Choline Chloride-$ZnCl_2$: Recyclable and Efficient Deep Eutectic Solvent for the [2+3] Cycloaddition Reaction of Organic Nitriles with Sodium Azide

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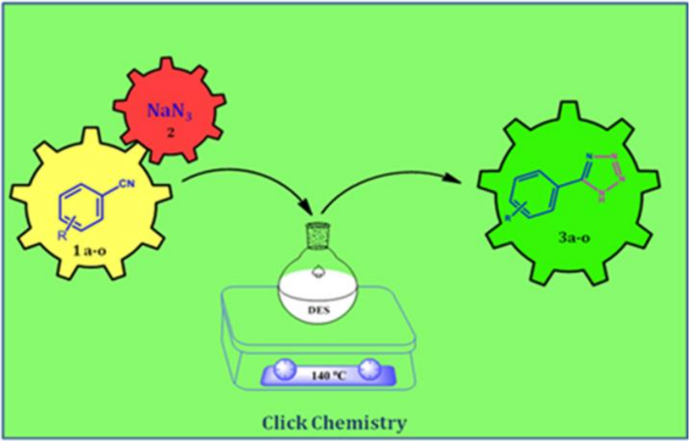
Abstract

Herein we report first time choline chloride-zinc chloride based deep eutectic solvent is a green and efficient reaction medium for the [2+3] cycloaddition reaction of organic nitriles with sodium azide to afford the corresponding 5-substituted 1H-tetrazoles. The present method provides an environment-friendly route, short reaction times with excellent yields, safe process and simple workup which make this method an attractive and useful contribution to the existing conventional processes for synthesis of 5-substituted 1H-tetrazoles.

Graphical Abstract



KEYWORDS: Tetrazoles; Choline chloride; Deep eutectic solvent; Green chemistry; Click chemistry

INTRODUCTION

The chemistry of tetrazoles has been grown tremendously in the past few years because tetrazoles are important and useful class of heterocyclic compounds which have a widespread applications such as anticancer,[1] antimicrobial,[2–4] analgesics,[5] antibacterial,[6] antifungal,[7] antihypertensive and anti-allergic[8] drugs in medicinal chemistry. Furthermore, tetrazoles have application in material sciences as explosives**,**[9] rocket propellants,[10–13] and in information recording systems.[14,15] In addition to this, they have a wide range of application in coordination chemistry as a ligand.[16–18]

The [2+3] cycloaddition of sodium azide to organic nitriles in a temperature range of typically 100-150°C is a most convenient route for the synthesis of 5-substituted 1H-tetrazoles derivatives.[19,20] The ‘‘click chemistry’’ approach for the synthesis of 5-substituted 1H-tetrazoles by [2+3] cycloaddition of corresponding nitriles and NaN_3 under water as a solvent and stoichiometric amounts or 50 mol% of Zn(II) salts is an alternative method developed by Sharpless.[21] After that much work has been done by many scientist and reports the several catalytic system for the synthesis of 5-Substituted 1H-tetrazoles such as homogeneous catalysts like TBAF under solvent-free conditions,[22] ionic liquid,[23]**.** Heterogeneous catalytic system using various catalyst such as Fe_2O_3,[24] Zn hydroxyapatite,[25] mesoporous ZnS hollow sphere,[26] and CSMIL,[27] ZnO nanoflakes,[28] $Fe_3O_4@SiO_2$,[29] AgNPs,[30] Grapheneoxide/ZnO nanocomposite,[31] Numerous lewis acid catalyst such as $CdCl_2$,[32] $ZnCl_2$,[33,34] $InCl_3$,[35] $B(C_6F_5)_3$,[36]. Some natural zeolite Montmorillonite K-10 clay,[37] and CoY,[38] zeolite also reported. These synthetic strategies give good results in many instances, still the search for greener method is progressively in demand for the synthesis of 5-substituted 1H-tetrazoles.

Deep eutectic solvents (DESs) have emerged over the current decade as a novel class of green reaction media.[39,40] The physical and chemical properties of DESs similar to the ionic liquids (ILs) such as low vapor pressure, non-volatility, high thermal stability and recyclability. As compared to ILs, DES are cheaply available, low-toxic, and biodegradable.[41–43] These unique features of DESs have interesting and impressive in many fields such as polymerizations,[44] enzyme-catalyzed reactions,[45,46] electrochemical processes,[47,48] biochemical process,[49,50] nanotechnology,[51] and organic synthesis.[52] While the ability of deep eutectic solvent as catalyst and reaction medium in organic synthesis have appreciable attention in recent years. which makes them predominantly required for large-scale applications effectively in industrial production. [53–58]

Recently our group has developed an efficient catalytic system [59,60] for the synthesis of 5-substituted 1H-tetrazoles. In continuation to this research work, we have report choline chloride-$ZnCl_2$ based deep eutectic solvent is a green and efficient reaction medium for the synthesis of 5-substituted 1H-tetrazoles.

RESULT AND DISCUSSION

The thermal properties of ChCl-$ZnCl_2$ were investigated using thermogravimetric analysis (TGA) and the observed result shown in Figure 1. The TGA curve of ChCl:$ZnCl_2$ shows three step degradation in that the first weight loss of water started from 29-157°C (2.67%) and second weight loss of Choline chloride started from 157-417°C (25.94%) and third weight loss began in the range of 418-762°C (68.11%). The ChCl:$ZnCl_2$ exhibit good thermal stability at 341°C.

In optimized the reaction conditions and role of ChCl-$ZnCl_2$ (1:2) as a catalyst and reaction medium, the reaction between benzonitrile, NaN_3 has been selected as a model reaction for synthesis of 5-phenyl 1H-tetrazole. Not many organic solvents are stable at high temperature (sometimes as high as 140°C), and for this reason DESs is used at high temperature. To develop the organic processes, among the several solvents were examined at variable temperature listed in Table 1, Without any solvent, this reaction is does not proceed within 24 hours. A rate of cycloaddition reaction is little beat increase on changing the solvents polar aprotic such as DMF, DMSO (Table 1, entry 2-3). While the polar aprotic solvent such as dioxane, DCM does not give the product. Thus, glycerol was identified as most effective solvent for this reaction due to good solubility of both organic nitriles as well as sodium azide at 140 °C but leads to lower yields (Table 1, entry 4) while protic solvents such as water, methanol, ethanol and acetic acid, toluene does not lead to expected product. Among all solvents, including six different types of choline chloride based deep eutectic solvent, choline chloride-$ZnCl_2$ (1:2) proved to be the most efficient media for the target product **3a** preparation in practically good yields. The yield of the model reaction in choline chloride-$ZnCl_2$ (1:2) at 80 °C in 3.5 hours was fair (63

%). Next, the reaction was performed in higher temperature, 80-160 °C (Table 2, entries 1-5), the best result is obtained at 140 °C thus, 140 °C was selected as optimized temperature and based on these result, we then investigated the amount of DES required for the reaction, and found that 10 mL of DESs (Table 3, entries 5), gives excellent yield. If the amount of DES was decreased from 10 mL to 1 mL (Table 3, entries 1-5), the time of reaction increase and yield was also decreased thus, 10 mL of DES was chosen as the optimum amount for the reactions. The recycling of DES was also examined under optimized conditions. After reaction was completed, cold water (10 mL) was added to the reaction mixture, stirred vigorously and solid was separated by filtration. Finally, DES was recovered by evaporating the water at 80 °C under vacuum and was reused for the next run and recycled again (Fig. 2).

A diversity of structurally different nitriles possessing a wide range of functional groups was selected to understand the range and simplification of the ChCl-ZnCl$_2$ (1:2) promoted [2+3] cycloaddition reaction to form 5-substituted 1H-tetrazoles and the results are summarized in Table 4. For all nitriles, ChCl-ZnCl$_2$ (1:2) was used as a catalyst and solvent and the reaction was conducted at 140 °C. In all cases, the conversion was completed within 0.5-7 h with good to excellent yields. Further increase in reaction time has no significant effect on yields. Aromatic nitriles containing both electron releasing and electron withdrawing groups were smoothly converted in to the product. The nitriles having electron releasing substituents give slower reaction (Table 4, entry 3d, 3e, 3g, and 3h). The benzyl nitriles require longer reaction times than benzonitriles (Table 4, entry 3i, 3j). The longer reaction time of 7 h was required with 88% yield for heterocyclic nitrile

(Table 4, entry 3h); this might be steric hindrance of rings. The 90% of yield was obtained for benzonitrile (Table 4, entry 3a) within very short reaction time of 0.5 h. we have extended the scope of this system to aliphatic nitriles but the aliphatic nitriles does not proceed in ChCl-ZnCl2 (1:2) (Table 4, entry 3m and 3l).

All synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy and compared with literature data. Finally, the role of ChCl-$ZnCl_2$ (1:2) for the synthesis of 5-phenyl 1H-tetrazole has been compared with previous reported catalysts (Table 5). This comparison clearly shows that the present method supportive to several of the others in terms of high product yield, short reaction time, no need of toxic metals and expensive reagents and hazardous solvent, easy isolation of final products by simple work-up.

CONCLUSION

In summary, the first time, we have attempted the [2+3] cycloaddition reaction of organic nitriles with sodium azide affords the corresponding 5-substituted 1H-tetrazoles in six different types of choline chloride based deep eutectic solvents under mild reaction condition. Choline chloride: $ZnCl_2$ (1:2) showed the best results for the synthesis of 5-substituted 1 H-tetrazoles as important pharmacophore in medicinal chemistry. This method reduces the disadvantages such as: the use of toxic metals and expensive reagents, drastic reaction conditions and the presence of dangerous hydrazoic acid. The approach provides environment-friendly, short reaction times, good to excellent yields;

safe process and simple workup make this method an attractive and useful contribution to present green organic synthesis of 5-substituted-1H-tetrazoles.

EXPERIMENTAL SECTION

Typical Experimental Procedure For Synthesis Of 5-Substituted 1H-Tetrazoles (3a-3k)

NaN_3 (0.975 g, 15 mmol) was dissolved in DES (10 mL) at room temperature by stirring until a clear solution was formed. Then benzonitrile (10 mmol) was added. The reaction mixture was constantly stirred at 140 °C and monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and poured into the cold water (10 mL). The solid was obtained and filtered. The obtained solid is taken into cold water (10 mL). Then it was acidified carefully to pH 5 with 5 M HCl. The organic material was extracted thrice with ethyl acetate; the resultant organic layer was washed with distilled water, dried over anhydrous sodium sulfate, and concentrated to give the crude solid crystalline 5-substituted 1H-tetrazole. The resulting product, although evident as a single compound by TLC, was purified by simple recrystallization from aqueous ethanol giving pure 5-substituted 1H-tetrazoles.

SUPPORTING INFORMATION

Supplementary material includes full experimental details, IR, ^{1}H NMR, ^{13}C NMR and Mass spectra of the product **(3a-3k)** for this article.

ACKNOWLEDGMENT

One of the authors, Swapnil A. Padvi, is sincerely thankful to the University Grants Commission, New Delhi, India for the award of "Rajiv Gandhi National Fellowship" (RGNF). We are also thankful to the University Grand Commission, New Delhi, India for facilities under the UGC-SAP-DSA-I programme to North Maharashtra University (NMU) and SAIF, Punjab University, for providing necessary characterization facilities.

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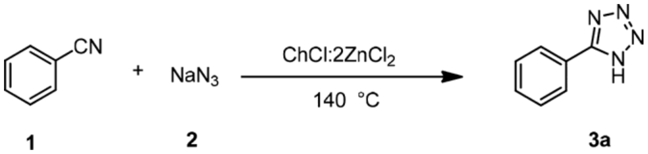
Table 1. Formation of 5-phenyl 1H-tetrazole (3a) using various reaction conditions [a]



Sr. No.	Solvent (10 mL)	Time (hrs)	Yield (%)[b]
1	-	24	NR
2	DMF	24	<20
3	DMSO	24	<20
4	Glycerol	3	60
5	Acetic Acid[c]	14	40
6	Choline chloride-urea (1:1)	24	Trace
7	Choline chloride-malonic acid (1:1)	18	72
8	Choline chloride-PTSA (1:1)	14	68
9	Choline chloride-glycerol (1:1)	2	70
10	**Choline chloride-$ZnCl_2$ (1:2)**	**30 min**	**90**
11	Choline chloride-$ZnCl_2$-1ml H_2O (1:2)	30 min	90

[a] Reaction was carried out with benzonitrile (10 mmol), NaN_3 (15 mmol).

[b] Isolated yields.

[c] Reflux.

Table 2. Formation of 5-phenyl 1H-tetrazole **3a** at various reaction temperature[a]

Sr. No.	**Temperature (°C)**	**Time (min)**	**Yield (%)[b]**
1	80	210	63
2	100	120	82
3	120	50	86
4	**140**	**30**	**90**
5	160	30	90

[a] Reaction was carried out with benzonitrile (10 mmol), NaN_3 (15 mmol) and Choline chloride-$ZnCl_2$ (1:2) (10 ml).

[b] Isolated yields.

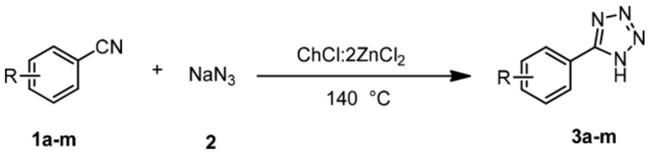
Table 3. The effect of amount of DES on the reaction yield and time[a]

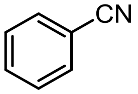
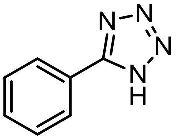
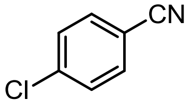
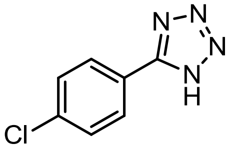
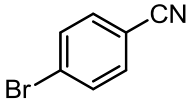
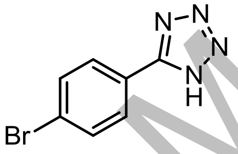
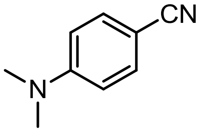
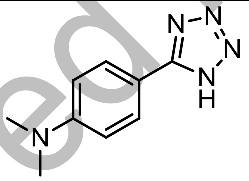
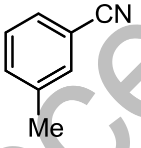
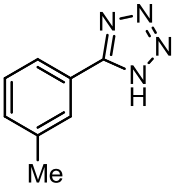
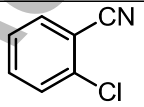
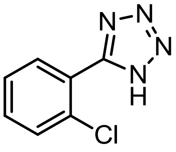
Sr. No.	**DES (mL)**	**Time (min)**	**Yield (%)[b]**
1	1	120	80
2	3	60	82
3	5	40	86
4	8	30	88
5	**10**	**30**	**90**

[a] Reaction was carried out with benzonitrile (10 mmol), NaN_3 (15 mmol) at 140 °C.

[b] Isolated yields.

Table 4. Synthesis of 5-substituted 1*H*-tetrazoles using (ChCl-$ZnCl_2$)[a]



entry	**Reactant**	**Product**	**Time (min)**	**Yield [b] (%)**
3a			30	90, 60[c]
3b			50	94
3c			80	94
3d			5 hrs	82
3e			90	86
3f			70	78

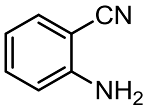
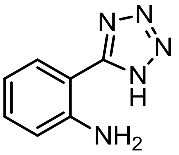
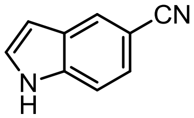
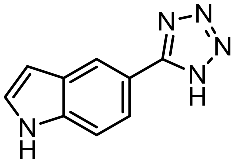
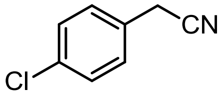
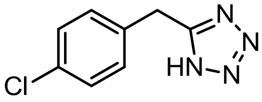
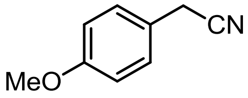
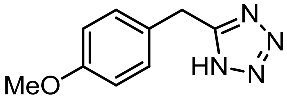
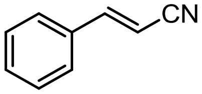
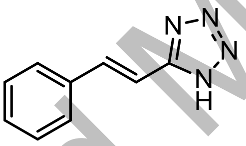
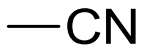
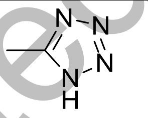
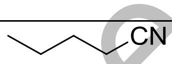
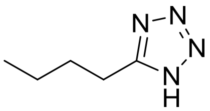
3g			45	80
3h			7 hrs	88
3i			4. 3 hrs	88
3j			3hrs	82
3k			4 hrs	76
3l			12hrs	NR
3m			12hrs	NR

Table 5. Comparison of various reported catalysts for synthesis of 5-phenyl 1H-tetrazole

Entry	**Catalyst**	**Temp. (°C)**	**Time (h)**	**Yield, (%)**	**Ref.**
1	$ZnBr_2$	100	24	76	21
2	ZnHAP	120	12	78	25
3	$ZnCl_2$	100	8	84	33
4	ZnO nanoflakes	125	14	87	28
5	ZnS hollow sphere	120	36	86	26
6	$ZnCl_2$	50	1	85	34
7	**DES**	**140**	**0.5**	**90**	**This Work**

Figure 1. TGA thermograms of $ChCl:ZnCl_2$

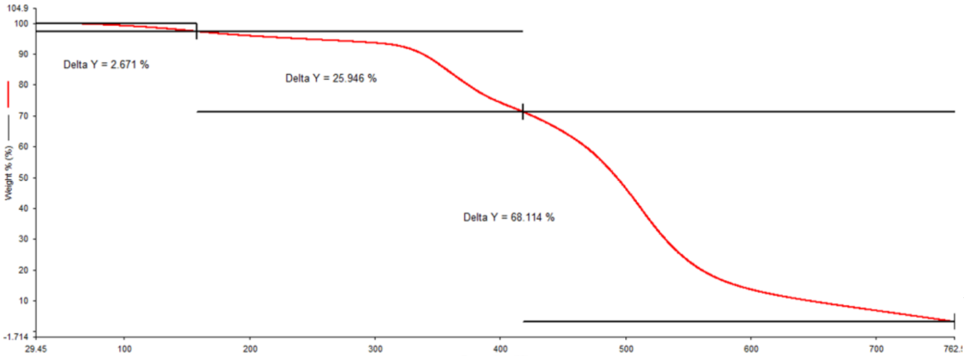


Figure 2. Recyclability of deep eutectic solvent (DES)