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1,3-Dipolar Cycloaddition of Alkanone Enolates with Azides in Deep Eutectic Solvents for the Metal-Free Regioselective Synthesis of Densely Functionalized 1,2,3-Triazoles

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Dedicated to Professor Cesare Gennari on the occasion of his 70th birthday.

An eco-friendly metal-free protocol was developed for the regioselective synthesis of densely functionalized 1,2,3-triazoles through a 1,3-dipolar cycloaddition reaction of alkanone enolates with azides performed in the environmentally responsible choline chloride/urea or choline acetate/urea eutectic mixture. This approach displays a broad substrate scope, straightforwardly furnishing the desired triazoles (including the challenging phenolic derivatives) in yields of up to 98%, while working at room temperature and under aerobic conditions. The practicability of the method is exemplified by the sustainable synthesis of some pharmaceutically relevant triazole derivatives carried out via telescoped, one-pot cycloaddition/reduction processes in the same eutectic mixture without any halfway isolation/purification step of intermediates.

Introduction

Among nitrogen-containing heterocycles, the triazole motif is widely present in many pharmacophore systems with anticancer, antimicrobial, anti-tubercular, antiviral, anti-inflammatory, antimalarial as well as neuroprotective properties (Figure 1).[1–4] As for the synthetic methods of 1,2,3-triazoles currently available, the thermal Huisgen 1,3-dipolar cycloaddition of alkynes to azides usually requires harsh conditions (100–150 °C), is conducted under an inert atmosphere with Schlenk techniques, and is known to proceed with very poor selectivities.[5] On the other hand, regioselective copper-catalyzed azide-alkyne cycloaddition (CuAAC) reactions are among widely pursued with the added advantage of catalyst recycling when heterogeneous conditions are used (Scheme 1a).[6a–f]

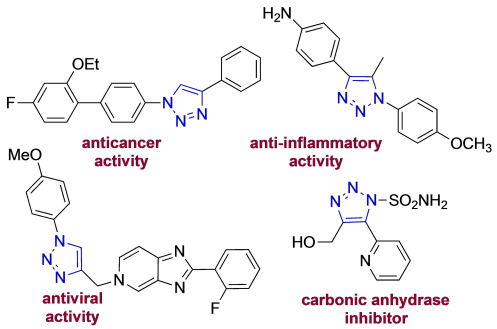

Figure 1. Selected examples of pharmacologically active 1,2,3-triazoles.

Direct metal-catalyzed arylation reactions with aryl halides permit further post-synthetic functionalization of the triazole moiety (Scheme 1a).[6g,h] Alternative, metal-free approaches especially include organocatalytic 1,3-dipolar cycloaddition strategies of aryl azides with enolizable compounds such as ketones,[7] alkylidene malononitriles, acetonitriles, β-ketoesters, β-keto-amides, and others[8] (Scheme 1b). It should be noted, however, that the aforementioned studies often involve the use of toxic, fossil-based, volatile organic compounds (VOCs) (e.g, DMF, CH_3CN, toluene, CH_2Cl_2), or organic solvents like DMSO, which limit their further practical applications.[9]

More eco-friendly CuAAC procedures rely on either the use of water as the reaction medium under heterogeneous conditions[10] or the employment of biodegradable, environmentally responsible, nature-inspired Deep Eutectic Solvents (DESs)[11] under homogeneous[12] or heterogeneous[13] conditions. Building upon our recent findings on the preparation of enolates[14] and variously functionalized nitrogen heterocycles (e.g., pyrazines, imidazoles, pyrimidines, 2-aminoimidazoles, 2-pyrazones, benzoxazines)[15–19] directly in DESs, in this work we

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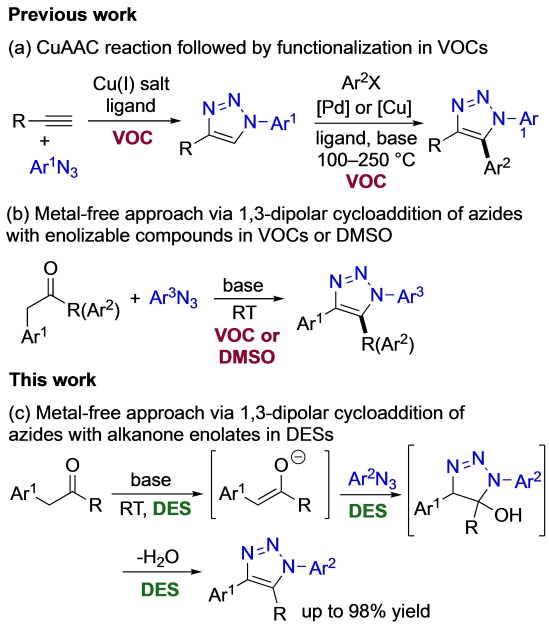


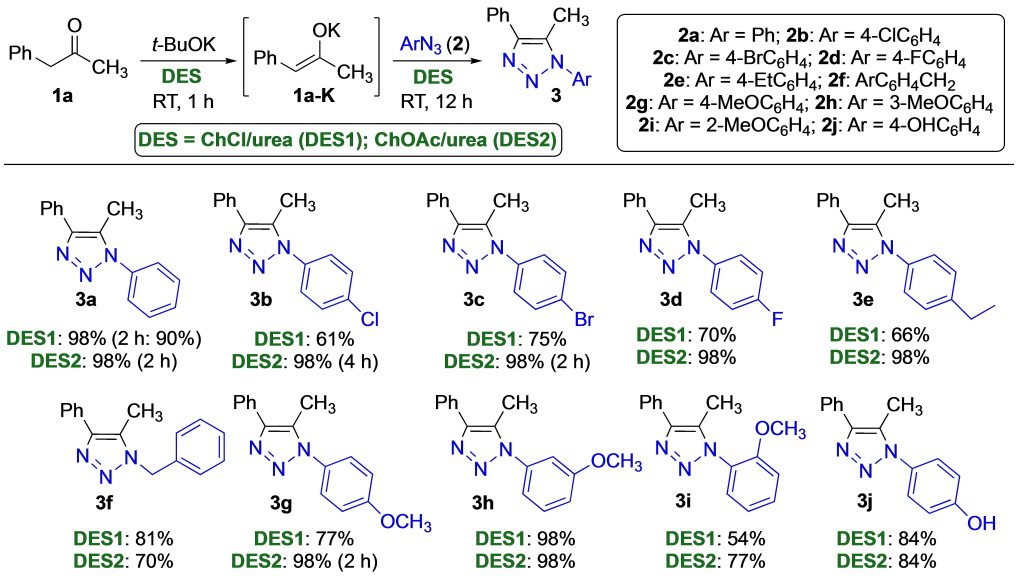
Scheme 1. Regioselective procedures for the synthesis of 1,2,3-triazoles via CuAAC and 1,3-dipolar cycloaddition reactions in VOCs or DMSO (a,b) and via 1,3-dipolar cycloaddition reactions in DESs (c). RT = room temperature.

demonstrate the versatility of type III eutectic mixtures (formed by an ammonium salt and an hydrogen bond donor) in enabling transition-metal-free cycloaddition reactions between enolates of alkanones and azides to afford densely functionalized 1,2,3-triazoles (Scheme 1c).

Notable features of our report include *i*) reactions run under mild conditions (room temperature), *ii*) broad substrate scope (26 examples) and high regioselectivity, with the desired educts prepared in good to excellent yields (up to 98%), *iii*) ability to telescope enolate formation/click cycloaddition/reduction or etherification reactions in a one-pot process to synthesize valuable pharmacologically active triazole derivatives.

Results and Discussion

We initiated our investigation using 1-phenylpropan-2-one (**1a**) as the model substrate, which was first treated with *t*-BuOK (3 equiv) for 1 h at room temperature (RT, 25 °C) in a choline chloride (ChCl)/urea (1 : 2 mol mol^{-1}) eutectic mixture to generate the enolate **1a-K**, according to our previous protocol.[14] The latter was then reacted with phenyl azide (**2a**) in the same eutectic mixture. After careful evaluation of the reaction time (see ESI), we found that the desired 5-methyl-1,4-diphenyl-1*H*-1,2,3-triazole (**3a**) could be isolated in 90% yield after 1 h, and quantitatively (98% yield) after 12 h reaction time (Scheme 2). We next studied the generality of this reaction in ChCl/urea between enolate **1a-K** and a variety of aromatic azides, in turn prepared from the appropriate aniline derivatives and $NaNO_2$/NaN_3 or *t*-BuONO/NaN_3 in aqueous solutions, according to reported procedures.[20] As shown from the results compiled in Scheme 2, a wide range of aryl azides decorated on the aromatic ring with various substituents at the *ortho*-, *meta*-, and *para*-positions including halogens (bromine, chlorine, fluorine), alkyl (Et) and benzyl substituents as well as electron-donating groups (MeO) (**2b–i**) proved to be competent partners, providing 1,2,3-triazoles **3b–i** in 54–98% yield after an overall time of 13 h (Scheme 2). Contrasting other synthetic multi-step procedures run in VOCs,[21] even the presence of an acidic hydroxy substituent at the *para*-position in azide **2j** was well tolerated, straightforwardly affording triazole **3j** in 84% yield. (Scheme 2). Of note, by replacing DES with an organic solvent



Scheme 2. Synthesis of 1-aryl-5-methyl-4-phenyl-1,2,3-1*H*-triazoles **3a–j** via cycloaddition reaction between enolate of 1-phenylpropan-2-one (**1a**) and aryl azides **2** in urea-based eutectic mixtures at room temperature (RT). In round brackets is reported the overall time for the transformation for the case examined.

like dimethyl sulfoxide, **1a** only underwent an aldol condensation reaction with itself in the presence of *t*-BuOK, while azide **2a** was quantitatively recovered.

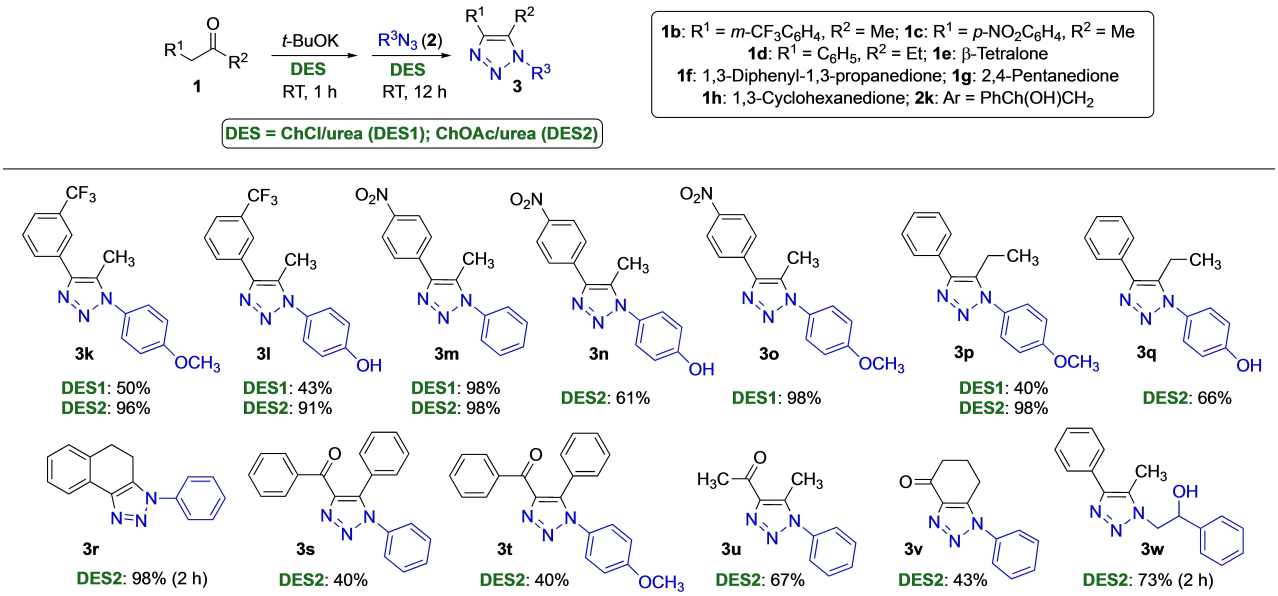
To the best of our knowledge, only one example of metal-free synthesis of 1,2,3-triazoles in DESs has been reported so far. This is based on a cycloaddition-elimination cascade reaction between aryl azides and enol ethers to access either 1,4-or 1,5-disubstituted triazoles.[22] Based on our previous findings that DESs can behave as non-innocent reaction media in catalyzing the cyclization/aromatization of nitrogen heterocycles,[15,16] we next turned our attention towards a different DES, namely choline acetate (ChOAc)/urea (1:2 mol mol^{-1}), whose components are both basic, and in which protons are more easily exchanged.[23] To our delight, using up to 2 equiv. of base, not only the range of yields increased up to 77–98% with 7 educts (**3a**–**e**, **3g**,**h**) now isolated in 98% yield, but the reaction time, in some cases, also shortened up to 2–4 h (**3b**,**c**,**g**) (Scheme 2). We envisage that the bidentate acetate anion of ChOAc could speed up the dehydration/aromatization process, which is the driving force of the overall triazole formation.

When further examining the scope of the enolate introducing additional substituents (e.g., CF_3, NO_2) on the aryl ring (**1b**,**c**) or changing the skeleton from 2-propanone to 2-butanone (**1d**) or starting from sterically hindered carbonyl compounds (β-tetralone, **1e**) or also using β-dicarbonyl derivatives [1,3-diphenyl-1,3-propanedione (**1f**), 2,4-pentanedione (**1g**), 1,3-cyclohexanedione (**1h**)], the cycloaddition reaction with aryl azides **2a**,**g**,**j** again proceeded smoothly in urea-based mixtures at RT to give regioselectively triazoles **3k**–**v** in 40–98% yield after overall 2–13 h (Scheme 3). Even a functionalized organic azide like 2-azido-1-phenylethan-2-ol (**2k**) proved to be a competent partner as well delivering in the cycloaddition reaction with carbonyl compound **1a** the triazole derivative **3w** in 73% yield after 2 h reaction time (Scheme 3). Of note, again, much better yields have been obtained for the synthesis of triazoles **3k**,**l**,**p** in ChOAc/urea (91–98%), when compared with those resulting from the reaction in ChCl/urea (40–50%) (Scheme 3). Structure of triazoles **3e**, **3k** and **3p** was secured by comparing NMR spectra with those reported for some analogues,[3] and unambiguously confirmed by single-crystal (**3p**) and powder diffraction data (**3e**,**k**) (Figure 2).[24] NOESY 2D experiments also confirmed the structure of phenylbutanone derivatives **3p** and **3q** (see ESI).

In order to prove the applicability of the method, we also carried out the synthesis of **3g** on a gram scale. The reaction between **1a** (11 mmol) and aryl azide **2g** (12 mmol) in 8.0 g ChOAc/urea again resulted in the formation of **3g** in 98% yield (2.86 g), and thus without any decrease in the reaction yield.

DES could also be easily recycled. The reaction between **1a** and **2g** in ChOAc/urea was chosen as a model reaction, since it delivered **3g** in almost quantitative yield. Upon completion of the first cycle, in-flask extraction with AcOEt afforded **3g** in 98% yield (number of recycles = 0). The DES phase was then dried under vacuum until a constant weight. Then, upon simply adding new, fresh reagents (**1a**, *t*-BuOK, **2g**), the recovered DES could be re-used for further reactions, thereby affording triazole **3g** in 94% yield after the second cycle, in 75% yield after the third cycle, and in 66% yield after the fourth cycle (see ESI for details).

Furthermore, we explored the direct preparation of aryl azides in the same eutectic mixture (ChCl/urea or ChOAc/urea), starting from the corresponding aniline derivative and using *t*-BuONO or $NaNO_2$, in combination with NaN_3, for diazotation. Gratifyingly, this reaction also worked well in DES at RT, and was compatible with several functional groups on the aniline core (e.g., MeO, OH, F, Br), thereby affording aryl azides



Scheme 3. Synthesis of 5-alkyl-1,4-diaryl-1*H*-1,2,3-triazoles **3** from alkanone derivatives **1** and azides **2** in urea-based eutectic mixtures at room temperature (RT). Typical conditions: **1b**–**d** (0.7 mmol), t-BuOK (DES1: 3 equiv; DES2: 2 equiv), DES (1.5 g), azide (0.82 mmol). In round brackets is reported the overall time for the transformation for the case examined.

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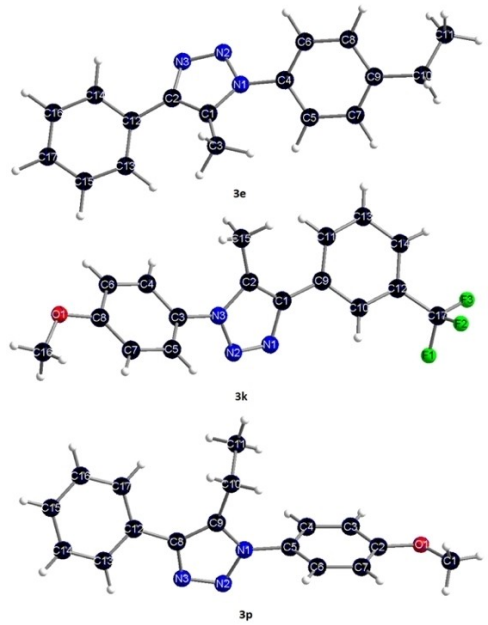
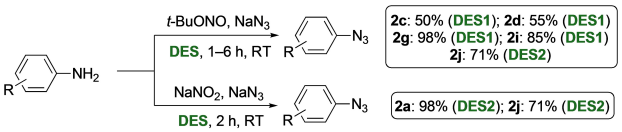


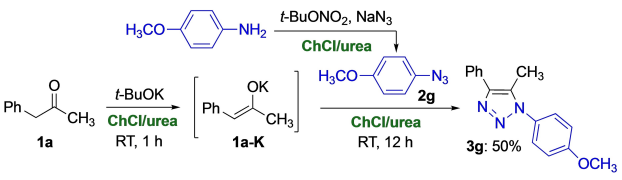
Figure 2. X-ray structures for triazoles **3e**, **3k** and **3p** showing the atom labelling scheme for non-H atoms.

2a,c,d,g,i,j in 50–98% yield within 1 to 6 h reaction time, according to the nature of diazotization reagent and the chemical stability of the azide (see ESI for further details) (Scheme 4).

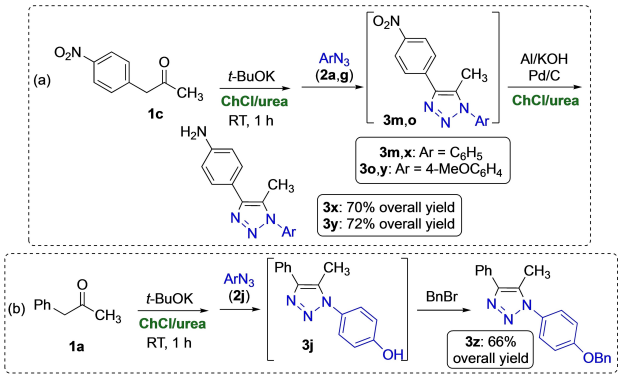
With these results in hands, we then planned a sequential three-step process aimed at regioselectively preparing functionalized 1,2,3-triazoles in DESs. The 1,3-dipolar cycloaddition between the enolate of **1a** and azide **2g** was chosen as a representative reaction. Working towards this goal, azide **2g** was first prepared from the corresponding aniline and *t*-BuONO/NaN_3 in a ChCl/urea mixture (1 h, RT), and then directly added to a suspension of 1-phenylpropan-2-one enolate (**1a-K**) in ChCl/urea, the latter in turn obtained from ketone **1a** and *t*-BuOK (3 equiv) after 1 h stirring at RT and under air. After 12 h



Scheme 4. Preparation of aryl azides **2** in DESs.



Scheme 5. Preparation of 1,2,3-triazole **3g** by sequentially reacting enolate of 1-phenyl-2-propanone **1a-K** with azide **2g** in ChCl/urea.



Scheme 6. Telescoped, one-pot cycloaddition/reduction (a) or cycloaddition/etherification (b) reactions from enolates of **1c** and **1a** and azides **2a,g,j**, in a ChCl/urea eutectic mixture, leading to functionalized triazoles **3x,y** (a) and **3z** (b) from triazole intermediates **3m,o** and **3j**, respectively.

stirring at RT, triazole **3g** could be isolated in 50% overall yield, as the sole product (Scheme 5).

Finally, we targeted telescoped, one-pot tandem processes for the preparation of triazole derivatives **3x,y** with anti-inflammatory properties[3] using ChCl/urea as the reaction medium. To this end, enolate of nitro-functionalized alkanone **1c** was first subjected to a cycloaddition reaction either with azide **2a** or with **2g**. After 12 h reaction time, the nitro group of the resulting triazoles **3m** and **3o** was chemoselectively reduced in the same eutectic mixtures, under aerobic conditions, by in-situ generated hydrogen, after adding to the above DES Al powder and KOH (10 equiv), under catalysis of cheap Pd/C (10 mol%).[25] The desired targets **3x,y** were isolated in 70–72% yields (Scheme 6a). Following a similar approach, the preparation of benzyl-substituted triazole **3z** (66% yield) was also feasible, by reacting the enolate of alkanone **1a** with azide **2j**, followed by the etherification of the phenolic group of triazole **3j** in DES with benzyl bromide, without any halfway isolation/purification step (Scheme 6b).

Conclusion

In summary, we have shown that 1,3-dipolar cycloaddition reactions between enolates of alkanones and azides can be conveniently carried out using a ChCl/urea or a ChOAc/urea eutectic mixture as an environmentally responsible reaction medium. Several densely functionalized 1,2,3-triazoles, including challenging phenolic derivatives, have been regioselectively synthesized in up to 98% yield according to this transition metal-free approach (26 examples),[26] working under air and at RT, thereby avoiding anhydrous VOCs (e.g., THF, Et_2O) or DMSO, and harsh reaction conditions, that are typically required for the formation of the enolate.

Sequential transformations as well as telescoped, one-pot cycloaddition/reduction or cycloaddition/etherification processes, which are of great value for chemical waste minimization,[27] have also been successfully accomplished in

the same eutectic mixture, targeting pharmaceutically relevant molecules. Further applications of DESs as green and sustainable reaction media for the preparation of other pharmacologically active molecules starting from alkanone enolates and different dipoles (e.g., nitrile oxides, nitrones) are underway and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of 1,4-Diaryl-1*H*-1,2,3-triazoles 3a–w in DESs. A suspension of *t*-BuOK (ChCl/urea: 2.25 mmol, 252 mg; ChOAc/urea: 0.75 mmol, 168 mg) and alkanone (0.75 mmol) in ChCl/urea or ChOAc/urea (1 : 2 mol mol^{-1}) (1.5 g) was vigorously stirred at RT (25 °C) for 60 min. During this time, the color of the mixture changed from slightly yellow to orange. Then, azide (0.82 mmol) was added under air and with vigorous stirring at RT, and the resulting mixture was left under stirring for 1–12 h. After the reaction was complete (TLC analysis), NH_4Cl (sat. aq. solution) was added, and the aqueous phase was extracted with EtOAc (3 × 1 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the volatile evaporated under reduced pressure. Triazoles **3a**–**e**, **3g**,**h**, **3j**,**k** **3m**, **3o**, **3r** and **3w** were isolated by precipitation and simple decantation from the reaction crude, after adding a few drops of Et_2O. In all the other cases, the crude was purified by flash chromatography (hexane/EtOAc, see ESI) to provide the desired triazole **3** (40–98 % yield, see Schemes 2 and 3).

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Cycloadditions · Deep Eutectic Solvents · Enolates · Green chemistry · Nitrogen heterocycles

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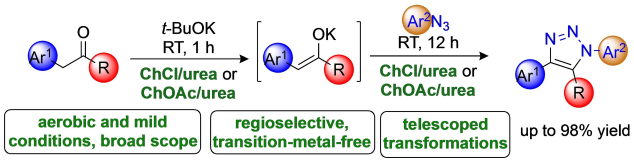

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1 – 8

1,3-Dipolar Cycloaddition of Alkanone Enolates with Azides in Deep Eutectic Solvents for the Metal-Free Regioselective Synthesis of Densely Functionalized 1,2,3-Triazoles

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