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Scott Handy, Kevin Lavender

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Organic Synthesis in Deep Eutectic Solvents: Paal-Knorr Reactions

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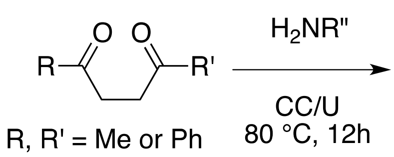

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Organic synthesis in deep eutectic solvents: Paal-Knorr reactions

Scott Handy[a] * and Kevin Lavender

[a] *Departmetn of Chemistry, Middle Tennessee State University, Murfreesboro, TN 37132*

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ABSTRACT

Deep Eutectic solvents (the combination of either urea or glycerol with choline chloride) are effective solvents/catalysts for Paal-Knorr reactions to form either pyrroles of furans. The reaction conditions are quite mild and do not require the addition of an additional Bronsted or Lewis acid catalyst. Given the inexpensive, non-toxic, and recyclable nature of the DES, these reaction conditions are simple and highly environmentally friendly.

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1. Introduction

Solvents play a very important role in a number of areas, perhaps most obviously in the area of synthesis. Because of this importance and because they are generally the largest single component by weight in most reactions, they are a clear target for concern and interest due to the growing importance placed upon "greenness." Many alternative solvents have been proposed, including water, supercritical fluids, and room temperature ionic liquids (RTILs).[1] Each of these alternatives has some great benefits, but each also has significant limitations, including reactivity problems, solubility issues, cost, the need for exotic reactors, and/or toxicity.

A recent alternative solvent is the category of deep eutectic solvents (DES). This family covers a considerable range of different mixtures.[2] The most commonly employed is the 1:2 molar mixture of choline chloride and urea which affords a viscous liquid at room temperature.[3] Advantages of this solvent are several-fold: it is relatively inexpensive (being comparable in price to conventional organic solvents such as acetonitrile and DMF),[4] it is non-toxic, exhibits no detectible vapor pressure under ambient conditions, and is based on biorenewable materials. Further, it should be readily recyclable (*vide infra*), improving its status as a promising green solvent.

DES have been extensively explored in certain contexts, particularly the area of electroplating,[5] however, they have not received as much attention for their potential in synthesis.[6] In examining the choline chloride/urea DES, we noted that urea should be able function as a modest organocatalyst.[7] It is nicely fixed such that it can form two hydrogen-bonds to a carbonyl and thus activate this carbonyl for addition reactions. (Figure 1) This, combined with the known hygroscopic nature of DES, made it appear that it could be a very promising solvent for a wide range of condensation reactions. The start of our study was the Paal-Knorr reaction.

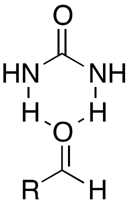

Figure 1. Urea as an Organocatalyst.

2. Results

The Paal-Knorr synthesis of pyrroles and furans is a powerful method for the synthesis of these valuable heteroaromatics.[8] (Scheme 1) Numerous different reaction conditions have been developed over the years, including Lewis acid catalysis,[9] heterogeneous catalysis,[10] microwaves,[11] different solvent variations (RTIL and solvent-free),[12] and ultrasound or microflow conditions.[13]

The first reactions studied in DES were those of simple amines with 2,5-hexanedione.[14] (Table 1) Rather conveniently, stirring an equimolar mixture of the dione and the amine as a 1-M solution in choline chloride/urea at 80 °C for 2 hours afforded the products in near quantitative yield. The pyrrole products could

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* Corresponding author. Tel.: +0-000-000-0000; fax: +0-000-000-0000; e-mail: author@university.edu

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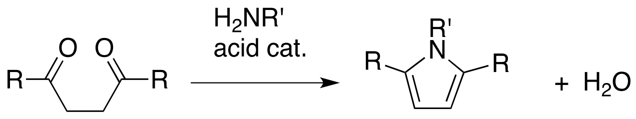
be very easily isolated by dilution with an equal volume mixture of water and methylene chloride, followed by separation of the organic layer and removal of the solvent to afford the pure pyrrole. For all known pyrroles, the spectral data matched that reported in the literature, while for the new pyrroles, the spectral data was consistent with the anticipated product.[15]

Attempting these reactions with less nucleophilic anilines was also successful, but only by applying longer reaction times (12 hours). (Table 1, entries 5-8) Again, the pyrrole products were obtained in near quantitative yields. Only in the case of the very poorly nucleophilic 4-nitroaniline was a lower yield obtained. (Table 1, entry 8) In this case, the lower yield was a result of competitive formation of the furan product (26%) in addition to the pyrrole product.



Scheme 1. The Paal-Knorr Synthesis.

Table 1. Paal-Knorr Reactions with 2,5-hexanedione

Entry	Amine	Yield[a]
1	**Benzyl**	**98**
2	**Hexyl**	**99**
3	**sec-Butyl**	**92**
4[b]	**Isopropyl**	**95**
5[b]	**Phenyl**	**78**
6[b]	**p-Iodophenyl**	**77**
7[b]	**p-Hydroxyphenyl**	**83**
8[b,c]	**p-Nitrophenyl**	**56**

a. Isolated yields. b. These reactions were allowed to run for 12 hours instead of 2. c. The remainder of the mass balance was 2,5-dimethylfuran.

Moving to other diones, it quickly became apparent that they were less reactive. For example, reaction of 1-phenyl-1,4-pentanedione (**1**) with benzylamine under the previous reaction conditions (2 hours), afforded very low conversion of the dione to the anticipated pyrrole. Fortunately, by simply extending the reaction time to 12-14 hours, this lower reactivity could be overcome. (Table 2, entries 1-3) With dione **2**, the reactivity was even further attenuated, so that complete conversion to the pyrrole products could only be achieved by allowing the reaction to proceed for 24 hours in the case of benzyl and hexyl amine and for 48 hours in the case of aniline. (Table 2, entries 4-6) Modest amounts (5-10%) of the furan product were also noted in the case of reaction with aniline.

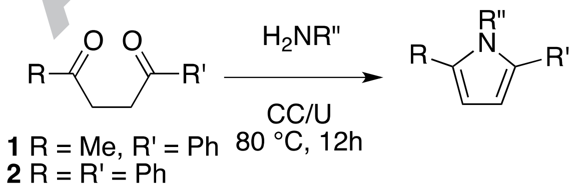
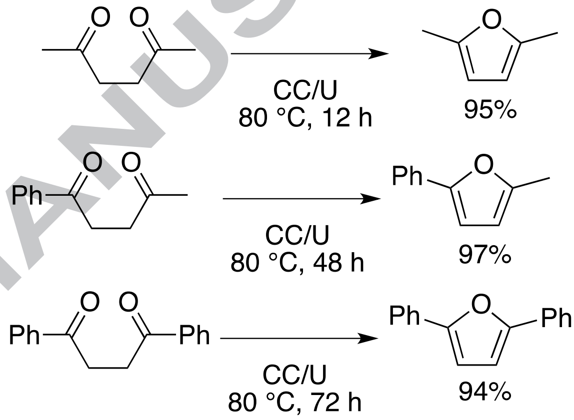


Table 2. Paal-Knorr Reactions with other Diones

Entry	Dione	Amine	Yield[a]
1	**1**	**Benzyl**	**94**
2	**1**	**Hexyl**	**91**
3[b]	**1**	**Phenyl**	**88**
4[b]	**2**	**Benzyl**	**87**
5[b]	**2**	**Hexyl**	**89**
6[b]	**2**	**Phenyl**	**82**

a. Isolated yields. b. These reactions were allowed to run for 24 hours instead of 12.

Given that we had already noted furan formation as a side reaction in the reactions with less nucleophilic amines, it was not surprising that reactions in the absence of any amine afforded the furan products in good yield. (Scheme 2) Also, as expected, complete conversion required longer reaction times for the less reactive diones.



Scheme 2. Paal-Knorr Furan Syntheses.

One definite limitation of the previously described reaction conditions is that the biphasic work-up at the end of the reaction renders recovery and recycling of the DES rather labor intensive. A superior alternative was developing by simply extracting the product from the reaction mixture at the end of the reaction using diethyl ether. This method is quite similar to that employed in many reactions using conventiona RTILs. The DES is not soluble in diethyl ether or ethyl acetate and can be recovered and reused, following separation, by brief evaporation of any residual ether on the rotovap. As seen in Table 3, the recovered DES could be used for at least four reactions with no significant loss of yield.

Table 3. Recycling Studies for the reaction of 2,5-hexanedione with benzylamine.

Entry	Recycling #	% Yield
1	Fresh	96
2	1	93
3	2	92
4	3	92
5	4	90

a. These reactions were allowed to run for 2 hours and were isolated via extraction with ether.

Although the bulk of our efforts focused on the choline chloride/urea DES, we did explore the use of another common DES for this same reaction – choline chloride/glycerol. As seen in Scheme 3, the Paal-Knorr reaction did proceed in this

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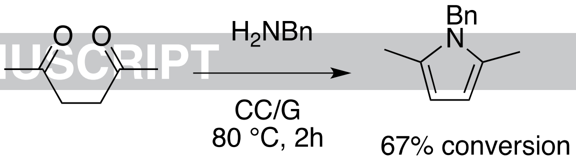
alternative DES, but much less rapidly, affording only 67% conversion under the same reaction conditions (time, temperature, and concentration) employed with choline chloride/urea. The reaction could be pushed to completion by allowing it to run for 12 hours, to afford 90% yields of the pyrrole product. Apparently, the weaker hydrogen-bonding activation of glycerol compared to urea results in much weaker catalysis of the Paal-Knorr reaction.



Scheme 3. Paal-Knorr in Choline Chloride/Glycerol.

In conclusion, the choline chloride/urea DES exhibits a number of interesting and useful features as a solvent for organic synthesis. It is easily prepared from inexpensive, bulk chemicals. It is non-toxic, non-volatile, and based on potentially biorenewable materials. In addition, the weak hydrogen-bonding ability of urea appears to be enhanced due to the high concentration of urea present in the DES, rendering it useful as an organocatalytic solvent. We anticipate that it will be of value in a number of other applications as well and efforts are currently underway to explore this potential.

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14 Representative Procedure: To a solution of dione (1 mmol) in choline chloride/urea or choline chloride/glycerol (1 mL) was added the amine (1 mmol). The reaction was heated to 80 C and stirred for the designated time. After cooling to room temperature, the reaction was diluted with water (2 mL) and extracted with methylene chloride (4 mL). The organic layer was separated, dried, filtered, and concentrated *in vacuo* to afford the pyrrole product in analytically pure form without need for further purification.

15 All products aforded spectroscopic data consistent with the assigned structure and matching the literature (where a known compound). This information can be found in the dupplementary material.

Supplementary Material

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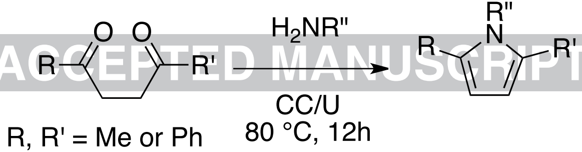

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