75 %), mp 246-248 °C (dec);[20] ^{1}H NMR (DMSO-d_6): δ = 2.35 (s, CH_3), 5.44 (brs, NH_2), 7.49 (d, J = 9.0 Hz, 2H–Ar), 7.59 (d, J = 9 Hz, H–Ar), 7.96 (d, J = 9 Hz, H–Ar), 8.05 (d, J = 9.0 Hz, 2H–Ar), 8.28 (s, H–Ar) ppm; ^{13}C NMR (DMSO-*d6*): δ = 18.35, 114.70, 121.18, 127.55, 128.20, 129.01, 129.23, 130.09, 131.62, 137.13, 138.26, 166.93 ppm.

2-(4-Bromophenyl)-6-methylimidazo[1,2-a]pyridin-3-amine (4b): White powder (53 mg, 71%), mp 220-224 °C (dec); ^{1}H NMR (DMSO-d_6): δ = 2.09 (s, CH_3), 6.21 (brs, NH_2), 6.50 (d, J = 9.0 Hz, H–Ar), 7.30 (d, J = 9.0 Hz, H–Ar), 7.56 (d, J = 9.0 Hz, 2H–Ar), 7.74 (s, H–Ar), 7.95 (d, J = 9 Hz, 2H–Ar) ppm; ^{13}C NMR (DMSO-d_6): δ = 17.35, 109.15, 120.51, 128.03, 129.06, 131.02, 131.58, 137.96, 139.66, 145.09, 157.52, 167.49 ppm.

2-(3-Amino-6-methylimidazo[1,2-a]pyridin-2-yl)-4-bromophenol (4c): Orange powder (48 mg, 61%), mp 267-270 °C (dec); ^{1}H NMR (DMSO-d_6): δ= 2.33 (s, CH_3), 5.56 (brs, NH_2), 6.84 (d, J = 9.0 Hz, H–Ar), 7.11 (d, J = 9.0 Hz, H–Ar), 7.25 (d, J = 9.0 Hz, H–Ar), 7.46 (d, J = 9.0 Hz, H–Ar),8.23 (s, H–Ar), 7.28 (s, H–Ar), 11.00 (brs, OH), ppm; ^{13}C NMR (DMSO-d_6): δ = 18.34, 110.28, 115.74, 119.17, 120.54, 121.78, 125.95, 126.82, 127.37, 129.20, 130.50, 137.19, 155.73, 160.35 ppm.

2-(3-Aminoimidazo[1,2-a]pyridin-2-yl)-4-bromophenol (4d): Orange powder (55 mg, 73%), mp 242-146 °C (dec); ^{1}H NMR (DMSO-d_6): δ = 5.47 (brs, NH_2), 6.87 (d, J = 9.0 Hz, H–Ar), 7.04 (t, J = 6.0 Hz, H–Ar), 7.25-7.31 (m, 2H–Ar), 7.58 (d, J = 9.0 Hz, H–Ar), 8.30 (d, J = 3 Hz, H–Ar), 8.44 (d, J = 6 Hz, H–Ar), 13.11 (brs, OH) ppm; ^{13}C NMR (DMSO-d_6): δ = 110.49, 112.69, 116.26, 119.16,121.05, 123.25, 124.61, 126.36, 129.30, 130.73, 137.94, 155.63, 160.07 ppm.

4. Conclusions

In conclusion, This study reported a three-component reaction leading new valuable pharmaceutical products from a simple and readily available reactant and using an eco-friendly and biodegradable deep eutectic solvent based on the choline chloride–urea mixture. In addition, the presented method has the advantages of not forming the by-product of N-arylidene-2-aryl-imidazo[1,2-a]azin-3-amines, good yield, and short reaction time.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

Amin Parvizi Moghadam: Investigation, Methodology, Data curation. Afshin Sarvary: Supervision, Conceptualization, Writing-Reviewing and Editing. Negin Dehghan: Writing-Original draft preparation, Visualization.

Supporting Information

The Supporting Information is available free of charge athttp://www.org.chem.res./doi: XXXX.

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Acknowledgements

The work presented in this paper was partially funded through the Internal Grant numbers BNUT/02390070/01 by Babol Noshirvani University of Technology.

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