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Urea decomposition: Efficient synthesis of pyrroles using the deep eutectic solvent choline chloride/urea

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ABSTRACT

A simple and efficient method is reported for the synthesis of pyrroles *via* condensation of a series of tri-carbonyl compounds with ammonia, which was generated *in situ* from decomposition of the deep eutectic solvent choline chloride/urea.

In recent years, deep eutectic solvents (DES), a low-cost and environmentally benign solvent system, have attracted significant attention.[1] DES are mixtures of two components; one of them a hydrogen bond donor (HBD) and the other a hydrogen bond acceptor (HBA).[2] The HBA is usually a phosphonium or quaternary ammonium salt, while the HBD are typically acids,[3] alcohols,[4] amines,[1a] amides,[1b] or carbohydrates.[1c] Due to hydrogen bond interactions between them, DES possess a freezing point much lower than that of either component.[5]

DES offer some notable advantages when compared with traditional solvents, including low volatility, wide thermal and electrical windows, water tolerance, biodegradability, renewability, low toxicity, wide liquid temperature range, and high solvation ability for a large number of organic or inorganic compounds. Furthermore, their properties such as freezing point, conductivity and viscosity can be fine-tuned by appropriate selection of the mixture components. Due to these advantages, the applications of DES have increased progressively in the fields of electrochemistry,[6] synthesis[1a,7], biotransformation,[8] separation processes,[9] and material preparation.[10] The DES based on choline chloride and urea was developed firstly by Abbott and coworkers.[11] Both choline chloride and urea are biodegradable, nontoxic, and readily available components.[12] Previously, the choline chloride based DES was reported as an efficient dehydrating medium for the preparation of pyrroles from amines and 1,4-diketones.[13]

Despite the applications of DES, their stability has been seldom studied.[14] The thermal decomposition temperature for an urea containing DES system is over 200 °C.[15] However, it was also reported that the partial decomposition of urea in DES took place at 80 °C in the presence of transition metal salts.[16]

Recently, we reported several methods for the synthesis of *para*-carbonyl compounds.[17] In an attempt at developing efficient condensation conditions,[18] we conducted the Paal–Knorr furan synthesis using tri-carbonyl compounds in the eutectic mixture of choline chloride/urea. Surprisingly, and without the addition of ammonia, this reaction afforded the corresponding pyrrole. Therefore, it was reasonable to infer that ammonia as a reactant could be generated *in situ* from the decomposition of urea in DES.

Thus, we began by examining the stability of different ureas in DES (Table 1). When triketone **1a** was stirred at 40 °C for 24 h using the eutectic mixture of choline chloride/urea as solvent, trace amounts of pyrrole **3a** was detected by TLC (Entry 1). However the condensation reaction proceeded efficiently when the temperature was increased to 100 °C. Triketone **1a** was completely transformed into pyrrole **3a** in 12 h without any furan product detected (Entry 2). No reaction occurred using the eutectic mixture of choline chloride/glycerol and one equivalent of urea to react with triketone **1a** at reaction temperatures lower than 80 °C. When the temperature was increased, both pyrrole and furan products were obtained (Entry 3). Furthermore, no pyrrole or furan product

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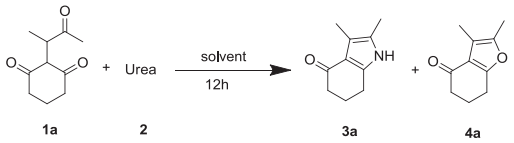
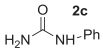
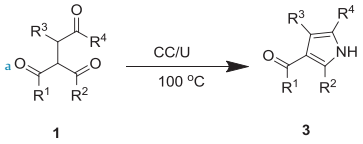
Table 1
Model Reaction Optimization.

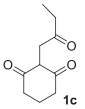
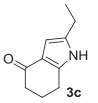
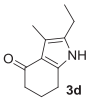
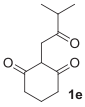
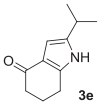
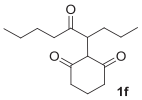
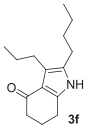


Entry	Urea	Solvent	°C	**3a** [%][a]	**4a** [%][a]
1	–[b]	CC/U[c]	40	Trace	–[f]
2	–[b]	CC/U[c]	100	75	–[f]
3	 **2a**	CC/G[d]	120	58	27
4	 **2a**	Solvents[e]	Reflux	–[f]	–[f]
5	 **2a**	DMSO	120	Trace	–[f]
6	 **2b**	CC/G[d]	120	Trace	62
7	 **2c**	CC/G[d]	120	Trace	64 [g]

[a] Isolated yield.
[b] Without urea.
[c] Choline chloride:urea (1:2).
[d] Choline chloride:glycerol (1:2).
[e] Solvents: CH_2Cl_2, $ClCH_2CH_2Cl$, and toluene.
[f] Not detected.
[g] 1,3-Diphenylurea was detected.

Table 2
Scope of tricarbonyl compounds for the pyrrole synthesis.



Entry	Ketone	Pyrrole	Time [h]	Yield **3** [%][b]
1	 **1a**	 **3a**	8	75
2	 **1b**	 **3b**	8	89
3	 **1c**	 **3c**	8	75
4	 **1d**	 **3d**	8	67
5	 **1e**	 **3e**	8	86
6	 **1f**	 **3f**	8	78

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