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# Urea mediated 5-substituted-1H-tetrazole via [3 + 2] cycloaddition of nitriles and sodium azide

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ABSTRACT

A simple, new and convenient metal free procedure for the synthesis of 5-substituted 1*H*-tetrazoles using various nitriles and sodium azide in the presence of urea and acetic acid with good to high yields is developed. The reaction plausibly proceeds through *in situ* formation of urea azide active complex without toxic and/or expensive metal catalysts.

## Introduction

Tetrazole is an impressive functionality with diverse applications in medicinal chemistry.[1] Research in tetrazole chemistry is found to be extremely important due to the fact that it acts as stable carboxylic acid surrogate and offers superior pharmacokinetic profile to the parent molecule.[2] Such an advancement led to the discovery of angiotensin II antagonistsas.[3] This functionality has also been frequently exploited as lipophilic spacers, ligands, precursors of a variety of nitrogen containing heterocycles in coordination chemistry[4,5] and in material sciences including photography, information recording systems, and explosives.[6]

Most widely practiced synthesis of 5-substituted 1*H*-tetrazoles is [3 + 2] cycloaddition reaction involving nitriles and azides. A number of synthetic protocols with variations are precedented in literature.[6a.c] In most instances, sodium azide ($NaN_3$) has been used as an inorganic azide source in combination with ammonium halides, as an additive employing dipolar aprotic solvents.[6a,7] In addition to this, aryl nitriles in the presence of sodium azide and an amine hydrochloride had been reported.[7b] In some cases, Brønsted[8] or Lewis acids[9] or stoichiometric amounts of Zn(II) salts[10] had been reported as suitable additives to afford the desired azide–nitrile addition product. As an alternative to inorganic azide salts, trimethylsilyl[11a] with TBAF catalyst,[11b] trialkyltin[12] and organoaluminum azides[13] had been introduced as comparatively safer azide sources which had an advantage of solubility in organic solvents. Several heterogeneous catalytic systems were also reported, for example, nanocrystalline ZnO,[14a] Zn/Al hydrotalcite,[14b] Zn hydroxyapatite,[14c] and $Cu_2O$,[15a] CuO,[15b] Cu(II) immobilized on $Fe_3O_4$@SiO2@l-Arginine,[15c] tungstate salts,[16] mesoporous ZnS nanospheres,[17] reusable catalyst $CuFe_2O_4$ nanoparticles,[18] CoY Zeolite,[19] montmorillonite K-10,[20] and $Fe(HSO_4)_3$[21] Recently $InCl_3$[22] and phosphomolybdic acid ($H_3Mo_{12}O_{40}$-P)[23] have been reported as catalysts for the synthesis of 5-substituted 1*H* tetrazoles. Organic azides e.g. triethyl ammonium azide[24] in a microwave reactor[24b] and sodium azide in the presence of the acidic resin amberlyst-15,[25] $CuSO_4{\cdot}5H_2O$,[26] $AgNO_3$,[27] DMAP acetate,[28a] Amine salt catalysed synthesis,[28b] silica supported Lanthanum triflate,[29] have also been reported to achieve similar cycloaddition reactions.

## Results and discussion

However, many of the above mentioned protocols have some disadvantages like use of toxic metals, expensive reagents, strong Lewis acids and harsh reaction conditions. Thus, in spite of the developments the synthetic method for the preparation of tetrazoles still remains as a fascinating research area. In our research we reported the development of a new synthesis of 5-substituted 1*H*-tetrazoles **2** via urea azide mediated cycloaddition. This [3 + 2]

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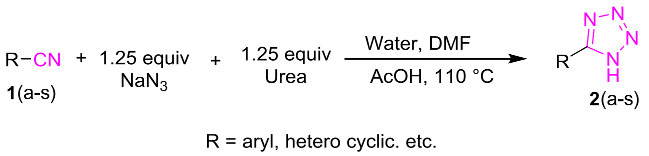
cycloaddition reaction involves use of nitrile **1** and sodium azide in mixture of water and DMF (Scheme 1).

Substrate **1a** was selected for the model studies to examine the reaction conditions (Table 1). Initial reactions were conducted using stoichiometric amount of urea (relative to sodium azide) in presence of DMF solvent and $NaN_3$ as azide source (entry 1&2, Table 1). We did not obtain promising results and hence we made efforts to understand the importance of solubility on reaction progress. We examined this by performing cycloaddition reaction between **1a** and $NaN_3$, to obtain tetrazole **2a** (Table 1) in different solvents e.g. DMF with or without water and with or without acetic acid, *o*-xylene and toluene. Among these combinations, water and DMF with acetic acid afforded good yields (95%) using 1.25 equivalents of $NaN_3$ and 1.25 equivalents of urea (Table 2). It was also found that DMF and acetic acid offered yield in the tune of 90% (Table 1; entry 4). Further studies by using water in combination with AcOH or only AcOH offered products in 15% and 10% yields respectively (Table 1; entry 5 and 6). In order to have better control over the reaction, we performed experiments by using 1.25 equivalents each of the $NaN_3$ and urea.

Towards establishing the generality of this method, we selected a variety of structurally divergent nitriles, **1** to understand the scope of the urea mediated [3 + 2] cycloaddition to form 5-substituted 1*H*-tetrazole.

The results are presented in Table 3. The reactions of the aryl nitrile, bearing electron donating substituent in para position afforded corresponding tetrazole in similar yields when compared with electron withdrawing substituent. Benzyl nitriles containing *p*-methoxy group offered tetrazole **2j** in good yield. Further, the reaction was extended to cyano indole derivatives and cyanothiophene offered tetrazoles **2p, 2q, 2r** and **2l** in moderate to high yields. Synthesis of sterically hindered structures like Sartan intermediates **2n** offered lower yield. Unfortunately the present method is not well suited for aliphatic ones due to alkyl groups which are considered to be electron donating enabling nitriles less reactive in comparison to the electron withdrawing aromatic nitriles (Table 3; yield of product **2s**: 20% to 50% in a two different conditions).

Based on experimental observations, a plausible mechanism as featured in Fig. 2 is being operated. Initially, urea reacts with acetic acid and produces an *in situ* generated acetate salt of urea **A**. Thereafter, in presence of sodium azide, the salt **A** gets converted into reactive species urea azide, **B** through salt metathesis. Urea azide, **B** underwent through [3 + 2] cycloaddition reaction with nitride derivative to generate the intermediate **C** followed by formation of **D**. Thus the process of cyclization is accelerated through protonolysis of the intermediate **D** by aqueous HCl. To support this mechanism, the reaction 1 with $NaN_3$ in DMF/water/AcOH was conducted in absence of urea and found that the reaction did not proceed to give the desired product (Table 2, entry **5**). Impact of pKa values of all the reactants on each other towards product formation favorably could not be ascertained during reaction due to the fact that this protocol involves solvent mixtures (DMF, AcOH and water).



**Scheme 1.** Synthesis of 1*H*-tetrazoles by urea mediated cycloaddition.

There are several other mechanistic pathways reported[30] but we believe that the proposed mechanism in our endeavor is another possibility. In order to support our mechanistic hypothesis, we conducted an experiment by using online Raman Spectroscopy. Raman spectroscopic measurements were performed with a Raman Rxn2™ Multi-channel Raman Analyzer. Spectra Physics Argon Ion Laser at 785 nm was used as the excitation source.

This experiment was carried out to establish whether it would be possible to monitor *in situ* tetrazole formation *via* urea and sodium azide complex using Raman spectroscopy or not. A model reaction regarding this is shown in Fig. 1.

Towards monitoring the spectral changes during the course of reaction, Raman scans were collected at the interval of exposure time ten seconds and scans to 5 for one minute over eight hours. The Raman spectra show the strong peak for sodium azide at 1358 $cm^{-1}$ —N═N stretching frequency in water medium. Whereas urea characterization peak observed at 1650 $cm^{-1}$ and 1012 $cm^{-1}$ in water medium and we could not able to monitor this peak due to overlap and very low intensity. At higher temperature, (60 °C), —N═N stretching frequency of sodium azide peak intensity did not decrease under maintenance for 40 min. It means azide-urea complex did not form.

Thereafter, addition of benzonitrile, *N*,*N*-dimethylformamide and acetic acid into reaction mass containing urea and sodium azide at 60 °C, as expected, —N═N stretching frequency of sodium azide peak intensity decreased with time and slowly disappears. In addition to this, new peak appeared at 1105 $cm^{-1}$ which is

**Table 2**
Effect of urea on the formation of **2a** from **1a**.

| Entry | Urea | Reaction time | Yield[b] (%) |
|---|---|---|---|
| 1 | 1.25 equiv | 8 h | 95 |
| 2 | 1.0 equiv | 10 h | 75 |
| 3 | 0.5 equiv | 14 h | 50 |
| 4 | 0.2 equiv | 24 h | 45 |
| 5 | _ | 24 h | 0[c] |

[a] Reaction conditions: Reactions were carried out on a 0.5 g scale of **1** withNaN$_3$ (1.25 equiv) at 110 °C;
[b] Isolated yields;
[c] No product formation.

**Table 1**
Solvent screening for the preparation[a] of **2a** from **1a**.

| Entry | Solvent | T °C | Solvent ratio(*vol* mL)[b] | Yield[c] (%) |
|---|---|---|---|---|
| 1 | DMF | 125 | 10(*10*) | 40 |
| 2 | DMF:Water | 130 | 5:5(*10*) | 60 |
| 3 | DMF:Water: AcOH | 110 | 5:5:1(*11*) | 95 |
| 4 | DMF:AcOH | 110 | 5:1(*6*) | 90 |
| 5 | Water:AcOH | 110 | 5:1(*6*) | 15 |
| 6 | Water | 110 | 5(*5*) | 10 |
| 7 | O-Xylene | 130 | 10(*10*) | 0[c] |
| 8 | Toluene | 110 | 10(*10*) | 0[c] |

[a] Reaction conditions: Reactions were carried out on a 0.5 g scale of **1** with $NaN_3$ (1.25 equiv) in the presence of urea (1.25 equiv) at 100–130 °C;
[b] Ratio with respect to **1** (volume with respect to **1**).
[c] Isolated yields.