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# Visible-Light-Mediated Amide Synthesis in Deep Eutectic Solvents

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Dedicated to Miquel A. Pericàs for his scientific contributions, on the occasion of his retirement from the ICIQ.

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**Abstract.** In the present study, for the first time environmentally friendly deep eutectic solvents (DESs) are used as reaction media to perform an efficient, simple and straightforward photocatalytic amide synthesis at room temperature using thioacids and amines. This method features mild conditions, a broad substrate scope, high yields (≤99%) under ambient conditions with air and moisture tolerance. Moreover, the applied operationally mild reaction conditions tolerate the presence of several different functional group substituents on the amine counterpart. Finally, the developed approach allows the recycling of the reaction medium and catalyst for at least three consecutive cycles without a significant decrease in the reaction yield.

## Introduction

The production of chemicals requires the implementation of new sustainable methodologies for their synthesis. Replacement of volatile organic compounds (VOCs) for more environmentally benign alternatives has improved the sustainability of organic processes. In this regard, due to their unique and tuneable properties,[1] DESs have been employed to perform traditional and novel reactions,[2] including organocatalysed processes,[3] as well as transition-metal mediated transformations.[4] Another important aspect to improve the sustainability of an industrial process is the development of efficient catalytic systems. Particularly, photoredox catalysis has stood up in recent years due to the possibility of employing (solar)light to facilitate a given reaction.[5] However, photoredox processes generally demand the use of inert conditions and a narrow range of VOC solvents.

Although the spectacular synthetic achievements of the use of DES as reaction media during the last 20 years, their combination with photocatalytic process remained mostly elusive. In this sense, a seminal work by Capriati *et al.* described an enzymatic photosynthetic process using DESs as solvents in 2017,[6] paving the way for further researcher. However, so far only a handful of reports can be found in the literature regarding the use of DESs as solvents and different types of photoirradiation, which include resveratrol isomerization,[7] the study of pyrene fluorescence dissolved in reline,[8] and very recently, the thiol-ene click reaction in ChCl:glycerol.[9] However, the implementation of recent photocatalyzed processes[5,10] in these neoteric solvents is still uncharted territory. The possible light absorption of some DES components, the presence of cations and anions which can interact with the photocatalyst excited state, or the non-homogeneous character of the DES 3D-network based on hydrogen bonds may be some of the reasons that could explain why these processes have remained out of reach in the field of DESs.

Therefore, we aimed to develop a synthetic method based on these premises, and more specifically, we focused on the formation of amides. Amides have great relevance to medicinal chemistry.[11] However, amide synthesis generally rely on the activation of a

carboxylic acid by the use of stoichiometric amounts of costly and toxic coupling reagents as well as VOCs as reaction media.[12] This led to a call for research into new strategies with high atom economy for amide synthesis with reduced environmental impact.[13] Although, several methods[14] have been developed for the construction of amide bonds in a green and sustainable manner, still take place at high temperatures and use unsustainable reaction media, among other issues.[15] Therefore, further considerations should be given to aspects like catalyst recyclability, waste disposal, safety, room temperature operation, and use of greener solvents.[16]

Photoredox catalysed amide synthesis offers several advantages, such as the ability to activate organic substrates under mild reaction conditions, as well as the capability of exhibiting higher selectivities than those found in traditional methods. [17] Among the most effective acyl sources, thioacids proved to play an essential role in the formation of amide bonds, through their capability of forming thioacid radicals.[18] As a result of visible light irradiation, thioacids can be activated to generate active intermediates that may act *in situ* as mild acylating reagents in the presence of amines, allowing the synthesis of amides of industrial significance and biologically meaningful peptides. In this scenario, Tan's research group employed $Ru(bpy)_3Cl_2$ as a photocatalyst to generate disulfide intermediates from thioacid potassium salts in order to produce amides (Figure 1a).[19] Later, the group of Biswas reported the efficient successful synthesis of amides from thioacids by using CdS nanoparticles as heterogeneous photocatalysts (Figure 1b).[20] Finally, it is worth mentioning that Song and co-workers reported the oxidative amidation of thioacids by using an organic dye as photocatalyst and air as an oxidant (Figure 1c).[18] All these previous works show the fine applicability of thioacids as an important source for photocatalytic amidation.
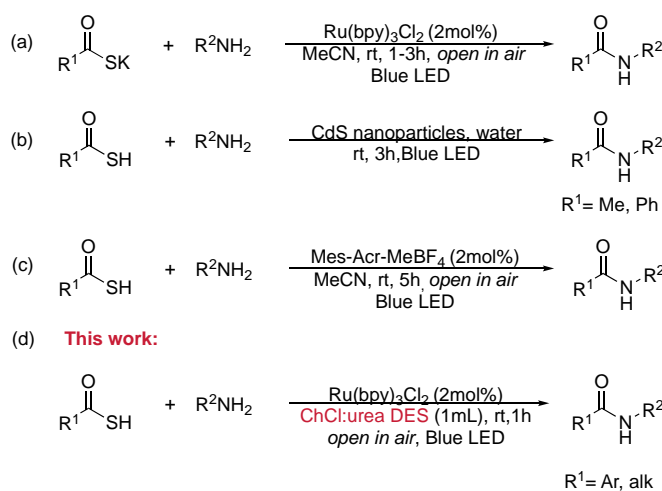


**Figure 1.** Approaches for amide bond formation under photoredox catalysis.

However, the use of highly diluted organic solvents, the required preformation of thioacid salt, the need of expensive, toxic or non-commercial catalyst or limitations on substrate scope still aspects to improve in order to transfer these procedures to industry.

Taking these previous results into account and being motivated by the valuable characteristics of DESs, we present for the first time a straightforward and rapid protocol for the synthesis of amides from thioacids using visible light under mild conditions in DES. $Ru(bpy)_3Cl_2$ was selected as a photocatalyst due to its easy availability. In light of these examples, DESs are now open for potential applications in any other photocatalyzed process.

This green approach showed excellent functional selectivity in forming an amide bond without affecting other functional groups at the aromatic ring such as alcohols, ethers and halogens. The obtained results were comparable or better in some cases than those previously described in toxic volatile organic solvents, while the sustainability of the process is greatly improved.

## Results and Discussion

The study started by testing the the amide formation merging thioacetic acid **1a** and aniline **2a**, catalyzed by visible light photosensitizer $Ru(bpy)_3Cl_2$[21] (Table 1, entry 1), using the mixture $K_2CO_3$:glycerol (1:4) as solvent. After exposure to a blue light-emitting diode (LED) (450 nm) irradiation for 5 h, the two substrates were converted to the corresponding amide product **3a** in moderate efficiency (71% yield). In an attempt to optimize the reaction conditions, we decided to explore the contributing factors such as DES systems, photocatalysts, substrate and catalyst loadings, that could facilitate this transformation (Table 1). Regarding the DESs systems, the best results were obtained with the eutectic mixture ChCl:urea without the need of an external base. Among the factors that can explain the better performance of this solvent, are the basic character of the system, which can deprotonate the thioacid facilitating the course of the reaction, in addition to the lower viscosity of ChCl:urea compared with other DESs.[22] Considering that the DES could work as both the reaction medium and the base, such photoredox catalytic amide formation could be achieved without the extra addition of an inorganic salt or base, compared with the previous reported protocols, thus reducing the chemical waste of the process. Concerning the efficiency of the photocatalysts, the best results were obtained with $Ru(bpy)_3Cl_2$, affording the desired product in 91% yield when it was used in combination with ChCl:urea (Table 1, entry 6). When the same reaction was performed for 1h, the amide was obtained in quantitative yield (Table 1, entry 23). This is probably due to degradation processes that could occur by extending the reaction time. Interestingly, increasing the catalyst loading to 3-5 mol% resulted in a decrease of the yield (Table 1, entries 21 and 22),

while a using equimolar amounts of amine and thioacid or using the thioacid as limiting reagent (Table 1, entries 24-25) caused a yield drop. Finally, it was observed a sharp decrease of the yield when the reaction was performed in darkness with or without a catalyst (Table 1, entries 26 and 27), supporting the photoredox catalysis-based mechanism. Interestingly, other photocatalysts gave similar results (entries 6-10), which is an important aspect for its implementation in further photocatalyzed processes in DES media.

With the optimized conditions in hand, we next began to assess the substrate scope and versatility of this methodology. As shown in Scheme 1, upon exposure of structurally variable aromatic aniline derivatives (**3b-3k**) to the standard conditions, the amide products were isolated in a highly efficient manner, with yields ranging from 68% to 96%.
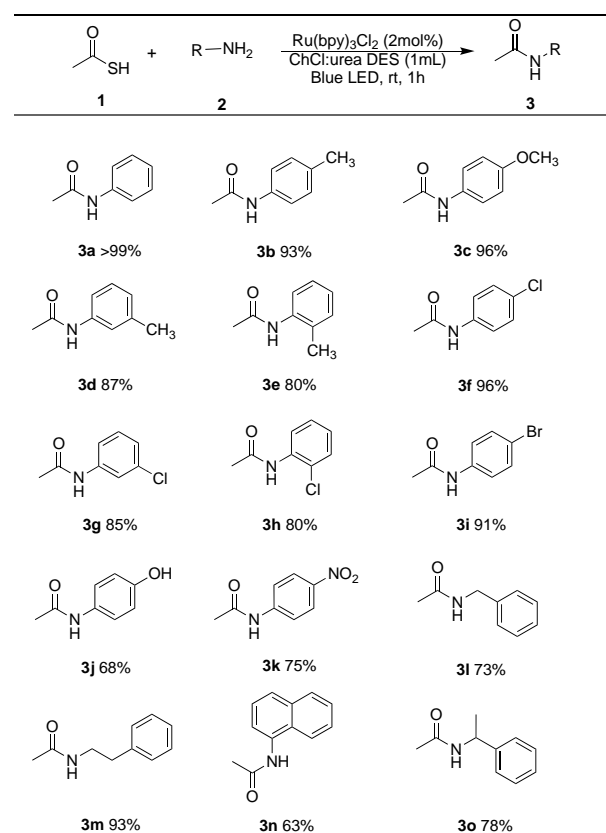
**Table 1.** Optimization of the reaction conditions[a]



| Entry | DES systems | Catalyst (mol%) | Yield (%)[b] |
|---|---|---|---|
| 1 | K$_2$CO$_3$: Gly (1:4) | Ru(bpy)$_3$Cl$_2$ (2 mol%) | 71 |
| 2 | K$_2$CO$_3$: Gly (1:4) | Mes-Acr-ClO$_4$ (2 mol%) | 91 |
| 3 | K$_2$CO$_3$: Gly (1:4) | Fluoresceine (2 mol%) | 74 |
| 4 | K$_2$CO$_3$: Gly (1:4) | Riboflavin (2 mol%) | 63 |
| 5 | K$_2$CO$_3$: Gly (1:4) | [Ir(ppy)$_3$] (2 mol%) | 81 |
| 6 | ChCl:urea (1:2) | Ru(bpy)$_3$Cl$_2$ (2 mol%) | 91 |
| 7 | ChCl:urea (1:2) | Mes-Acr-ClO$_4$ (2 mol%) | 87 |
| 8 | ChCl:urea (1:2) | Fluoresceine (2 mol%) | 83 |
| 9 | ChCl:urea (1:2) | Riboflavin (2 mol%) | 77 |
| 10 | ChCl:urea (1:2) | [Ir(ppy)$_3$] (2 mol%) | 86 |
| 11 | ChCh:glycerol (1:2) | Ru(bpy)$_3$Cl$_2$ (2mol%) | 78 |
| 12 | ChCh:glycerol (1:2) | Mes-Acr-ClO$_4$ (2 mol%) | 79 |
| 13 | ChCh:glycerol (1:2) | Fluoresceine (2 mol%) | 65 |
| 14 | ChCh:glycerol (1:2) | Riboflavin (2 mol%) | 73 |
| 15 | ChCh:glycerol (1:2) | [Ir(ppy)$_3$] (2 mol%) | 85 |
| 16 | Bet:HFIP (1:2) | Ru(bpy)$_3$Cl$_2$ (2 mol%) | 89 |
| 17 | Bet:HFIP (1:2) | Mes-Acr-ClO$_4$ (2 mol%) | 61 |
| 18 | Bet:HFIP (1:2) | Fluoresceine (2 mol%) | 65 |
| 19 | Bet:HFIP (1:2) | Riboflavin (2 mol%) | 71 |
| 20 | Bet:HFIP (1:2) | [Ir(ppy)$_3$] (2 mol%) | 87 |
| 21 | ChCl:urea (1:2) | Ru(bpy)$_3$Cl$_3$ (3 mol%) | 93 |
| 22 | ChCl:urea (1:2) | Ru(bpy)$_3$Cl$_2$ (5 mol%) | 89 |
| **23**[c] | **ChCl:urea (1:2)** | **Ru(bpy)$_3$Cl$_2$ (2 mol%)** | **>99** |
| 24[d] | ChCl:urea (1:2) | Ru(bpy)$_3$Cl$_2$ (2 mol%) | 46 |
| 25[e] | ChCl:urea (1:2) | Ru(bpy)$_3$Cl$_2$ (2 mol%) | 78 |
| 26[f] | ChCl:urea (1:2) | Ru(bpy)$_3$Cl$_2$ (2 mol%) | 27 |
| 27[g] | ChCl:urea (1:2) | - | 19 |

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), catalyst (2–5 mol%) at rt in 1 mL of DES. [b]Yield determined by $^1$H NMR using 1,2,4,5-tetramethylbenzene as internal standard. [c]The reaction was performed in 1 h. [d] **1a** (0.2 mmol), **2a** (0.2 mmol), catalyst (3 mol%) at rt in 1 mL of DES. [e] **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (3 mol%) at rt in 1 mL of DES, [f]The reaction was performed in darkness. [g] The reaction was performed in darkness with or without a catalyst.

The electronic effect of the substituents present in the amines did not seem to have relevant effect for this transformation, since aniline derivatives decorated with electron-withdrawing or electron-donating substituents afforded similar results. Namely, the reaction yields obtained for electron-donating *p*-methylphenyl (**3b**) and *p*-methoxyphenyl (**3c**) products were comparable to those of electron-deficient *p*-chlorophenyl (**3f**) and *p*-bromophenyl (**3i**) ones. In addition to the *para*-substituted anilines, the corresponding *m*- and *o*-methylanilines (**3d** and **3e**) or chloroanilines (**3g** and **3h**) were also smoothly transformed into the corresponding amides in reasonable yields. Furthermore, a superior selectivity toward the acylation of the amine motif to the free hydroxyl group was also proven using *p*-aminophenol as substrate leading to the amide **3j** bearing a phenolic group, without any ester detected as by-product.

Finally, *N*-(naphthalen-1-yl) acetamide (**3n**) was achieved from 1-naphthylamine with 63% yield. It can be inferred that stearic issues on the amine are more relevant in this transformation, as slightly lower yields were obtained when *ortho*-substituted anilines were employed (**3e**, **3h**, **3n**). It is worth noting that aliphatic amines (**3m-3o**) were also tolerated under the same reaction conditions, affording the desired amide products in moderate to excellent yields (73%−93%). To further extend the scope of this protocol, other aromatic and aliphatic thioacids beyond thioacetic acid were screened.





3a >99%  3b 93%  3c 96%
3d 87%  3e 80%  3f 96%
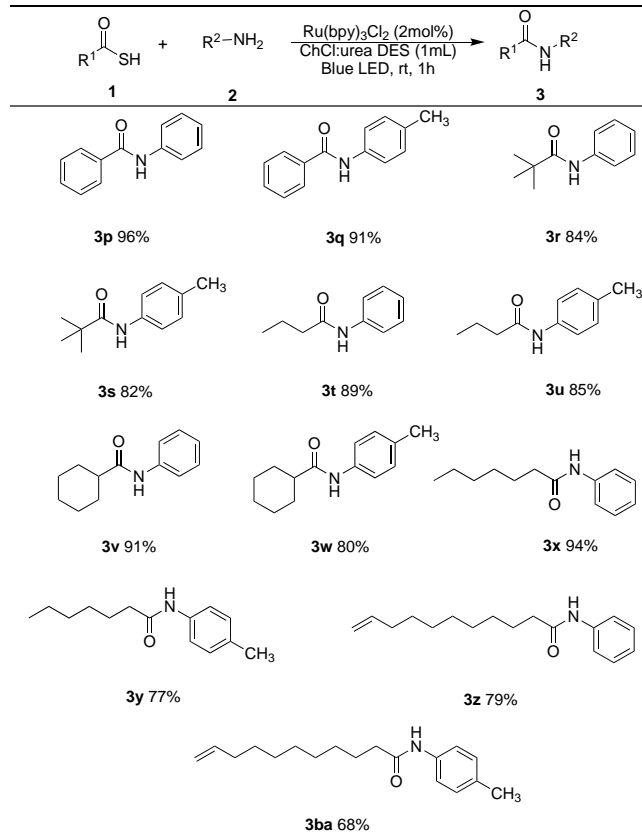3g 85%  3h 80%  3i 91%
3j 68%  3k 75%  3l 73%
3m 93%  3n 63%  3o 78%

**Scheme 1.** Reaction scope of visible light-mediated N-acylation reaction. Reaction conditions: **1a** (2.0 equiv), **2** (1.0 equiv), Ru(bpy)$_3$Cl$_2$ (2 mol %), DES (1 mL), rt for 1 h. Yield of the isolated product.
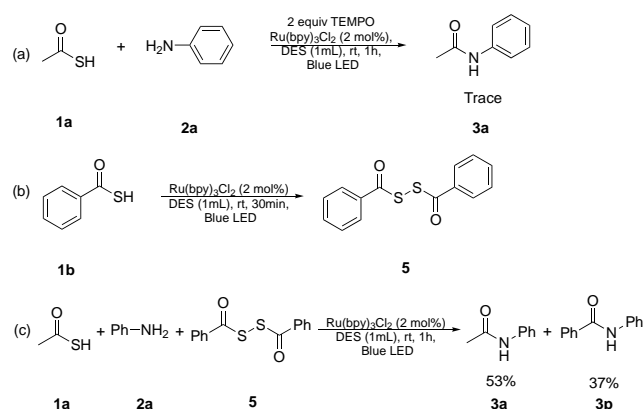
As shown in Scheme 2, aniline and *p*-toluidine could react with thiobenzoic acid to afford **3p** and **3q** in high yields (96% and 91% respectively). For alkyl thioacids, good yields were obtained in the case of cyclohexyl, *tert*-butyl, *n*-pentyl, and *n*-heptyl substrates (**3r-3y**). Even terminal alkene moieties, a typical scavenger of radical intermediates, were tolerated, since undec-10-enoic thioacid could be efficiently employed as coupling partner with aniline and *p*-toluidine (**3z** and **3ba**), without observing any side reaction.

In order to shed light on the potential reaction pathway, mechanistic experiments were conducted, as summarized in Scheme 3. The results obtained are in line with the previously reported works.[5, 8-9] In this sense, when 2.0 equiv. of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) was added to the mixture of thioacetic acid (**1a**) and aniline (**2a**), the corresponding amide (**3a**) was obtained only in trace amounts (Scheme 3a). Therefore, a mechanism involving the thioacid radical was suggested.

To gain a deep insight into the reaction associated with the isolation of active intermediates, thiobenzoic acid **4a** was exposed to visible light for 30 minutes and yielded an instructive disulfide intermediate with almost 57% yield (Scheme 3b). An orthogonal experiment using thioacetic acid **1a** and disulfide intermediate **5** was set up under standard conditions (Scheme 3c). A mixture of **3a** and **4a** was obtained, which clearly demonstrated that disulfide intermediate **5** would be involved in the mechanism.
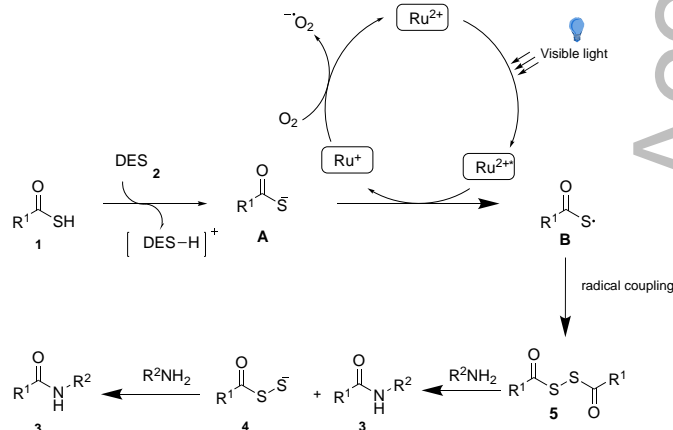


**Scheme 3.** Experimental tests on reaction mechanism

Finally, the involvement of atmospheric oxygen was evaluated by performing the model reaction under argon atmosphere. Thus, a much lower reaction rate was observed, obtaining only 46% yield of **3a** after 2 h instead of the 99% yield observed under aerobic conditions.

Based on the results of the above-mentioned studies, a plausible mechanism is proposed for the synthesis of amides (Scheme 4). Initially, thioacid **1** was deprotonated by the DES to form the intermediate **A**, although the role of the starting amine should not be ruled out. The blue LED should photoexcite the Ru$^{2+}$ to generate excited Ru$^{2+*}$, which was subsequently reduced to Ru$^{1+}$ by the electron-rich thioacetic anion. Then, the involvement of atmospheric oxygen,[23] converting Ru$^{1+}$ back to Ru$^{2+}$, closed the whole catalytic process. This single-electron transfer (SET) resulted in the generation of thioacetic acid radical **B**, which was transformed to the disulfide intermediate **5** by diradical coupling reaction and then induced the amide formation by means of a nucleophilic attack of amine **2** to afford the amide **3**. At the same time, intermediate **4** could further generate amide **3** through aminolysis.

Since the recycling of the DES and the catalyst is a crucial point for the sustainability of the process from the industrial point of view, we also evaluated the possibility to recover the DES-catalyst system and reuse it.



**Scheme 2.** Scope of thioacids substrates. Reaction conditions: **1** (2.0 equiv), **2** (1.0 equiv), Ru(bpy)$_3$Cl$_2$ (2 mol %), DES (1mL), rt for 1 h. Yields of the isolated products.



**Scheme 4.** Proposed mechanism for photocatalytic amide synthesis

4

Therefore, the extraction of the organic compounds using different immiscible organic solvents was performed. The best results were obtained when ethyl acetate was employed. The mixture of DES and photocatalyst was reused, after being vacuum dried, performing a new reaction cycle under the same reaction conditions. It was possible to recycle the DES and catalyst for up to three cycles, even though a decrease in the reaction yield was observed after the third cycle (Figure 2). ICP-MS analysis showed that only 0.2% of the initial Ru loading was extracted with EtOAc. Therefore, most of the catalyst remains in the DES phase and the lost in activity should be attributed to other factors such as the cumulative presence of different salts that could affect the DES structure.

To assess the efficiency of the developed method, some green metrics were analysed and compared with the previously reported photoredox amide synthesis from amines and thioacids. In this regard, a semiquantitative analysis which takes into account the quality of a protocol based on reaction yield, cost, safety and ease of purification known as EcoScale[24] was determined. Thus, the EcoScale value of the present protocol performed in DES was 64, with values ranging from 50 to 75 being classified as acceptable. This fact is particularly relevant when compared with the values of those reports performed with the same catalyst but using MeCN as the solvent,[19] or those using MesAcrBF$_4$[18] or CdS[20] as the catalyst, with values of 53, 57 and 52, respectively.[25] Regarding the atom economy[26] for the synthesis of **3a**, a value of 79.9% was obtained for the methods that make use of thioacetic acid, while a lower value of 65.2% is observed when potassium thioacetate is employed as reactant.
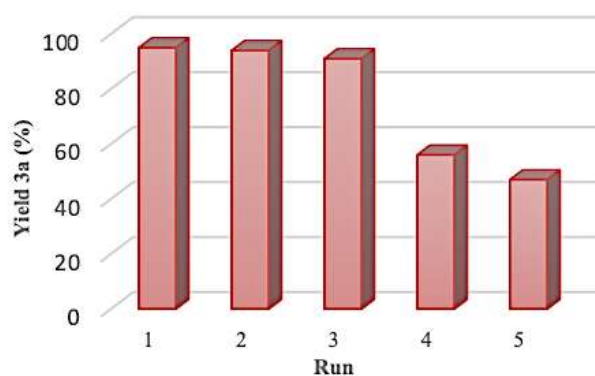


**Figure 1**. Recyclability of the system.

## Conclusion

In summary, we have described, for the first time, a visible-light-promoted photo-redox catalytic amide formation in an eco-friendly and biodegradable DES based on the ChCl:urea mixture. This method features operational simplicity, excellent functional selectivity, DES recoverability, short reaction time, broad substrate and photocatalyst scope and high yields (up to 99%). The recyclability of the DES and its

synergistic effect on the reaction outcome has also been demonstrated, highlighting the possibility to reuse the system for at least three consecutive cycles without a significant decrease in the reaction yield. This protocol proves the possibility of performing photoredox catalysis using DESs as reaction media, thus combining the use of sustainable solvents and a mild and efficient photoinduce activation process, which can open the gates to further studies in this field.

## Experimental Section

### General procedure for the preparation of DESs

A mixture of hydrogen-bond donor and hydrogen-bond acceptor compound, with the previously specified molar ratio, was added in a round bottom flask under an inert atmosphere. The mixture was stirred for 30 minutes in a T range between 65 and 80 °C obtaining the corresponding DES.

### General procedure for the synthesis of amides

To a vial containing Ru(bpy)$_3$Cl$_2$ (2.6 mg, 2 mol%) in DES (1 mL), the thioacid (0.4 mmol, 2 equiv.) and the amine (0.2 mmol, 1 equiv.) were added. The mixture was stirred under blue LED at rt for 1 h. Then, the mixture was quenched with water (2 mL) and extracted with EtOAc (3×4 mL). The organic phase was washed with brine and dried over MgSO$_4$. The crude organic phase was concentrated *in vacuo* and purified by preparative thin layer chromatography on silica gel (usually with hexane/EtOAc = 5:1) to afford the pure product.

### General procedure for the recycling experiments

The reaction was performed according to the general procedure. Once the reaction was complete, the formed product was extracted with a small amount of EtOAc (3 × 3 mL). The resulting biphasic mixture was stirred at room temperature for 10 min, and the upper phase was separated by decantation. Then, the residual eutectic mixture (bottom phase) was dried under vacuum and re-charged with fresh reagents, repeating the process.

## Acknowledgements

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## RESEARCH ARTICLE

Visible-Light-Mediated Amide Synthesis in Deep Eutectic Solvents

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Debora Procopio, Xavier Marset*, Gabriela Guillena, Maria Luisa Di Gioia, and Diego J. Ramón*

• visible light  • broad scope  • highly selectivity  • recyclability

7