

Multicomponent reaction in deep eutectic solvent for synthesis of substituted 1-aminoalkyl-2-naphthols

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Abstract One-pot multicomponent synthesis of Betti bases (aminoalkyl naphthols) from aldehydes, β -naphthol, and secondary amines in deep eutectic solvent (DES) based on urea and choline chloride has been developed. A broad range of aminoalkyl naphthols can be obtained smoothly in good to excellent yield in biodegradable choline-chloride-based deep eutectic solvent, being compatible with functional groups and operationally straightforward. In addition, DES could be readily recycled at least four times without obvious loss of activity.

Keywords Betti bases · Deep eutectic solvent · Aminoalkyl naphthols · Green chemistry

Introduction

Multicomponent reactions (MCRs) are not only powerful tools in organic, combinatorial, and medicinal chemistry, but also represent an excellent framework for green chemistry [1–3]. Some fundamental aspects of multicomponent reactions include atom economy and generation of molecular diversity. Furthermore, MCRs offer significant advantages over conventional, linear-type syntheses in organic, combinatorial, and medicinal chemistry because large libraries of compounds can be easily synthesized from commercial starting materials [4–10].

The multicomponent reaction between aldehydes, primary aromatic amines, and phenols or naphthols to produce α -aminobenzyl phenols via a modified Mannich

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reaction is known as the Betti reaction, first discovered by Mario Betti at the beginning of the 20th century [11]. This MCR provides a valuable framework for obtaining compounds that have several interesting biological applications, such as antibacterial, hypotensive, and bradycardiac activities [12], as well as pharmacological properties [13, 14]. Furthermore, there is growing interest in Betti bases as chiral inductors or chiral precursors for asymmetric synthesis of α -aminophosphonic acids [15]. Owing to the wide variety of applications of Betti bases in chiral drug synthesis, various modifications have been made to prepare Betti base derivatives under operationally straightforward and green conditions [16–24]. Furthermore, several asymmetric procedures for these multicomponent reactions have also been successfully developed [25–28].

Deep eutectic solvents (DESs) are a new type of ionic solvent introduced in 2003 by Abbott and coworkers [29]. DESs are mainly low-melting mixtures of a quaternary ammonium salt (e.g., choline chloride) and a hydrogen-bond acceptor such as urea, carboxylic acids, or polyols [30–35]. The properties of DESs are similar to those of ionic liquids, including negligible vapor pressure and low flammability, while overcoming several limitations associated with ILs such as intolerance to humidity [36–38]. The main advantages of DESs include their straightforward synthesis, comparatively low cost, high biodegradability, and low toxicity. These interesting features of DESs have made these natural green solvents increasingly popular for use in electrochemistry, material chemistry, and organic synthesis [39–41].

Results and discussion

In continuation of our ongoing research towards development of multicomponent reactions in novel and green reaction media [42–46], we describe herein the dual role of a widely studied deep eutectic solvent based on urea and choline chloride as catalyst and solvent for convenient synthesis of Betti bases.

After preparation of DES, three-component reaction of β -naphthol (1.0 mmol), morpholine (1.0 mmol), and benzaldehyde (1.0 mmol) as model reaction was tentatively run in DES (1.0 mL) at room temperature. The yield of the model reaction in urea–choline chloride at room temperature in 4 h was fair (40 %). Next, the reaction was performed at higher temperatures (40, 60, and 80 °C). While the yield was higher at 60 °C than at 40 °C, there was no meaningful difference between yield at 60 and 80 °C. Hence, 60 °C was selected as the optimized temperature. The corresponding product **4d** was formed as the only product, isolated in 95 % yield (Table 1). To test the suitability of other DESs, the model reaction under optimized conditions was carried out in different DESs, such as oxalic acid–ChCl (Table 1, entry 5), SnCl₂–ChCl (Table 1, entry 6), LaCl₃–ChCl (Table 1, entry 7), glycerol–ChCl (Table 1, entry 8), ZnCl₂–ChCl (Table 1, entry 9), and mandelic acid–ChCl (Table 1, entry 10) at 60 °C for 2 h. The results incorporated in Table 1 demonstrate low activity of other DESs, maybe due to direct interaction of morpholine with DES.

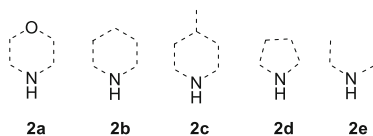
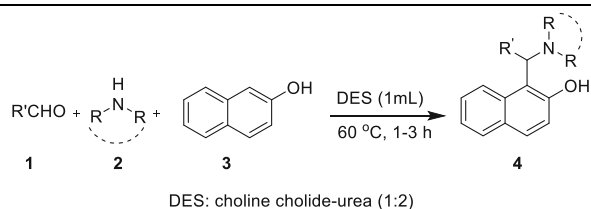
Table 1 Optimization of model reaction conditions

Entry	DES	Temp. (°C)	Yield (%) ^a
1	Urea–ChCl (2:1)	25	40
2	Urea–ChCl (2:1)	40	52
3	Urea–ChCl (2:1)	60	95
4	Urea–ChCl (2:1)	80	95
5	Oxalic acid–ChCl (1:1)	60	30
6	SnCl ₂ –ChCl (2:1)	60	58
7	LaCl ₃ ·6H ₂ O–ChCl (2:1)	60	64
8	Glycerol–ChCl (2:1)	60	20
9	ZnCl ₂ –ChCl (2:1)	60	55
10	Mandelic acid–ChCl (1:1)	60	10

Furthermore, the DES was recycled by washing with water (5 mL) after reaction completion. The DES was recovered by evaporation of water under vacuum and used for the next run without much loss of product yield.

With the optimized reaction conditions established, a number of Betti base products were synthesized to investigate the reaction scope; the results obtained are presented in Table 2. Aromatic aldehydes **1** with various substituents including benzaldehyde, 4-methoxybenzaldehyde, methyl 4-formylbenzoate, 4-chlorobenzaldehyde, and 4-methylbenzaldehyde reacted with secondary amines **2** and β -naphthol **3** in good to excellent yield. Heteroaromatic, as well as sterically hindered aromatic, aldehydes also gave good product yield. However, aliphatic aldehydes failed to produce corresponding Betti base under these reaction conditions (Table 2). Reaction of secondary amine (**2a–f**) with aldehydes and β -naphthol proceeded smoothly under the standard reaction conditions to give a broad range of aminoalkyl naphthols in good to excellent yield. However, the reaction did not work with α -naphthols and phenols, due to the lower reactivity of these compounds under the same reaction conditions.

The reusability of DES was further investigated using the reaction between benzaldehyde (5 mmol), piperidine (5 mmol), and 2-naphthol (5 mmol) in DES (5 mL) under the optimized conditions (Table 2, entry 2). After reaction completion, water (15 mL) was added to the reaction medium to dissolve the DES. The product was separated by simple filtration, washed with water, and purified by recrystallization from ethanol. The water of the aqueous layer was evaporated under vacuum, and the residue washed with ethyl acetate to recover DES, which was used for the next cycle. Using this procedure, DES could be reused up to four times without any significant loss of the initial catalytic activity (Fig. 1).

Table 2 Optimized reaction conditions for synthesis of Betti base products in DES

Entry	Aldehyde (1)	Amine (2)	Product (4)	Yield (%) ^a	Melting point (°C)	Found Rep. [Lit]
1		2a	4a	95	176–178	175–177 [47]
2		2b	4b	95	199	196–198 [48]
3		2c	4c	91	146–148	147–149 [50]
4		2d	4d	95	176–177	176–177 [49]
5		2e	4e	74	117	117–118 [50]
6		2a	4f	84	125–126	124–125 [51]
7		2b	4g	91	139	137–140 [52]
8		2c	4h	90	118–120	120–122 [52]
9		2d	4i	92	97–99	99 [53]
10		2b	4j	94	145–146	144–146 [52]
11		2a	4k	96	130–131	130–132 [54]
12		2b	4l	84	165–166	165–166 [52]
13		2d	4m	88	119–121	118–120 [54]
14		2e	4n	80	133–134	133–135 [53]
15		2a	4o	82	180–182	182–184 [55]
16		2b	4p	88	166–168	167–169 [55]
17		2d	4q	78	140–142	140–142 [54]
18		2b	4r	82	160–162	162–163 [56]
19		2b	4s	76	160–162	162–163 [56]
20		2a	4t	72	180–182	184–188 [55]
21		2a	4u	00	–	–

^a Isolated yields

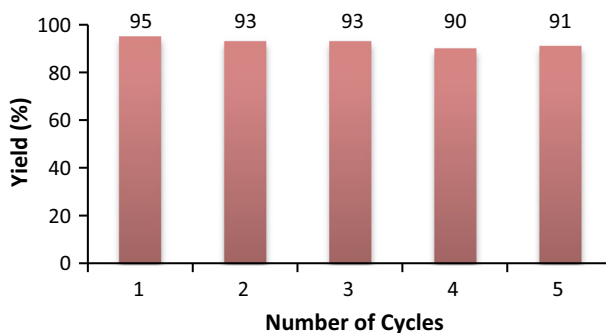


Fig. 1 Recyclability study of deep eutectic solvent

Conclusions

We developed an efficient, simple, and green protocol for synthesis of Betti bases in deep eutectic solvent based on urea and choline chloride. In this reaction medium, product separation is convenient and DES is reusable.

Experimental

Materials and methods

All reagents, solvents, and DES components were purchased from commercial suppliers and used without further purification. All products were confirmed by ^1H nuclear magnetic resonance (NMR) and Fourier-transform infrared (FT-IR) spectroscopy. ^1H NMR spectra were recorded on a FT-NMR Bruker Ultra Shield TM 500 spectrometer at 500 MHz using dimethyl sulfoxide (DMSO)- d_6 as solvent. Chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS). Melting points were determined using a Büchi 535 melting point apparatus and are uncorrected. FT-IR spectra were recorded on a Bruker Vector-22 infrared spectrometer by using KBr disks.

DES preparation

DES based on urea and choline chloride was prepared according to literature procedure [32]. Thus, urea (200 mmol) and choline chloride (100 mmol) were mixed and heated under stirring at 60 °C until clear liquid appeared.

General procedure

A mixture of DES (1 mL), β -naphthol (1 mmol), aromatic aldehyde (1 mmol), and amine (1 mmol) was stirred and heated to 60 °C. Stirring was continued at 60 °C until reaction completion. The reaction mixture was diluted with water (5 mL),

whereupon the desired Betti base separated as solid that was isolated by filtration. Further purification was done either by recrystallization from ethanol or by flash column chromatography. All resulting compounds were characterized by melting points, which were found to be the same as reported in literature.

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