Journal of Molecular Liquids 206 (2015) 268–271

Contents lists available at ScienceDirect

Journal of Molecular Liquids

journal homepage: www.elsevier.com/locate/molliq

Eco-efficiency and scalable synthesis of bisamides in deep eutectic solvent

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ARTICLE INFO

Article history:
Received 21 October 2014
Received in revised form 21 January 2015
Accepted 24 February 2015
Available online 26 February 2015

Keywords:
Deep eutectic solvent
Green chemistry
Bisamide
Urea
Aldehyde

ABSTRACT

Solvents define a major part of the environmental performance of processes in chemical industry and also impact on cost, safety and health issues. In order to minimize the environmental impact resulting from the use of volatile organic solvents in chemical production, a deep eutectic solvent (DES) consisting of choline chloride and urea (1:2 molar ratio) was prepared and used as the co-solvent for the preparation of gem-bisamides starting from aldehydes. The deep eutectic solvent fulfills the triple role of being a solvent, as a catalyst and as reagents, and provides a green, safe and cost-effective access to various gem-bisamides without a tedious work-up. The desired compounds were obtained in a few min (15–120 min) with moderate to good yields (52–90%) and amenable to large scale production without significant loss in its efficiency.

1. Introduction

Due to their toxicity and flammability common organic solvents were used in industries and laboratories and it is necessary to design and elaborate new processes in order to avoid waste and to substitute benign chemicals for toxic hazardous solvents. In this regard, the development of a cleaner process is more attractive in green chemistry [1–3]. Among the several principles of green chemistry, the reduction of volatile organic solvents and catalysts from the reaction medium or in the work-up procedure is of utmost importance. The use of a huge amount of volatile organic solvents required to conduct a chemical process creates adverse effects on organisms. The search for a safer solvent and catalyst alternative is thus holding a key role in the green chemistry. Deep eutectic solvents (DESs) that mix quaternary ammonium salts such as choline chloride and hydrogen bond donor's compounds have attracted much attention due to their significant advantages [4–10]. DESs have a promising alternative to ionic liquids and conventional organic solvent because they are easier to prepare from biodegradable, renewable and natural starting materials with high purity at a low cost. After the first report by Abbott and co-workers in 2003, the number of papers on the use of DESs in chemistry and biology has significantly increased over the past few years [11–19].

The development of environmentally benign procedures to access functional amide derivatives has infused continuing interest, as such compounds have been used widely in the construction of natural products and pharmaceutical compounds. Gem-bisamides are important not only for intriguing biological activities and their versatile role in the treatment of high blood pressure, but also for particular importance as key synthons in the organic synthesis [20–22]. Therefore, many synthetic methods for Gem-bisamides were achieved via condensation reaction between aldehyde and amide in the presence of catalyst or activator [23–30]. Although these methodologies are useful tools and serve as the synthetic requirements for simple gem-bisamides, most of them suffer from limitation such as expensive catalyst, harmful organic solvent, and harsh reaction conditions and prolong reaction times. Furthermore, despite the efficiency of the used catalyst in this reaction, insolubility of bisamides in the common organic solvents, separation of products from the catalyst was difficult and this leads to the tedious work-up in most cases. Thus, the development of a catalyst free method for the synthesis of bisamides was the major goal of our research.

2. Experimental section

2.1. Materials and instrumentation

All chemicals, solvents and DES components were commercially available. All products were confirmed by ^{1}HNMR, FT-IR spectroscopy and mass spectrometry. ^{1}H NMR spectra were recorded on 500 and 300 MHz ^{1}H NMR, ^{13}C NMR 125.7 and 75 MHz NMR spectrometer using DMSO-d_6 as a solvent and chemical shifts have been expressed in (ppm) downfield from TMS. Water and ethanol were distilled before used. Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected. FT-IR spectra were determined on a Bruker Vector-22 infrared spectrometer using KBr disks. ^{1}H NMR spectra were recorded at r.t. on a FT-NMR Bruker Ultra Shield TM (500 and

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http://dx.doi.org/10.1016/j.molliq.2015.02.033
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300 MHz). EI-MS data was collected on an Agilent Technologies 5973 Mass Selective Detector (MS model).

2.2. DES preparation

Choline chloride-urea deep eutectic solvent was prepared according to the literature [5]. Urea (200 mmol) and choline chloride (100 mmol) were mixed, stirred and heated at 60 °C for 50 min until a clear liquid appeared. The obtained deep eutectic solvent was used without any further purification (Fig. 1).

2.3. General procedure

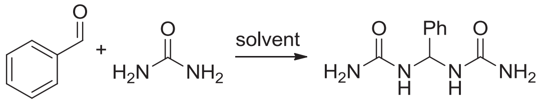
A dried test tube, equipped with a magnetic stir bar, was charged with an aldehyde (1.0 mmol), and DES (0.5 mL contain 4.67 mmol urea) and the mixture was heated at 80 °C until the reaction was complete (monitored visually, the reaction mixture was solidified). After this time, water was added and the residue collected by filtration. The resulting solid was washed with water and recrystallized from ethanol to give pure products. All compounds were characterized by melting found to be identical with the ones described in literature.

3. Results and discussion

In our research on organic transformation in green reaction media, we recently reported that a one-pot three component reaction accelerated in water and deep eutectic solvent [31–36]. In our continued work, we became interested in exploring the reaction of aldehydes with DES as a solvent, as a reagent and as a catalyst.

In an initial endeavor, the reaction of benzaldehyde with urea–choline chloride based DES was studied as a model reaction to determine the temperature and reaction times required to complete the transformation (Table 1). Low yields were observed at room temperature after prolong reaction time (41% after 12 h) (Table 1, entry 1). It was observed that the mixture which was initially in a partial semiliquid state, solidified during increasing the temperature to 80 °C to a light white solid mass for 15 min and thin layer chromatography (TLC) indicated the complete conversion to the desired product. Further increasing the temperature to 140 °C did not change the time and yields of products. Further studies were conducted to optimize the volume of the DESs, and 0.5 mL urea-choline chloride gave higher yields at a short reaction time. Under optimized temperature, we also carried out the model reaction in various solvents including H_2O, THF, CH_3CN, ethyl acetate, toluene and DMF. All of these solvents turned out to be less efficient than DES in promoting the reaction (Table 1, entries 14–19). Most importantly, the reaction setup is very simple and easy. Mixing of aldehydes and DES and heating of reaction mixture at 80 °C gave the solid mass at a short reaction time, that was washed with water to remove DES and recrystallized from ethanol to give pure gem-bisamides with simple work-up.

Table 1
Optimization of reaction condition.



Entry	Solvent (mL)	Temp. (°C)	Reaction time (min)	Yield (%)[a,b]
1	DES (0.5 mL)	rt	720	41
2	DES (0.5 mL)	40	90	58
3	DES (0.5 mL)	60	40	62
4	DES (0.5 mL)	80	15	82
5	DES (0.5 mL)	100	15	82
6	DES (0.5 mL)	120	15	86
7	DES (0.5 mL)	140	15	80
8	DES (0.1 mL)	80	10	72
9	DES (0.2 mL)	80	10	72
10	DES (1.0 mL)	80	30	80
11	DES (2.0 mL)	80	30	80
12	DES (5.0 mL)	80	80	84
13[c]	DES (5.0 mL)	80	15	78
14	Water (1.0 mL)	100	600	10
15	Ethyl acetate (1.0 mL)	100	600	40
16	DMF (1.0 mL)	100	600	48
17	CH_3CN (1.0 mL)	100	600	32
18	Toluene (1.0 mL)	100	600	45
19	THF (1.0 mL)	100	600	20

[a] DES: urea-choline chloride based deep eutectic solvent.
[b] Isolated yields.
[c] Reaction was carried out in 10 mmol scale.

After optimization of the reaction conditions, we carried out the generality and synthetic scope of this condensation reaction with various electronically divergent aldehydes (Table 2). The presence of an electron-withdrawing group in the aromatic ring can influence reactivity of aldehydes and higher yield of the products was obtained in short reaction times. On the other hand, the presence of electron-donating groups exerts the reverse effects. The bromo-, chloro-, methyl- and methoxy-substituted benzaldehydes were successfully converted and gave the corresponding products in 58–90%. Several heterocyclic aldehydes such as 2-furaldehyde, thiophene-2-carbaldehyde and pyridine-3-carbaldehyde were applied as substrates because of the important biological topics of heterocycles, the corresponding bisamides were synthesized in good yields and short reaction times. On the other hand, for the first time we have shown that aliphatic aldehydes (entry 19), still displayed good reactivity and clean reactions under this standard condition.

In order to show the practical applicability of this green procedure, the model reaction was carried out in a scale of 10 mmol (Fig. 2). The reaction was completed in 15 min with 78% isolated yield after simple work-up (Table 1, entry 13). After completion of the reaction, the mixture was cooled to room temperature and the product was filtered and washed with water and purified with recrystallized from hot ethanol.

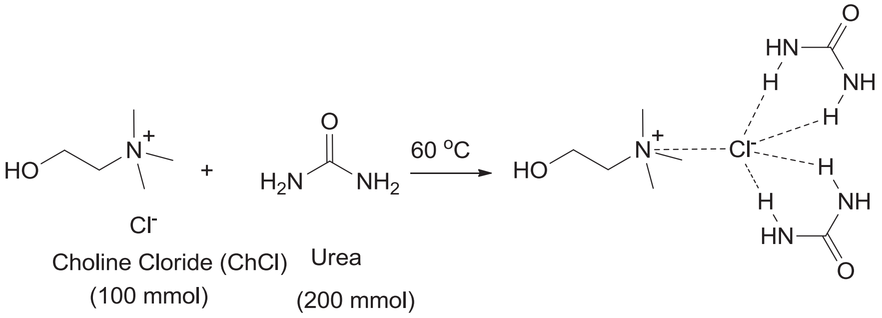
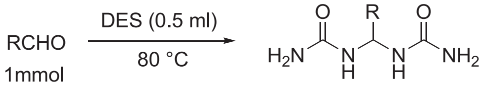
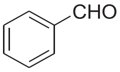
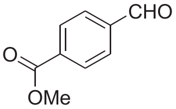
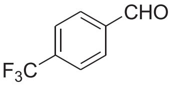
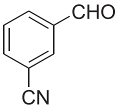
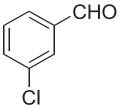
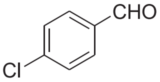
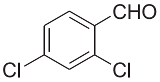
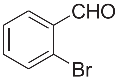
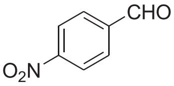
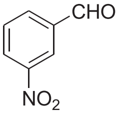
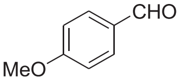
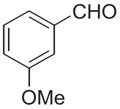
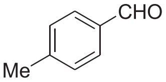
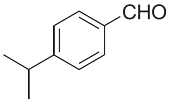
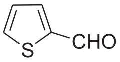
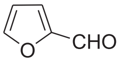
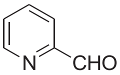
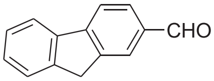
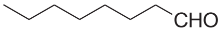


Fig. 1. Deep eutectic solvent preparation from urea and ChCl.

Table 2
Synthesis of various gem-bisamides from aldehydes and DES.



Entry	Aldehyde	Yield (%)	Time (min)	M.P. (°C)
1		82	15	205–207
2		86	15	202–205
3		90	20	198–201
4		76	30	188–191
5		85	20	188–190
6		74	40	189–191
7		80	30	222–225
8		71	45	218–222
9		62	30	199–201
10		78	30	198–200
11		54	120	199–202
12		61	120	153–156
13		64	90	210–213
14		65	120	173–175
15		52	60	179–181
16		56	60	188–190
17		60	15	203–206
18		56	40	196–199
19		58	90	188–191

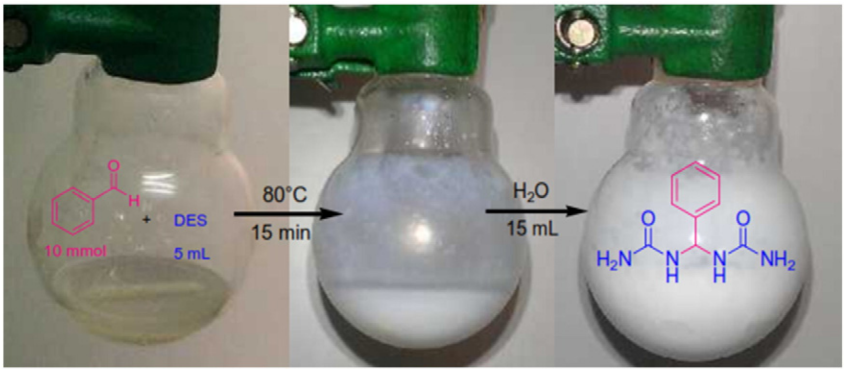


Fig. 2. Large-scale synthesis of substituted bisamides.

4. Conclusion

In summary, we have demonstrated for the first time, a unique property of DES as a solvent, reagent and catalyst for the clean and efficient synthesis of bis-amide derivatives due to high concentration of urea present in the reaction medium. Remarkable advantages of this green procedure include the use of biodegradable DES, short reaction times, and a simple separation and purification. Further investigations of organic reactions in DESs are now underway in our laboratory.

Acknowledgments

Partial financial support of this work by the Chemistry and Chemical Engineering Research Center of Iran is gratefully appreciated.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.molliq.2015.02.033.

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