Diisopropyl Ethylammonium Acetate (DIPEAc): An Efficient and Recyclable Catalyst for the Rapid Synthesis of 5-Substituted-1*H*-Tetrazoles

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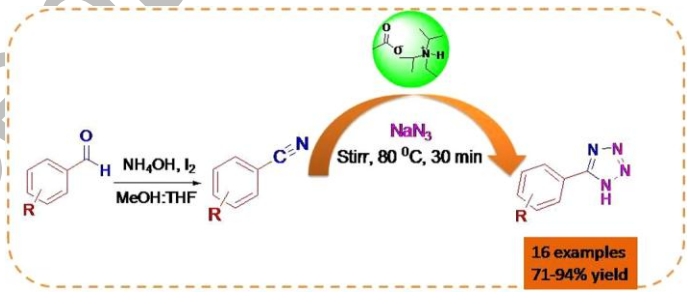
Abstract

A simple and efficient protocol developed for the synthesis of 5-substituted 1*H*-tetrazole derivatives *via* [2+3] cycloaddition reaction between benzonitriles and sodium azide using diisopropyl ethylammonium acetate as a recyclable reaction medium is described. The reactions proceed well at 80 ºC and provide the corresponding tetrazoles in good to excellent yields (up to 94% yield). Developed method has notable advantages, such as simple and mild conditions, easy workup, reusability with consistent catalytic activity and safer alternative to hazardous, corrosive conventional lewis acid catalysts.

Graphical Abstact



KEYWORDS: 5-Substituted 1*H*-tetrazole, DIPEAc, Ionic liquid, Cycloaddition reation

INTRODUCTION

Tetrazoles and their derivatives are very important nitrogen containing heterocycles which exhibit wide range of applications in the field of organic synthesis, coordination chemistry, material science and medicinal chemistry.[1] The tetrazole ring, particularly, 5-substituted-1*H*-tetrazole, known as tetrazolic acid is widely employed in medicinal chemistry as a bioisostere for carboxylic acid group.[2] The compounds having tetrazole building block in their molecular frame work, possess various biological and pharmacological activities, such as antidiabetic,[3] antihypertensive,[4] antifungal,[5] antimicrobial,[6] antibacterial,[7] anti-inflammatory,[8] hormonal,[9] anti HIV[10] and diuretics.[11] Additionally Several biologically relevant scaffolds incorporating a tetrazole moiety have been developed as pharmaceutical agents (Figure 1).[12] In view of such a tremendous significance of tetrazoles, there is a great surge in the utility and applications of tetrazoles.

The most direct and convenient route towards the synthesis of 5-substituted-(1*H*)-tetrazoles is [2+3] cycloaddition between a nitrile and an azide.[13] Various synthetic approaches have been developed for this transformation. Most of them rely on *in situ* generation of highly toxic and explosive hydrazoic acid through activation of the azide by expensive and toxic metals, strong Lewis acids or amine salts.[14] Apart from this number of reports are available in the literature for this cycloaddition reaction which involves the use of cyanuric chloride, $CuFe_2O_4$ nanoparticles, CAN supported HY-zeolite, etc.[15] Sharpless *et al.* have reported an efficient and safe procedure for the synthesis of tetrazoles using stoichiometric amounts of $ZnBr_2$ in water.[16] However, reported methods

have one or more drawbacks such as vigorous reaction conditions, tedious work-up procedure, use of expensive reagents, longer reaction times, low yields, etc. Thus, there is a need to develop convenient and rapid high-yielding synthetic method to fulfill timely supply of library of 5-substituted-(1*H*)-tetrazoles.

Organic reactions using sustainable reaction media such as ionic liquids (ILs), avoiding the use of volatile organic solvents, have attracted a great deal of attention of synthetic organic chemist. ILs are not only easily available, environmentally safe, but also excellent catalysts and medium having weakly coordinating ions, i.e. organic cation and inorganic/organic anion.[17, 18] ILs having nonvolatility, nonflammability, and are endowed with unique properties such as high thermal/chemical stability.[19] ILs act as 'neoteric solvents' for a broad range of chemical and industrial processes. Recently, ILs have been found to be useful as green media for numerous organic transformations.[20] The ability to dissolve many organic and inorganic substances makes ILs eco-friendly reaction media/catalysts.[21]

Encouraged by the intense ongoing research activity in the field of ILs and in pursuit of our continuous interest in the area of green chemistry[22] herein, we report a simple, green, and efficient protocol for the synthesis of 5-substituted-(1*H*)-tetrazoles employing diisopropylethylammonium acetate (DIPEAc) as IL (Scheme 1). Literature survey reveals that there are no methods reported in the literature for the synthesis of 5-substituted 1*H*-tetrazoles using DIPEAc as a catalyst and reaction medium.

RESULTS AND DISCUSSION

Synthesis

A series of 5-substituted-(1*H*)-tetrazoles (**3a-p**) were synthesized by the reaction of substituted benzonitriles and sodium azide in diisopropylethylammonium acetate (DIPEAc) at 80 ºC. The required starting precursors, substituted benzonitriles (**2a-p**) were synthesized by reaction of aromatic carbaldehydes with iodine/ammonia in MeOH:THF at room temperature.[23] Reaction of phenyl nitrile (**2a**) and sodium azide was considered as a model reaction.

Initially, to develop better reaction conditions, different green and volatile organic solvents such as toluene, acetonitrile and methanol along with various freshly prepared ILs[24] were screened at 80 ºC for performing the model reaction (Table 1, **entries 1-7**) and we found that DIPEAc showed excellent catalytic behavior and afford product in 92% yield within 30 min. (Table 1, **entry 7**). However, no product formation was observed in toluene, acetonitrile and methanol within 30 min (Table 1, **entries 1-3**).

In order to optimize the suitable amount of DIPEAc, model reaction was conducted using acetonitrile as solvent in the presence of 20, 40, 60, 80 mol% of DIPEAc and neat. It was observed that neat DIPEAc yielded 92% of conversion at 80 ºC. It was noted that, at 80 ºC in the absence of DIPEAc, condensation could not occur in acetonitrile media (Table 1). This confirms DIPEAc plays a role of a medium and as a catalyst in this cyclocondensation. Therefore, DIPEAc was chosen as the medium and catalyst of choice for further optimization studies.

With the optimized conditions in hand, influence of other experimental parameters such as temperature, amount and reusability of catalyst were also optimized. The model reaction was performed using DIPEAc as a reaction medium at different temperatures (35, 40, 60, 80, 100 ºC). Model reaction in DIPEAc at 80 ºC was found to proceed with excellent yield (92%) in 30 min (**Table 2**). There was no reaction at room temperature (35 ºC) within 30 min. As temperature increased from 35 to 100 ºC, the yield of the product also increased 74%, 83%, 92%, 93% (**Table 2**). There was no significant change in the product yield when model reaction was carried out above 80 ºC.

To generalize the scope of the DIPEAc promoted [2+3] cycloaddition reaction of variety of structurally divergent benzonitriles were choosen to synthesize 5-substituted 1*H*-tetrazoles. All the results are presented in Table 3. Unsubstituted as well as benzonitriles with electron donating substituents at both para and meta positions reacted well and gave the corresponding products in good to excellent yields (Table 3). Further, the reaction was extended to di and tri substituted benzonitriles such as 3,5-dimethoxybenzonitrile and 3,4,5-trimethoxybenzonitrile respectively, to generate tetrazoles in moderate to excellent yields (Table 3, **entries 9, 11**). Furthermore, the reaction was equally effective with benzonitriles having substituted electron-withdrawing groups and gave the expected tetrazoles in good yields.

Recycling Of Catalyst

To check reusability of the catalyst, the reaction was performed between benzonitrile and sodium azide under the optimized reaction condition. DIPEAc was separated from the reaction mixture by the following procedure. After completion of the reaction, reaction mixture was cooled to room temperature and to it water and ethyl acetate were added. The product (**3a**) was extracted with ethyl acetate. As the DIPEAc is highly water soluble it goes in to the aqueous layer. Evaporation of aqueous layer under reduced pressure provided the catalyst (DIPEAc). Catalysts purity was checked by ^{1}H NMR for subsequent reactions. Reusability of the DIPEAc was tested for four consecutive cycles, but a decrease in the catalytic activity of DIPEAc was observed after the third cycle (Figure 2).

Plausible Reaction Mechanism

On the basis of the experimental results and available literature,[25] possible mechanism for the formation of 5-substituted-(1*H*)-tetrazoles using diisopropylethylammonium acetate (DIPEAc) is presented in Scheme 2. Rate of acceleration for the formation of 5-substituted-(1*H*)-tetrazoles has been found to be enhanced due to the dual nature of IL, as a catalyst and reaction medium. IL might be helping to create a high initial concentration of the reactants via solvation. Initially, coordination of nitrogen atom of phenyl nitrile with DIPEA forms intermediate **A** which accelerates the cyclisation by increasing its electrophilic character of nitrile carbon. This gets further attacked by the azide component and [2+3] cycloaddition takes place readily to form the intermediate **B**. Then acidic work up, afford the final product 5-substituted-(1*H*)-tetrazole.

CONCLUSION

To summarize, we have demonstrated an exceedingly simple and efficient protocol for transforming variety of nitriles into corresponding 1*H*-tetrazoles using diisopropylethylammonium acetate as a green catalyst as well as medium. The developed protocol for [2+3] cycloaddition is associated with several advantages such as simple procedure, mild reaction conditions, an alternative to hazardous, corrosive, and polluting conventional Lewis acid catalysts and solvents. Reusability of DIPEAc with consistent activity for at least four cycles is also established, indicating DIPEAc as a greener reaction medium. DIPEAc can substitute metal salts and other heterogeneous catalysts, and all these consign this method at an advantageous position compared to already reported methods for these molecules of commercial value.

EXPERIMENTAL

General

All the solvents and reagents were purchased from commercial suppliers Spectrochem Pvt. Ltd., Sigma Aldrich and Rankem India Ltd., and were used without further purification. The progress of each reaction was monitored by ascending TLC using TLC aluminum sheets, pre-coated silica gel F_{254} (Merck, Germany) and by locating the spots using ultraviolet (UV) light as the visualizing agent or iodine vapors. Melting points were taken in an open capillary method and are uncorrected. ^{1}H NMR spectra were recorded (DMSO) on a Bruker Avance 400 NMR spectrometer. ^{13}C NMR spectra were recorded (DMSO) on a Bruker Avance 100 NMR spectrometer. Chemical shifts (δ) are reported in

parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. The splitting pattern abbreviations are designed as singlet (s); doublet (d); double doublet (dd); bs (broad singlet), triplet (t); quartet (q) and multiplet (m).

General Procedure For The Synthesis Of Diisopropylethylammonium Acetate (Dipeac)

A mixture of glacial acetic acid (0.02 mol) and *N*-ethyl-*N*-isopropylpropan-2-amine (0.02 mol) was stirred at 0-10 ºC for 30 min. to obtain diisopropylethylammonium acetate as a viscous liquid [26].

***General Procedure For The Synthesis Of 5-Substituted-(1H)-Tetrazoles* (3a-P)**

A mixture of benzonitriles (**2a-p**) (0.009 mol), sodium azide (0.009 mol) was dissolved in DIPEAc (5 ml) and allowed to stirr for 30 min at 80 ^{0}C. After completion of the reaction (monitored by thin-layer chromatography, TLC), the reaction mixture was cooled to room temperature and poured on crushed ice. To it 5N HCl (10 mL) was added and stirred vigorously. Otained solid products was filtered and crystallized from ethanol. The synthesized compounds were confirmed by melting points, IR, ^{1}H and ^{13}C NMR and which are in good agreement with those reported in the literature. [15, 16]

Spectral Data Of Representative Compounds

5-Phenyl-1H-tetrazole **(3a)** White solid; mp 215-216°C; IR (KBr): υ_{max} cm^{-1} 3132, 2935, 1604, 1433, 1272, 748; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.59-7.71 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 148.28, 133.06, 131.22, 125.66, 121.50.

5-(4-Methylphenyl)-1H-Tetrazole (3b)

White solid; mp 248-250°C; IR (KBr): υ_{max} cm^{-1} 3138, 3000-2400, 1612, 1571, 1504, 1458, 1401, 1165, 1085, 679. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.67 (s, 3H, CH_3), 7.75 (d, 2H, Ar-H), 8.13-8.34 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 146.86, 133.45, 126.03, 125.40, 124.54, 21.56.

SUPPORTING INFORMATION (SI)

Supplementary data associated with this article can be found in the online version on web page.

ACKNOWLEDGMENTS

The authors are thankful to Professor D. B. Ingle for his invaluable discussions and guidance. The authors are also thankful to Central Drug Research Institute (CDRI), Lucknow for spectral analysis.

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Table 1: Screening of the solvents for the synthesis of 5-substituted-(1*H*)-tetrazole (**3a**)

Entry	**Solvent**	**Time (min)**	**Yield (%)[a]**
1	Toluene	30	b
2	Acetonitrile	30	b
3	Methanol	30	b
4	Piperidine ammonium acetate	30	69
5	Pyrrolidine ammonium acetate	30	60
6	Triethylethylammonium acetate	30	67
7	Diisopropylethylammonium acetate (DIPEA)	30	92
8	DIPEA(20, 40, 60, 80, **100** mol %)/Acetonitrile	30	65, 69, 81, 83, **92**

Reaction conditions: **2a** (0.009 mol), sodium azide (0.009 mol), in solvent (5 ml), stirred at 80 ºC

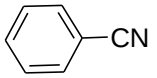
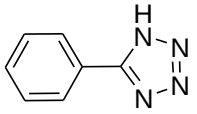
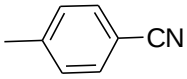
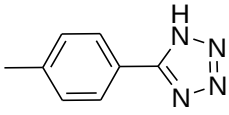
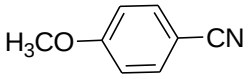
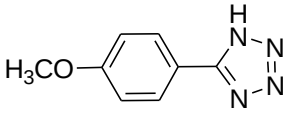
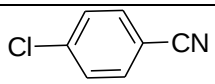
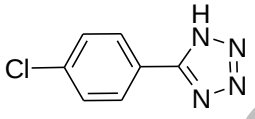
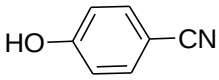
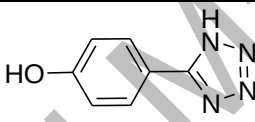
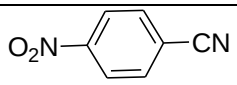
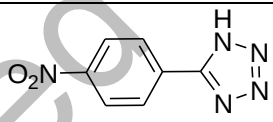
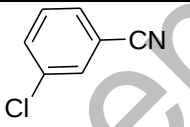
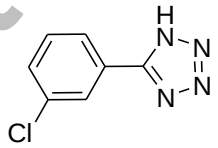
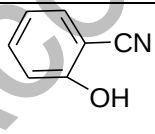
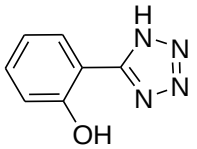
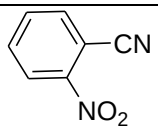
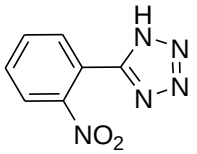
[a]Isolated yields b: No condensation

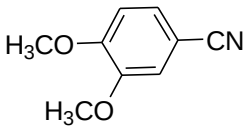
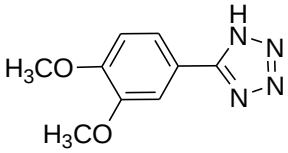
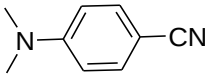
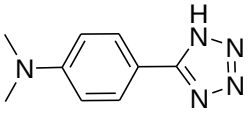
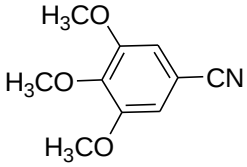
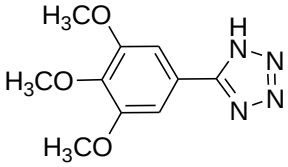
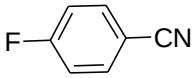
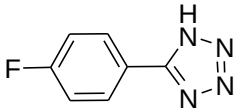
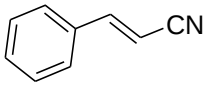
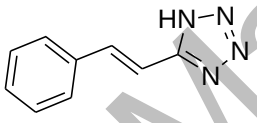
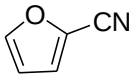
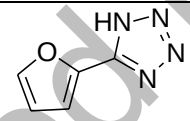
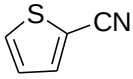
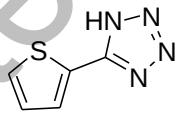
Table 2: Effect of catalyst DIPEAc at varying temperatures

Temp	35 ºC	40 ºC	60 ºC	80 ºC	100 ºC
Yield (%)	No condensation	85	87	92	93

Reaction conditions: **2a** (0.009 mol), sodium azide (0.009 mol), in DIPEA (5 ml), stirred for 30 min. [a]Isolated yields

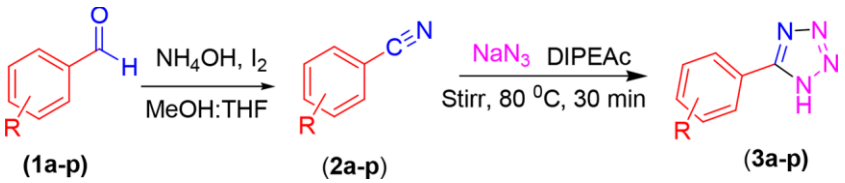
Table 3: Physical data of 5-substituted-(1*H*)-tetrazoles (**3a-p**)

Entry	Substrate	Product[b]		Yield (%)
1			**3a**	92
2			**3b**	89
3			**3c**	87
4			**3d**	90
5			**3e**	94
6			**3f**	86
7			**3g**	89
8			**3h**	81
9			**3i**	79

10			**3j**	89
11			**3k**	90
12			**3l**	85
13			**3m**	81
14			**3n**	75
15			**3o**	79
16			**3p**	71

Reaction conditions: benzonitriles (2a-p) (0.009 mol), sodium azide (0.009 mol), DIPEAc (5 ml) stir at 80 °C. [a]Isolated yields. [b] Melting points, ^{1}H & ^{13}C NMR are in good agreement with those reported in the literature.[15, 16]

Scheme 1: Synthesis of 5-substituted-(1*H*)-tetrazoles (**3a-p**)



(1a-p) (**2a-p**) (**3a-p**)

Scheme 2: Plausible mechanism for the synthesis of 5-substituted-(1*H*)-tetrazoles

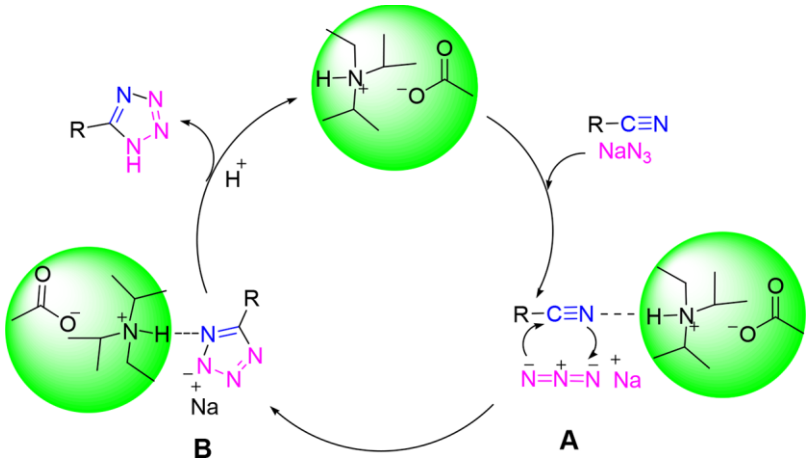


Figure 1. Examples of relevant pharmacologically active substances

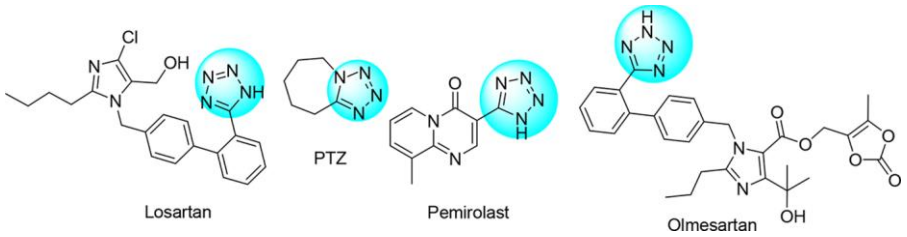


Figure 2: Reuse and recovery of DIPEAc and its effect on yield.