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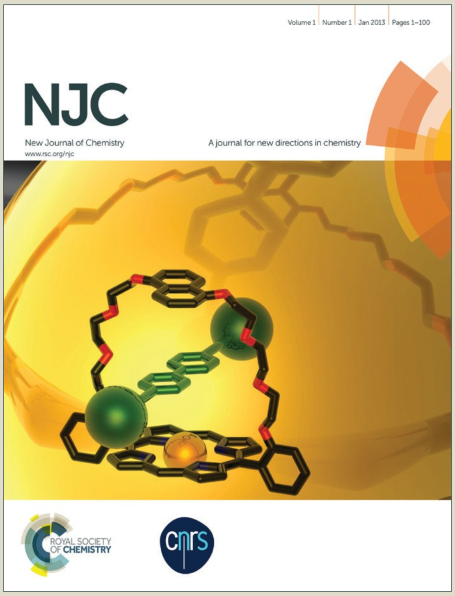

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Deep Eutectic Solvents Promoting 1,3-Dipolar Cycloaddition Between Azide and β-enaminones

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Marcos Antonio Pinto Martins*[a] , Guilherme Caneppele Paveglio[a], Leticia Valvassori Rodrigues[a], Clarissa Piccinin Frizzo[a], Nilo Zanatta[a], and Helio Gauze Bonacorso[a]

A simple procedure to obtain 4-acyl-1-substituted-1,2,3-triazoles, using a deep eutectic solvent (DES) — ChCl and ethylene glycol at a 1:2 ratio — as reaction media is described. The products were obtained at high selectivity and good yields (70–84%). The advantages of the method include: easy work-up, metal-free conditions, its inexpensiveness, and the ability to be used four times without a loss in yield.

The reaction of alkynes and azides is the most commonly described 1,3-dipolar cycloaddition, and it is also the most used synthetic route for 1,2,3-triazoles.[1a-c] The importance of this synthetic route increased when Sharpless and Meldal introduced copper as the catalyst in this reaction, which made it possible to obtain 1,4-dissubstituted 1,2,3-triazoles with high regioselectivity.[1d] Heterocycles containing a triazole skeleton have become important pharmacophores for the development of drugs, mainly because they are stable compounds that can mimic peptide bonds.[2] In particular, 4-acyl-1-substituted-1,2,3-triazoles have shown bactericidal[3] and anti-histamine activity,[4] and they are also potassium channel activators[5] and tuberculosis and protein inhibitors.[6,7] The 4-acyl-1-benzyl-1,2,3-triazoles have been synthesized from ynones[8–10] or propargylic alcohol[11] by 1,3-dipolar cycloaddition with alkyl azides. Often, 4-acyl-1-substituted-1,2,3-triazoles are synthesized from substrates which contain triple bonds and need copper or other additives, which, in some cases, is not sufficient for a highly selective reaction.[5] Additionally, these protocols employ toxic and expensive solvents and catalysts, which are difficult to dispose,[12,10] thus making numerous difficult work-up stages necessary (e.g., evaporation of solvent, distillation, column chromatography, etc.). Other routes have many reaction steps,[8,9] low yields,[2,9,12] and use reagents that are difficult to access and handle.[8,10] The 1,3-dipolar cycloaddition of phenylacetylene and alkyl azide in deep eutectic solvents (DES) has been reported a few times in the literature, and DES have become an environmentally friendly alternative to hazardous (organic) solvents due to their low vapour pressure (reduced air pollution), non-flammability (process safety), and nontoxicity.[13,14] Despite the current DES being used in organic reactions, there are only three articles that have used DES to promote the 1,3-dipolar cycloaddition. In 2015, Ramón et al. used the DES ChCl:Urea (1:2) as reaction media for the synthesis of 3,5-disubstituted isoxazoles and related isoxazolines, employing aldehydes, hydroxylamine hydrochloride, NCS, and phenylacetylene in a one-pot reaction.[14] The other works involved the 1,3-dipolar cycloaddition between phenylacetylene and alkyl azide.[15,16] In 2009, Konig et al.[15] employed a mixture of D-sorbitol and urea and NH_4Cl (type IV DES) at a ratio of 7:2:1, with CuI as catalyst. and this led to the product being isolated at high selectivity. Recently, García-Álvarez et al.[16] evaluated the effect of type III DES, using CuI as catalyst in the same reaction. Product was obtained with high selectivity, and the best results were obtained when glycerol was used.

The 1,3-Dipolar cycloaddition reaction of α,β-unsaturated ketones such as 1,1,1-trihalomethyl-4-alcoxy-3-alken-2-ones and β-enaminones is limited. Recently, Bonacorso et al. [17] were successful in the synthesis of rufinamide analogues from the 1,3-dipolar cycloaddition of 1,1,1-trihalomethyl-4-alcoxy-3-alken-2-ones and alkyl azides. However, the reaction involved long times, difficult work-up, and low selectivity.

Considering our previous experience with catalysed ionic liquid reactions,[18,19] as well as the fact that DES are promising in organic syntheses[13-16,20-23], we envision that DES could improve the reactivity of α,β-unsaturated ketones [CCC block] in 1,3-dipolar cycloaddition reactions.

Thus, the aim of this work was to evaluate the use of type III DES in a reaction between β-enaminones and organic azide for the synthesis of 4-acyl- 1-substituted-1,2,3-triazoles by 1,3-dipolar cycloaddition. We propose an alternative synthetic route without solvents, which involves high boiling points, difficult disposal[10] (Toluene, DMSO, and DMF), easy work-up, and is metal-free and highly selective.

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[a] Núcleo de Química de Heterociclos (NUQUIMHE), Departamento de Química, Universidade Federal de Santa Maria, 97105-900 Santa Maria, RS, Brazil.

E-mail: mmartins@base.ufsm.br

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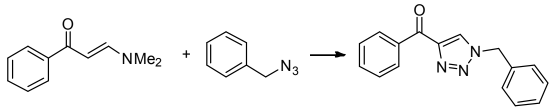
Table 1. Optimization of 1,3-dipolar cycloaddition of enaminone **1a** and benzyl azide **2**.

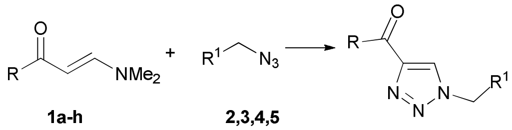


1a **2** **6a**

Entry	Time (h)	T (°C)	Catalyst	Conversion (%) [a]	Yield (%) [b]
1	15	80	ChCl:Urea (1:2)	17:83 [c]	-
2	18	120	ChCl:Urea(1:2)	59:41[c]	-
3	24	120	ChCl:Urea(1:2)	88:12[d]	-
4	24	130	ChCl:Urea(1:2)	>99 [d]	84 [e]
5	24	130	-	83:17[d]	-
6	24	118	Toluene[f]	17:83 [d]	-
7	24	130	ChCl:Glycerol(1:1)	88:12[d]	-
8	24	130	ChCl:Glycerol(1:2)	99:1 [d]	78
9	24	130	ChCl:Ethyleneglycol(1:1)	99:1 [d]	79
10	24	130	ChCl:Ethyleneglycol(1:2)	>99 [d]	81
11	24	130	1 Equiv. ChCl	91:9 [d]	-
12	24	130	2 equiv. Ethyleneglycol	92	75

[a]Percentage for **6a:1a** obtained by NMR; [b]Yields of purified product; [c] Reaction conditions: Enaminone **1a** (1.0 eq): azide 2 (1.0 eq):DES (1.0 eq); [d] Reaction conditions: Enaminone **1a** (1.0 eq): azide **2** (1.5 eq): DES (1.0 eq). [e] Product not purified. [f] 5 mL.

Table 2. 1,3-dipolar cycloaddition of enaminones **1a-h** and benzyl azide **2**, using DES (ChCl:ethylene glycol at 1:2).



1a-h **2,3,4,5** **6a-h,7a,8a,9a**

i: ChCl:ethylene glycol (1:2), 24 h, 130 °C

Product	R	R1	Yield (%) [a]
6a	Ph	Ph	81
6b	4-MeC$_6$H$_4$	Ph	84
6c	4-OMeC$_6$H$_4$	Ph	83
6d	4-BrC$_6$H$_4$	Ph	82
6e	4-IC$_6$H$_4$	Ph	83
6f	4-O$_2$NC$_6$H$_4$	Ph	77
6g	Naft-2-yl	Ph	83
6h	4,4'-Biphenyl	Ph	84
7a	Ph	Octyl	70
8a	Ph	4-OMeC$_6$H$_4$	83
9a	Ph	4-ClC$_6$H$_4$	77

[a] Yields of purified products.

We started our study from the reaction of β-enaminone **1a** and azide **2**, by evaluating DES performance in order to determine the best condition for the synthesis of 4-acyl-1-substituted-1,2,3-triazoles, as shown in Table 1. Firstly, we examined a **1a**:**2**:DES molar mixture (starting with a ratio of 1:1:1), stirred and heated at 80 °C for 15 h (Table 1, entry 1). However, it was not sufficient for complete conversion. The increase in the time to 18 h and 24 h, and temperature to 120°C, did not result in complete conversion either (Table 1, entries 2 and 3, respectively). Satisfactory conversion was achieved only when the reaction was conducted at 130 °C for 24 h (Table 1, entry 4). Furthermore, the reaction without DES did not produce good results (Table 1, entry 5). In the next step, toluene was evaluated; however, low conversions were obtained compared to DES (Table 1, entry 6). A ChCl and glycerol mixture (ratio of 1:1) was the least efficient reaction medium among the DES studied (Table 1, entry 7). ChCl and glycerol (ratio of 1:2) and ChCl and ethylene glycol (ratio of 1:1) did not achieve full conversion (Table 1, entries 8 and 9, respectively), but they showed very similar results to the ChCl and urea mixture (ratio of 1:2). The reaction in ChCl and ethylene glycol (ratio of 1:2) resulted in the β-enaminone **1a** being fully converted into product (Table 1, entry 10). The reaction in the presence of choline chloride was not effective (Table 1, entry 11). Finally, the reaction with 2 equiv. of the ethylene glycol resulted in good conversion, but unsatisfactory yield. Despite the ChCl and urea mixture (ratio of 1:2) having the best yield, it could be seen that the isolated product contained impurities (observed in ^{1}H NMR spectrum). Simeonov and Afonso[24] showed that during synthesis of the ChCl and urea mixture, urea can be decomposed to form ammonia. Ammonia formation could be responsible for impurities observed in the NMR spectra of product **3a**. The TGA analysis of the ChCl and urea mixture showed that the decomposition of ChCl started at 179 °C. Thus, in order to avoid the ammonia effect in the reaction, the ChCl and ethylene glycol mixture (ratio of 1:2) was chosen as the best medium.

The product obtained with the ChCl and ethylene glycol

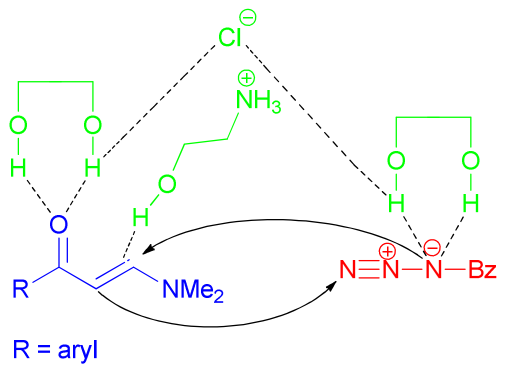


Figure 1. Possible pathway of the proposed mechanism.

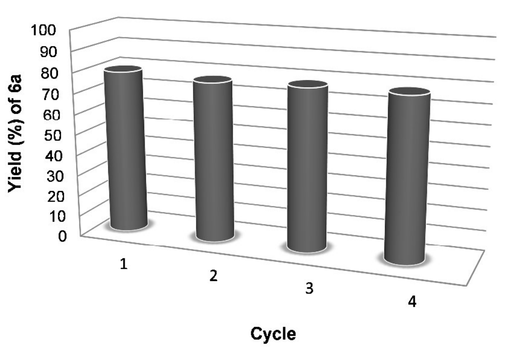


Figure 2. Recyclability of the ChCl and ethylene glycol mixture (ratio of 1:2) in the 1,3-dipolar cycloaddition of enaminone **1a** and azide **2**. Yield of isolated products.

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mixture (ratio of 1:2) was isolated without impurities. Simply washing with hexane was sufficient to remove excess benzyl azide and also furnish the triazoles in a pure form. In order to gain insight into the generality of this 1,3-dipolar cycloaddition reaction, azide **2** was reacted with other β-enaminones (**1a–h**), using the established reaction conditions. Furthermore, different organic azides **3,4,5** were reacted with β-enaminone **1a**. All products were obtained at good yields (77–84%), as shown in Table 2. The reactions were accompanied by ^{1}H NMR spectroscopic data, in which one can see the disappearance of a doublet signal of α-carbonyl hydrogen in the β–enaminones (~5.75 ppm) and the appearance of the singlet signal at ~8.2 ppm associated with the aromatic hydrogen of the 4-acyl-1-substituted-1,2,3-triazole (product). Compounds **6a-h** were fully characterized by ^{1}H and ^{13}C NMR. Compounds **6b**, **6d**, **6e**, and **6g and 9a** are described here for the first time (see data in the Electronic Supplementary Information). The chemical shifts corroborate with the literature and confirm the well-defined regiochemistry of compounds **6a-h**.[9,11]

Results showed that the synthesis of 4-acyl-1-substituted-1,2,3-triazoles by the 1,3-dipolar cycloaddition reaction of organic azide **2** and β-enaminones (**1a–h**) in a mixture of ChCl and ethylene glycol (ratio of 1:2) was not influenced by the presence of electron-withdrawing groups (EWG) or electron-releasing groups (ERG) in the aromatic ring of the β-enaminones (**1a-h**) — see Table 2.

Interestingly, the ChCl and ethylene glycol mixture (ratio of 1:2) has been used as an electrochemical solvent.[25] However, to the best of our knowledge; it has not been successfully used in organic reactions. The success of the ChCl and ethylene glycol mixture (ratio of 1:2) in comparison with the ChCl and urea mixture (ratio of 1:2) in this reaction is evidenced by the non-formation of byproducts, which ensures further product purification steps are avoided. The ChCl and urea mixture (ratio of 1:2) has more basic sites (for forming hydrogen bonds) than the ChCl and ethylene glycol mixture (ratio of 1:2), and probably allows the formation of byproducts. A possible hypothetic mechanism for the interaction of the ChCl and ethylene glycol mixture (ratio of 1:2) with azide and β-enaminones is depicted in Figure 1. It was based on the mechanism proposed by Pérez and Ramón[14] for a ChCl and urea mixture (ratio of 1:2) in the synthesis of 3,5-disubstituted isoxazoles/isoxazolines. In the proposed mechanism (Figure 1), one equivalent of the ethylene glycol interacts with the azide, whereas the other equivalent interacts with the carbonyl of the β-enaminone via hydrogen bonds. Additionally, the choline hydroxyl group can complex with the double bond of β-enaminone. These interactions probably decrease the energy gap of the frontier orbitals involved in the reaction, thus favouring the reaction.

Finally, investigation of the recovery and reuse of DES was performed in order to determine their efficiency as reaction media for the synthesis of 4-acyl-substituted-1,2,3-triazoles. For these studies, we used the model reaction involving β-enaminone **1a** with azide 2. After the extraction, hexane was added to the aqueous phase and the water was evaporated under reduced pressure. The DES was obtained in a pure form, without further purification. The recycled DES was used for up to four runs without significant loss in conversion and yields (Figure 2).

In conclusion, we have established an efficient synthesis of a series of 4-acyl-1-substituted-1,2,3-triazoles using the DES ChCl and ethylene glycol (at a ratio of 1:2) as reaction media. This is the first time that the DES ChCl and ethylene glycol (ratio of 1:2) has provided the best result in an organic reaction. The results presented in this paper demonstrate that a ChCl and ethylene glycol mixture (at a ratio of 1:2) is able to promote the synthesis of these compounds via an alternative synthetic route without using solvents that are difficult to separate of the products.

Furthermore, the use of it as reaction media made a highly selective synthesis possible in metal-free conditions, with an easy work-up. Additionally, a ChCl and ethylene glycol mixture (ratio of 1:2) is cheap, biodegradable, and allows recycling and reuse without a significant loss of yield.

Experimental

Preparation of DES: The DES were prepared by combining ChCl with different HBDs, in accordance with the procedures in the literature.[26]

General procedure for DES catalysed synthesis of 4-acyl-1-substituted-1,2,3-triazoles: The β-enaminone (1.0 eq), DES (1.0 eq), and organic azide (1.5eq) were mixed together in a 10 mL round-bottomed flask. The reaction was stirred at 130 °C for 24 h. Chloroform (10 mL) was added, and the resulting product (**6a-h,7-9**) was extracted from the DES (3 x 2 mL H_2O). The chloroform was dried over anhydrous Na_2SO_4 and evaporated until dry, thus leaving the desired triazoles. Product **6e** was separated using column chromatography for purification (Hexane and EtOAc at a 3:1 ratio). The other products were purified by washing with hexane. The structures of compounds (**6a-h,7-9**) were confirmed by ^{1}H/^{13}C NMR spectroscopy. This information is available in the Supplementary material.

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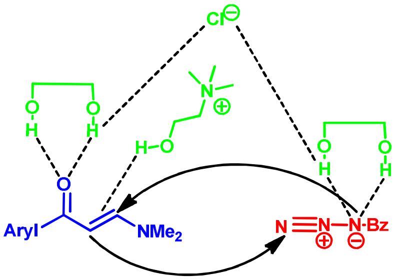

Metal-free, high selectivity and efficient synthesis of 4-acyl triazoles in DES (ChCl:ethylene glycol)