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A practical multigram-scale method for the green synthesis of 5-substituted-1*H*-tetrazoles in deep eutectic solvent

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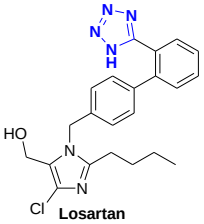
ABSTRACT

A series of 5-substituted-1*H*-tetrazoles have been efficiently synthesized in moderate to excellent yields (68–90%) under mild reaction conditions by combining aryl aldehydes, hydroxylamine hydrochloride with sodium azide in the presence of catalytic amount of $Cu(OAc)_2$ in deep eutectic solvent (DES). The new synthetic method has many advantages, such as high conversion, green reaction medium, easy work-up, low cost, and environment friendly.

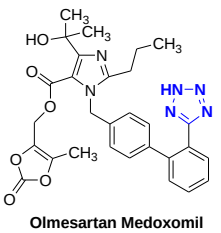
1. Introduction

The tetrazole ring is an important five-membered heterocyclic nucleus that has been widely found in nature such as pyrimidine, purine, and other natural products [1]. In addition, many synthetic pharmaceutical drugs and agrochemical products also contain tetrazole groups. Not surprisingly, therefore, research on efficient synthesis of tetrazoles has been a hot topic in the field of organic chemistry, which not only attracted extensive attention from academic research, but also drew high attention from industrial field [2].

The tetrazole-based drugs can interact with many enzymes and receptors in the organism and they possess different kinds of biological activities [3]. Several drugs and drug candidates with tetrazole moiety endowed with promising biological activity against dreadful diseases, such as hypertension, cancer and HIV [4-6]. Among them, 5-substituted-1*H*-tetrazoles have been recognized as privileged structural motifs and they have become increasingly important and useful in drugs due to its broad range of biological activities (Fig. 1) [7]. All of them have good clinical therapeutic effect.



Losartan
(Antihypertensive drug)



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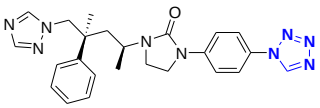
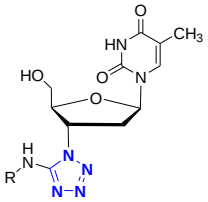


TAK-456
(Antifungal drug)

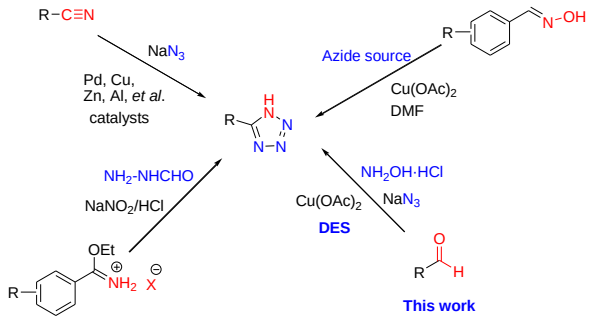


(Anti-HIV drug)

Fig. 1. Some examples of biologically active tetrazole-containing compounds.

In general, there are several conventional methods to synthesize 5-substituted 1*H*-tetrazoles through reaction of nitriles with hydrazoic acid (HN_3), trimethylsilyl azide ($TMSN_3$), and sodium azide (NaN_3), respectively (Scheme 1). Among these methods, the [3+2] cycloaddition reaction between nitriles and $TMSN_3$, or between nitriles and NaN_3 has been an attractive and useful method. The reactions were carried out by using catalysts such as Pd-2A3HP-MCM-41 [8], Pd-SBT@MCM-41 [9], Pd-isatin-boehmite [10], Pd@polymer [11], Cu/Zn alloy nanopowder [12], $ZrOCl_2 \cdot 8H_2O$ [13], zinc oxide [14], $Fe(OAc)_2$ [15], $NaHSO_4 \cdot SiO_2$ [16], $AlCl_3$ [17], $Zn(OTf)_2$ [18], $ZnBr_2$ [19], *β*-cyclodextrin [20], polymeric copper (II) complex [21], Fe_3O_4@SiO_2-aminotet-Cu(II) [22], CuO nanoparticles [23], L-proline [24], nano-Cu_2O–MFR [25], Cu-MCM-41 [26], $Cu(OAc)_2$ [27], Fe_3O_4@SiO_2-TCT-PVA-Cu(II) [28], Fe_3O_4@SiO_2-dendrimer-encapsulated Cu(II) [29], urea-CH_3COOH [30], Cu(II)-adenine-MCM-41 [31], Ni (II)-Fe_3O_4@tryptophan [32], Fe_3O_4@AMPD@Ni [33] *et al*. The reported methods suffer from drawbacks such as use of high-boiling-point organic solvents (such as DMF and DMSO), expensive metals (Pd catalyst), harsh reaction conditions (>200°C), and formation of highly volatile and toxic HN_3 as by product. Therefore, a simple and green approach for the synthesis

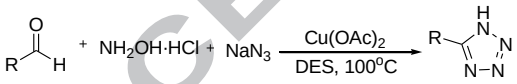
of 5-substituted 1*H*-tetrazoles is still highly desired and in demand.



Scheme 1. Synthetic methods of 5-substituted-1*H*-tetrazoles.

With the rise of green chemistry, clean and efficient chemical reaction has become an inevitable trend of chemical industrial development. At present, most chemical reactions need to be carried out in traditional organic solvents, while organic solvents have obvious disadvantages, such as high toxicity and volatilization. Thus, emission of volatile organic solvents is one of the major contributors to chemical pollution and it is urgent to find environmentally friendly media and solvents. DESs are eutectic mixtures of quaternary ammonium salts and hydrogen bond donors with melting points low enough [34]. DESs are known to be a good alternative to traditional solvents and ionic liquid (ILs) [35, 36]. In recent years, much attention has recently been paid to their applications in organic synthesis as green solvents with many successful results because the components of the DESs are widely available in nature, inexpensive, non-toxic, and biodegradable [37-45].

In the field of 5-substituted 1*H*-tetrazoles synthesis, nitrile compounds have been widely used as starting materials. However, most nitriles are toxic and difficult to biodegrade. Compared with nitriles, aldehydes are more available, cheaper, and less toxic. In addition, in order to avoid using high-boiling-point organic solvents and harsh reaction conditions in the reaction process, herein we report for the first time a simple, convenient, and green protocol for the synthesis of 5-substituted 1*H*-tetrazoles by reaction of aldehydes, $NH_2OH{\cdot}HCl$ and NaN_3 in the presence of 20 mol % of $Cu(OAc)_2$ as catalyst in DES of choline chloride (ChCl)-urea (Scheme 2).



Scheme 2. One-pot synthesis of 5-substituted 1*H*-tetrazoles in DES.

2. Results and discussion

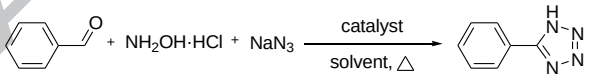
The main aim of this study was to optimize the conditions of 5-substituted 1*H*-tetrazoles synthesis. Therefore, the catalytic performance was investigated in one-pot three-component synthesis of 5-phenyl 1*H*-tetrazole as a model product under several reaction conditions, such as amount of the catalyst, temperature, and solvent nature. The obtained results were shown in Table 1.

All reactions reacted at 100°C or 75°C for 12 h in different solvents, such as DES, DMF, CH_3CN, EtOH, and H_2O. Initially, the mixture of benzaldehyde and $NH_2OH{\cdot}HCl$ was reacted with NaN_3 in the DES mixture of ChCl and urea without the addition of metal catalyst (Table 1, entry 1). However, no desired product was observed. When $FeCl_3$ was added into the system as catalyst, the corresponding product 5-phenyl 1*H*-tetrazole was obtained with very low yield (<5%, table 1, entry 2). $Zn(OAc)_2$ (Table 1, entry 3) and $ZnCl_2$ (Table 1, entry 4) gave low yields of 38 and 47%, respectively. $CuCl_2{\cdot}2H_2O$ (Table 1, entry 5) also gave low yield of 46%. When we used Cu_2O (Table 1, entry 6) and $Cu(NO_3)_2{\cdot}3H_2O$ (Table 1, entry 7) as catalysts, the yields were improved to 70 and 79%, respectively. To our delight, an excellent yield was obtained when $Cu(OAc)_2$ (20 mol%) was applied (Table 1, entry 8). However, no further improvement in the yield could be achieved, when the amount of $Cu(OAc)_2$ was increased up to 25 mol% at 100°C (Table 1, entry 9).

The choice of the solvent also played a crucial role. Very low yields (<5% and 23%) were obtained in the DES of ChCl-glycerol, and sorbitol-urea-NH_4Cl when $Cu(OAc)_2$ (20 mol%) was applied (Table 1, entries 10 and 11), respectively. Further research showed that the moderate yields could be obtained by using DMF and CH_3CN as solvent (66 and 72%, Table 1, entries 12 and 13). However, when EtOH and H_2O were used as solvents, very low yields could be obtained and most of the starting materials could be recovered (Table 1, entry 14 and 15).

Therefore, the $Cu(OAc)_2$-ChCl-urea catalytic system, integrating the advantages of $Cu(OAc)_2$ and DES, show great potential for synthesizing 5-substituted 1*H*-tetrazole derivatives. It was concluded that the optimal conditions for the synthesis of 5-substituted 1*H*-tetrazoles was $Cu(OAc)_2$ dosage of 20 mol%, reaction temperature of 100°C in ChCl-urea, and reaction time for 12 hours.

Table 1 Effect of different catalysts, solvents and temperature on the synthesis of 5-phenyl 1*H*-tetrazole.[a]

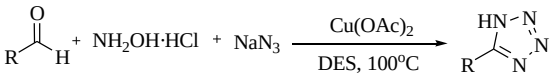


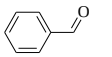
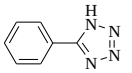
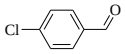
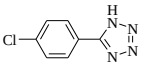
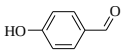
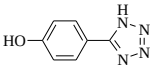
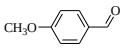
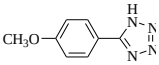
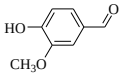
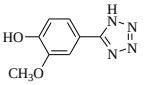
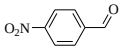
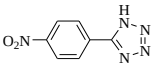
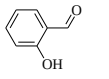
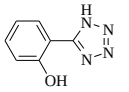
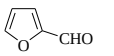
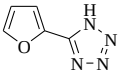
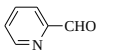
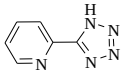
Entry	Catalyst (mol%)	Solvent	Temp (°C)	Yield (%)[b]
1	None	ChCl-urea	100	0
2	$FeCl_3$ (20%)	ChCl-urea	100	<5
3	$Zn(OAc)_2$ (20%)	ChCl-urea	100	38
4	$ZnCl_2$ (20%)	ChCl-urea	100	47
5	$CuCl_2{\cdot}2H_2O$ (20%)	ChCl-urea	100	46
6	Cu_2O (20%)	ChCl-urea	100	70
7	$Cu(NO_3)_2{\cdot}3H_2O$ (20%)	ChCl-urea	100	79
8	**$Cu(OAc)_2$ (20%)**	**ChCl-urea**	**100**	**90**
9	$Cu(OAc)_2$ (25%)	ChCl-urea	100	90
10	$Cu(OAc)_2$ (20%)	ChCl-glycerol	100	<5
11	$Cu(OAc)_2$ (20%)	Sorbitol-urea-NH_4Cl	100	23
12	$Cu(OAc)_2$ (20%)	DMF	100	66
13	$Cu(OAc)_2$ (20%)	CH_3CN	75	72
14	$Cu(OAc)_2$ (20%)	EtOH	75	<5
15	$Cu(OAc)_2$ (20%)	H_2O	100	<5

[a] Reaction conditions: benzaldehyde (2.0 mmol), $NH_2OH{\cdot}HCl$ (2.0 mmol), NaN_3 (2.4 mmol), DES (2.0 mL), catalyst (20 mol%) at 100°C for 12 h; [b] Isolated yield.

Prompted by the aforementioned excellent result of $Cu(OAc)_2$-ChCl-urea catalytic system, we further investigate the practicality of the catalytic system. Using the optimized reaction condition, the one-pot conversion was further expanded to a broader range of various aryl/alkyl aldehydes in order to evaluate the scope and limitations of the method. The obtained results are summarized in Table 2. We were pleased to find that various aryl aldehydes with electron-withdrawing groups as well as electron-donating groups reacted smoothly with $NH_2OH{\cdot}HCl$ and NaN_3 to give the desired 5-substituted 1*H*-tetrazoles in moderate to excellent yields (68-90%, Table 2, entries 1-9). The results obviously indicated the generality and scope of the reaction with respect to various aryl aldehydes. Unfortunately, when propionic acid was used as the starting material, the reaction could not be carried out normally (Table 2, entry 10).

Table 2 Synthesis of 5-substituted 1*H*-tetrazoles under the optimized reaction condition.[a]

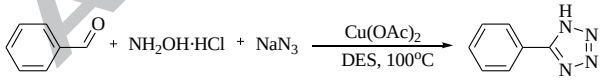


Entry	Substrate	Product	Yield (%)	m.p. (°C)	Lit m.p. (°C)
1			90	215-216	215-216 [19]
2			68	264-265	264-266 [19]
3			85	236-237	234-235 [19]
4			74	230-231	231-232 [46]
5			81	215-216	215-217 [46]
6			70	217-219	218-219 [19]
7			89	223-225	220-222 [47]
8			86	203-204	204-205 [47]
9			88	210-212	211 [19]
10	CH_3CH_2CHO		NR[b]	--	--

[a] Reaction conditions: aldehyde (2.0 mmol), $NH_2OH·HCl$ (2.0 mmol), NaN_3 (2.4 mmol), DES (2.0 ml), catalyst (20 mol%) at 100°C for 12 h; [b] NR=No reaction.

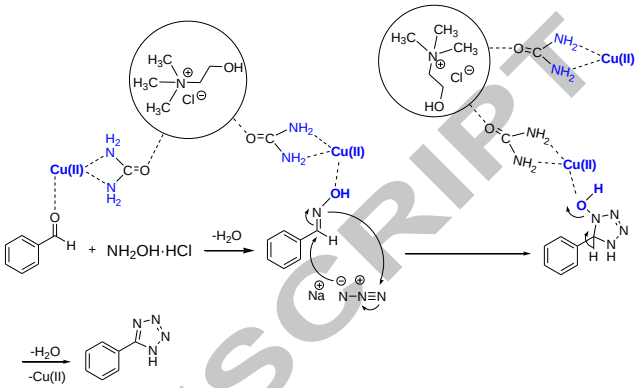
Finally, the multi-gram scale synthesis of the 5-substituted 1*H*-tetrazoles was investigated in the case of 5-phenyl-1*H*-tetrazole as a model reaction. The detailed results were summarized in Table 3. Encouraged by the above results, we increased the scale of the reaction to 5.0, 25.0, 50.0, 100.0 mmol, respectively, keeping the reaction stoichiometry unchanged. The reactions were found to proceed smoothly and the corresponding product was obtained in good to excellent yields.

Table 3 Scale-up synthesis of 5-phenyl 1*H*-tetrazole.



Entry	Scale (mmol)	Time (h)	Isolated yield (%)	Isolated Product (g)
1	5.0	12	91	0.66
2	25.0	15	85	3.14
3	50.0	20	90	6.58
4	100.0	28	88	12.88

We propose a mechanism of the $Cu(OAc)_2$ catalyzed C-N coupling reaction for the synthesis of 5-substituted 1*H*-tetrazoles as shown in Scheme 3. After the activation of the carbonyl group of benzaldehyde catalyzed by $Cu(OAc)_2$ and the nucleophilic attack of the nitrogen atom of hydroxylamine to the active carbonyl group, and then benzaldehyde oxime is obtained. Then, $Cu(OAc)_2$ readily activated C=N bond by cocoordinating with oxygen atom of benzaldehyde oxime. This might facilitate the [3+2] cycloaddition between azide ion and the C=N bond of benzaldehyde oxime, and finally H_2O elimination gives the corresponding 5-phenyl-1*H*-tetrazole product.



Scheme 3. Plausible mechanism for the synthesis of 5-phenyl-1*H*-tetrazole catalyzed by $Cu(OAc)_2$ in DES of ChCl-urea.

3. Conclusions

In summary, we have reported herein a highly efficient and green method for the multi-gram scale synthesis of 5-substituted 1*H*-tetrazoles without isolation of the intermediate through the one-pot cascade reaction from aryl aldehydes by using $Cu(OAc)_2$ as catalyst in DES of ChCl-urea for the first time. In all cases, the desired 5-substituted 1*H*-tetrazoles were isolated in moderate to excellent yields. This newly developed method avoids the usage of toxic chemicals/high-boiling-point organic solvents, or avoids formation of highly volatile and toxic HN_3 by-product as previously reported. We believe that our strategy could be broadly applicable for the facile and high-yield production of other novel 5-substituted 1*H*-tetrazoles with great promise for various applications.

4. Experimental section

4.1 Materials and instrumentation

All chemicals were purchased from Aladdin Reagent Company. The progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel plates.

The IR spectra were obtained using a FT-IR (4000~400 cm^{-1}) spectrometer (Nicolet Nexus FT-IR spectrometer, USA) at 4 cm^{-1} resolution and 32 scans. Samples were prepared using the KBr disc method. NMR spectra were acquired in $CDCl_3$ on a Bruker DMX-400 spectrometer at 400 MHz for ^1H NMR, the chemical shifts are given in δ values from TMS as an internal standard.

4.2 Typical procedure for the preparation of DES

The DESs were synthesized according to the reported procedures in the literatures [48-50]. ChCl (100 mmol) and urea (200 mmol) were mixed in a round-bottomed flask in the ratio of 1:2, then the solid mixture was heated and maintained at 80°C with stirring until formation of a colorless homogeneous liquid with 100% atom economy. The ChCl-urea was allowed to cool to room temperature, which was used directly for the synthesis of 5-substituted 1*H*-tetrazoles without any further purification.

4.3 Typical procedure for the synthesis of 5-substituted 1H-tetrazoles

In a typical reaction, a mixture of aldehyde (2.0 mmol), hydroxylamine hydrochloride (2.0 mmol), NaN_3 (2.4 mmol) and DES (2.0 mL) in a round-bottomed flask were added $Cu(OAc)_2$ (20 mol%). Then the reaction mixture was heated to 100°C in an oil bath for 12 hours. After completion of reaction, as detected by TLC, the mixture was cooled to room temperature then treated with 5 N HCl (5 mL) and extracted with EtOAc (3×10 mL). The organic phase was concentrated and washed with 1 N HCl, saturated aqueous sodium chloride, then dried over anhydrous Na_2SO_4 and concentrated under vacuum by rotary evaporator. The crude products were purified by column chromatography to give the desired 5-substituted 1*H*-tetrazoles.

4.4 Multi-gram scale synthesis of 5-phenyl 1H-tetrazole

To a 150 mL round-bottomed flask equipped with a magnetic stirrer was added benzaldehyde (10.6 g, 0.1 mol), hydroxylamine hydrochloride (4.2 g, 0.1 mol), NaN_3 (0.5 g, 0.11 mol), $Cu(OAc)_2$ (20 mol%) and DES (30 mL). Then the reaction mixture was heated to 100°C for 28 h with vigorous stirring. After completion of reaction, as detected by TLC, the mixture was cooled to room temperature, adjusted pH to 1.0 with concentrated HCl, and extracted with EtOAc (3×50 mL). The organic phase was concentrated and washed with 1 N HCl, saturated aqueous sodium chloride, then dried over anhydrous $MgSO_4$ and concentrated under vacuum by rotary evaporator. The crude product was purified by column chromatography to give 5-phenyl 1*H* tetrazole as a white solid (12.9 g, 88% yield).

4.5 Spectroscopic data of 5-substituted 1H-tetrazoles

5-Phenyl-*1H*-tetrazole (Table 2, entry 1): m.p. 215-216°C; FT-IR (KBr disc) cm^{-1}: 3132, 3055, 2980, 1876, 1606, 1566, 1485, 1464, 1410, 1256, 1055; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.05 (dd, *J*=6.3, 2.7 Hz, 2H), 7.66–7.56 (m, 3H), 3.31 (s, 1H).

5-(4-Chlorophenyl)-*1H*-tetrazole (Table 2, entry 2): m.p. 264-265°C; FT-IR (KBr disc) cm^{-1}: 3383, 3180, 2920, 2854, 2720, 2625, 1660, 1606, 1487, 1408, 1278, 1095, 840; ^{1}HNMR (400 MHz, DMSO-d_6) δ: 8.06 (d, *J*=8.4 Hz, 2H), 7.70 (d, *J*=8.3 Hz, 2H).

4-(*1H*-Tetrazol-5-yl)phenol (Table 2, entry 3): m.p. 236-237°C; FT-IR (KBr disc) cm^{-1}: 3103, 2933, 2847, 2746, 2634, 1612, 1505, 1408, 1294, 1180; ^{1}HNMR (400 MHz, DMSO-d_6) δ: 10.15 (s, 1H), 7.87 (d, *J*=8.5 Hz, 2H), 6.96 (d, *J*=8.5 Hz, 2H), 3.33 (s, 1H).

5-(4-Methoxyphenyl)-*1H*-tetrazole (Table 2, entry 4): m.p. 230-231°C; FT-IR (KBr disc) cm^{-1}: 3058, 2985, 2914, 1604, 1561, 1481, 1380, 1342, 1282; ^{1}HNMR (400 MHz, DMSO-d_6) δ: 7.98 (d, *J*=8.3 Hz, 2H), 7.17 (d, *J*=8.4 Hz, 2H), 3.85 (s, 3H), 3.32 (s, 1H).

3-Methoxy-4-(*1H*-tetrazol-5-yl)phenol (Table 2, entry 5): m.p. 215-216°C; FT-IR (KBr disc) cm^{-1}: 3446, 3109, 2914, 1604, 1525, 1380, 1340, 1288; ^{1}HNMR (400 MHz, DMSO-d_6) δ: 9.76 (s, 1H), 7.66–7.52 (m, 1H), 7.50 (d, *J*=8.2 Hz, 1H), 6.96 (d, *J*=8.2 Hz, 1H), 3.87 (s, 3H), 3.32 (s, 1H).

5-(4-Nitrophenyl)-*1H*-tetrazole (Table 2, entry 6): m.p. 217-219°C; FT-IR (KBr disc) cm^{-1}: 3446, 3109, 2914, 1604, 1525, 1340, 1288, 860; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.45–8.37 (m, 2H), 8.32 (dd, *J*=24.3, 9.0 Hz, 2H).

2-(*1H*-Tetrazol-5-yl)phenol (Table 2, entry 7): m.p. 223-225°C; FT-IR (KBr disc) cm^{-1}: 3254, 3057, 2939, 1604, 1545, 1475, 1361, 1292, 1071, 813, 744; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.92 (s, 1H), 7.99 (d, *J*=7.7 Hz, 1H), 7.42 (t, *J*=7.7 Hz, 1H), 7.13–6.97 (m, 2H), 3.36 (s, 1H).

5-(Furan-2-yl)-*1H*-tetrazole (Table 2, entry 8): m.p. 203-204°C; FT-IR (KBr disc) cm^{-1}: 3115, 2930, 2362, 1641, 1527, 1388, 1240, 1020, 890, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.68 (d, *J*=1.1 Hz, 1H), 7.36 (d, *J*=3.6 Hz, 1H), 6.68 (dd, *J*=3.5, 1.8 Hz, 1H).

2-(*1H*-Tetrazol-5-yl)pyridine (Table 2, entry 9): m.p. 210-212°C; FT-IR (KBr disc) cm^{-1}: 3093, 2920, 1600, 1560, 1483, 1450, 1288, 1160, 1018; ^{1}HNMR (400 MHz, DMSO-d_6) δ: 8.81 (d, *J*=4.2 Hz, 1H), 8.24 (d, *J*=5.7 Hz, 1H), 8.12 (dt, *J*=15.4, 7.6 Hz, 1H), 7.67–7.59 (m, 1H), 3.33 (s, 1H).

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Highlights

• Practical one-pot reaction for preparation of 5-substituted-1*H*-tetrazoles.

• Without using high boiling point or volatile organic solvents in the reaction.

• Easy reaction set-up and multigram scale.

Deep Eutectic Solvent

Yields up to 90%

$Cu(OAc)_2$  DES

Metal Catalysis Green Chemistry