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Synthesis of ureas in the bio-alternative solvent Cyrene†

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Cyrene as a bio-alternative solvent: a highly efficient, waste minimizing protocol for the synthesis of ureas from isocyanates and secondary amines in the bio-available solvent Cyrene is reported. This method eliminated the use of toxic solvents, such as DMF, and established a simple work-up procedure for removal of the Cyrene, which led to a 28-fold increase in molar efficiency *versus* industrial standard protocols.

Introduction

Ureas are an important class of compound that have been exploited in a number of fields, such as pharmaceuticals, agrochemicals and materials science. In the pharmaceutical sector the utility of ureas can be observed in the variety of biological activities that they exhibit.[1] For example, ureas are found in anti-malaria compounds,[2] hepatitis C protease inhibitors,[3] HIV-protease inhibitors,[4] anti-obesity therapeutics,[5] anticancer agents,[6] antibiotics,[7] anticonvulsants[8] and antimicrobials[9] (Fig. 1). Furthermore, ureas themselves are increasingly exploited as catalysts,[10] ligands,[11] reagents,[12] solvents[13] and substrates[14] for a multitude of synthetic transformations.

Due to their importance a variety of methods have been developed for the synthesis of ureas,[15] with a recent emphasis on developing greener, more sustainable processes.[16,17] One of the most common ways to synthesize ureas is from the reaction of isocyanates with amines. For example, a series of phenyl isocyanates **1** was reacted with *N*-aryl-*NH*-piperazine **2** to give a series of ureas **3** that was screened for inhibition of platelet-derived growth factor receptor phosphorylation (Fig. 2, eqn (1)).[18] In this typical example using DMF as solvent, a variety of ureas **3** were formed in good yields, though extended reaction times and extensive work-up/purification procedures needed to be employed. Whilst this reaction can be carried out in a variety of different solvents/reaction media, nearly 80% of the reactions in the literature use DMF or halogenated solvents.[19] There are strong environmental, safety and regulatory pressures to minimize the use of solvents that are designated as being high risk. Replacement for dipolar aprotic solvents,[20] such as problematic solvents DMF, NMP and DMAc, was recently highlighted as a priority within the pharmaceutical industry.[21] In turn, companies and academic researchers have put significant amounts of time, effort and expense into the development of more sustainable chemical processes that do not rely on high risk solvents.[22,23] A possible alternative to DMF and other polar aprotic solvents is Cyrene (**7**, dihydrolevoglucosenone, Fig. 2).[24] Cyrene is synthesised in a two-step process from waste cellulose.[25,26] Importantly, it has similar physical properties to other dipolar aprotic solvents, including DMF. The viability of Cyrene as a DMF replacement was recently demonstrated by Watson *et al.* in palladium mediated cross-coupling reactions.[27] In addition, Cyrene[28,29] was shown to be an effective solvent in S_N2 and S_NAr reactions[24] as well as for the synthesis of MOFs.[30] Interestingly, the use of Cyrene as a solvent for the addition of a nucleophile to a carbonyl has not been investigated despite the fact that these processes are known to be promoted by polar aprotic solvents.[31] Herein, we present the development and scope of the use of the bio-available solvent Cyrene (**7**) for the synthesis of ureas **6** from the reaction of isocyanates **4** with amines **5** (Fig. 2, eqn (2)). An emphasis was placed on minimizing the amount of waste produced during the work-up, isolation and purification of the product.

Results and discussion

To begin the investigation, the reaction of phenylisocyanate (**4a**) and pyrrolidine (**5a**) in Cyrene (**7**) was investigated (Scheme 1). Whilst the optimization of the reaction was straightforward, the isolation of the pure urea was more problematic. In order to minimize by-products, the reagents were added together at 0 °C and allowed to warm to rt for 1 h.

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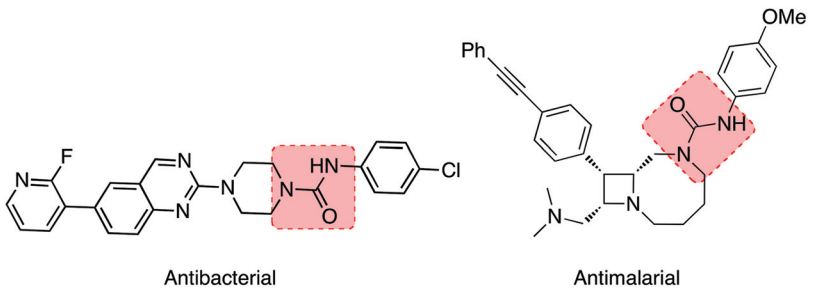


Fig. 1 Biologically active ureas.

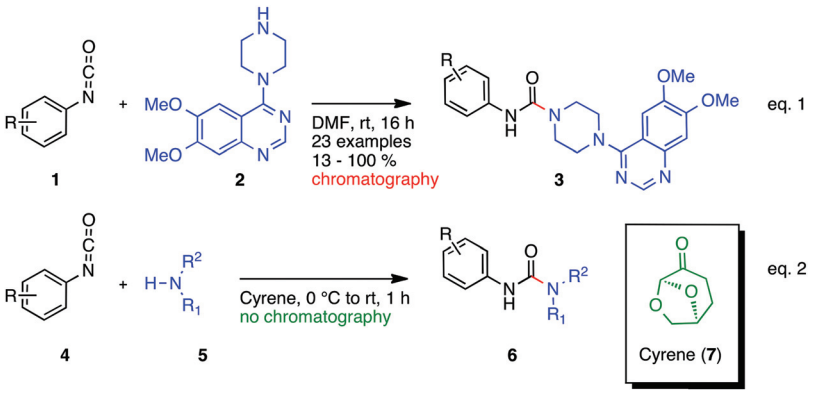
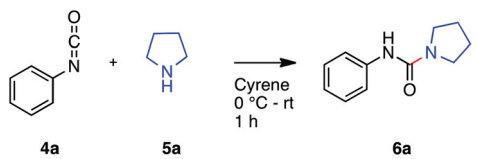


Fig. 2 Reaction of isocyanates and amines in DMF and Cyrene.



Scheme 1 Optimization of the synthesis of urea **6a** in Cyrene.

This protocol allowed for the development of a general procedure for both electron rich and electron deficient isocyanates (*vide infra*). Initially, the product was isolated by the addition of water and dichloromethane, liquid–liquid extraction, washing with water/brine, drying over magnesium sulphate and purified by column chromatography (hexanes/ethyl acetate). This extended procedure resulted in a high yield of the desired urea **6a**, 90%, but also led to a significant amount of waste in the form of organic solvents and contaminated aqueous waste. In addition, the Cyrene was found to co-elute with the product and additional column purification was sometimes required in order to get pure compounds. In order to minimize the use of organic solvents as well as the amount of waste produced in the isolation of the product, it was decided to examine alternative work-up procedures. The use of various acid/base work-up procedures all led to decomposition of both the urea and Cyrene. Finally, it was found that the addition of water to the Cyrene solution at the conclusion of the reaction resulted in precipitation of the desired urea. Filtration and washing with water gave analytically pure *N*-phenylpyrrolidine-1-carboxamide (**6a**) in a synthetically useful yield of 80% (*cf.* Scheme 2).

In order to access the efficiency of the two protocols, molar efficiency calculations were undertaken using the method of Watson *et al.*[32] in which:

$$\text{molar efficiency(Mol. E\%)} = [\text{moles product/moles starting material} + \text{additives} + \text{catalysts} + \text{solvents}] \times 100$$

The Mol. E% was calculated for each step of the process and the total molar efficiency ($\text{molE}_{\text{total}}$) is the multiplication of these values. Comparison of the molar efficiency of our original process, which was based on the industrial standard protocol, *versus* the optimized water washing method showed that use of the latter gave a 28-fold increase in molar efficiency (Fig. 3).[33] Similar water addition work-up procedures have been employed to help minimize the *E*-factors.[34] This simple procedure also removed all of the Cyrene from the product, which has been shown to be one of the key challenges of using this solvent.[27] Importantly, this method allowed for elimination of all non-bioderived solvents from the process with only Cyrene and water required.

With the optimized reaction and isolation procedure in hand the scope of the reaction of amines with phenyl isocyanates (**4a**) in Cyrene was examined (Scheme 2). A variety of secondary cyclic **5a–d** and acyclic amines **5e–n** were subjected

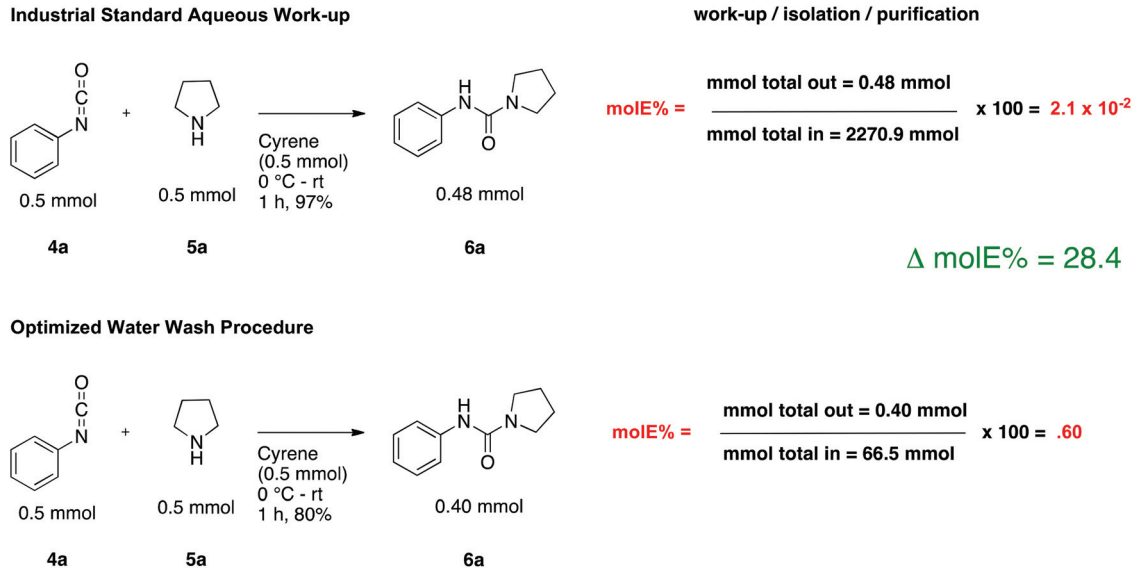
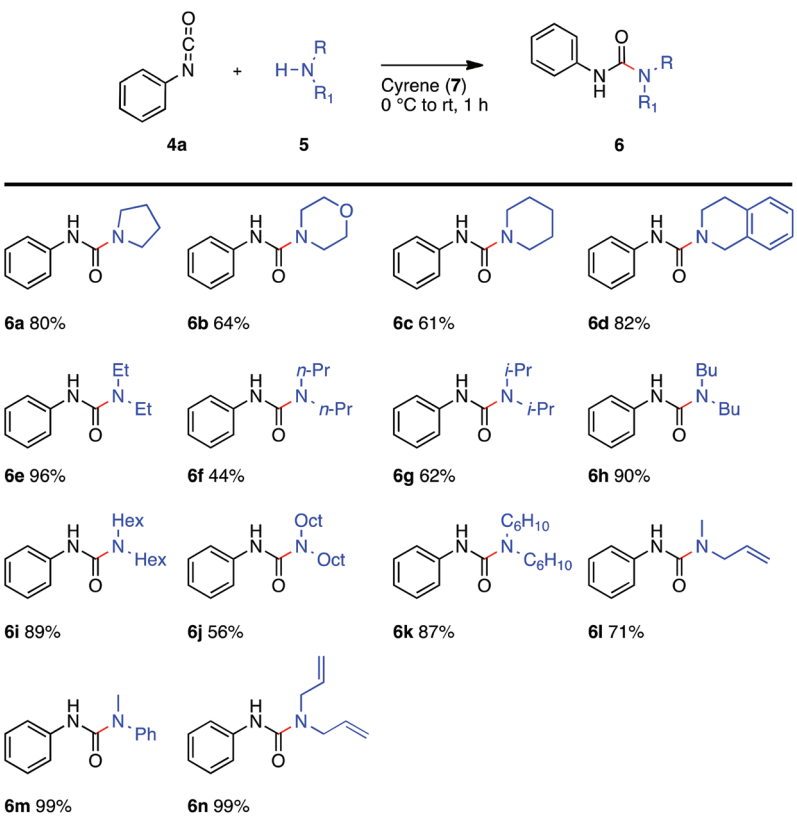


Fig. 3 Comparison of molar efficiency for the synthesis of ureas in Cyrene.



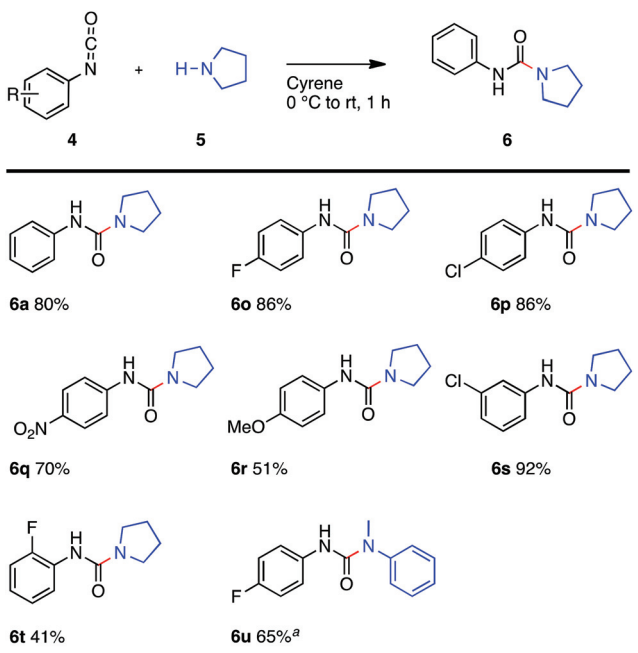
Scheme 2 Synthesis of ureas **6** from phenyl isocyanate **4a** and amines **5** in Cyrene **7**.

to the reaction conditions.[35] It was found that in addition to pyrrolidine (**5a**), cyclic amines piperidine (**5b**), morpholine (**5c**) and 1,2,3,4-tetrahydroisoquinoline (**5d**) gave the desired ureas, **6a–d** in good yield. *N*,*N*-Dialkyl amines **5e–j** with chain length between 2–8 carbons afforded ureas **6e–j** in good yields. In addition, *N*,*N*-dicyclohexylamine (**5k**) gave urea **6k** in 87% yield. Next, unsymmetrical secondary amines were subjected to the reaction conditions. Both *N*-methyl-*N*-allyl-amine (**5l**) and *N*-methylaniline (**5m**) gave the desired ureas, **6l** and **6m**, in good yields when subjected to the standard

conditions. Finally, bis-*N*-allylamine (**5n**) afforded 1,1-diallyl-3-phenylurea (**6n**) in excellent yield when reacted with phenyl isocyanate (**4a**).

Next, the effects of a substituent on the aryl isocyanates were investigated. Thus, a series of substituted aryl isocyanates **4** were reacted with pyrrolidine (**5a**) to give ureas **6o–u** (Scheme 3). Using the optimized conditions for phenyl isocyanate (**4a**) afforded the desired ureas **6o–u** in moderate to good yield. Having an electron-withdrawing group at the 4-position, such as in 4-fluoro-, 4-chloro- and 4-nitrophenyl isocyanates (**4b–d**), led to increased yields relative to the more electron rich 4-methoxyphenyl isocyanate. The use of 2-fluorophenyl isocyanate gave the desired urea **6t** in a lower yield than the 4-fluorophenyl isocyanate isomer. This result suggests that the steric hindrance imposed by having an *ortho* substituent on the aromatic ring leads to a decrease in yield. Finally, 4-fluorophenyl isocyanate was reacted with *N*-methylaniline under the standard conditions to give 1-methyl-1,3-diphenylurea (**6u**) in good yield.

In situ ^{19}F NMR was used to compare the rate of the formation of ureas from isocyanates and amines in Cyrene *versus* the industrial standard solvents DMF and CH_2Cl_2. The room temperature reaction of 4-fluorophenyl isocyanate (**4b**) and pyrrolidine (**5a**) to give urea **6o** in the three solvents of interest was monitored by NMR spectroscopy. All of the reactions were found to be complete in less than 5 minutes when run at 1 M concentration. The relatively fast rates of these reactions is due to the activating 4-fluoro moiety on the phenyl isocyanate. Importantly, this analysis provided further support for the viability of Cyrene to replace the industrial standard solvents DMF and CH_2Cl_2 in this process.



[a] *N*-methylaniline was used

Scheme 3 Effect of substituent on isocyanate reactivity.

Conclusions

In summary, a green, mild and efficient approach towards the synthesis of ureas from aryl isocyanates and secondary amines in the bio-alternative solvent Cyrene was developed. Both the scope of the amine nucleophile and the effect of substitution on the aryl isocyanate were investigated. This method provides an important alternative to the current industrial use of DMF and halogenated solvents for this process. Importantly, it eliminates the need for the use of both these toxic solvents as well as any non-bioderived organic solvent. Of even more importance is the fact that simply treating the reaction mixture with water solved one of the key problems associated with the use of Cyrene as a solvent, its removal from the product.

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