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$AgNO_3$ catalyzed synthesis of 5-substituted-1*H*-tetrazole via [3+2] cycloaddition of nitriles and sodium azide

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Dedicated to the memory of late
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ABSTRACT

An efficient one-pot, convenient catalysis for the synthesis of 5-substituted-1*H*-tetrazoles is reported. The [3+2] cycloaddition involves various nitriles, sodium azide in refluxing DMF and $AgNO_3$ as catalyst to give corresponding 5-substituted-1*H*-tetrazoles in good to excellent yields. It is expected that the reaction proceeds via in situ formation of a silver azide species, which participates in coordination of nitrile moiety followed by cycloaddition of azide ion to give tetrazole.

Tetrazoles are heterocyclic compounds having a five membered ring containing one carbon and four nitrogen atoms. Such heterocyclic systems are not found in nature.[1] The preparations of substituted tetrazoles have been the subject of intense investigation especially from the nitrile functionality, which is widely recognized as a useful intermediate in organic synthesis.[2] Synthetic, medicinal, and pharmaceutical applications of tetrazoles are well explored and documented in the literature.[3] Biphenyl tetrazoles are also well known and used to synthesize sartan family drugs.[4] The other class of its use includes propellants, explosives,[5a] and in photography.[5] In addition to the above it is found useful in agriculture as plant growth regulators[6] and in crop protection, its derivative plays a key role as herbicides, and fungicides.[7]

The synthesis of 5-substituted-1*H*-tetrazoles was found fascinating and many new processes and revision of existing processes since Finnegan's invention have appeared.[8] The principle of most of them is almost common that is cycloaddition of nitrile with an azide moiety, under the influence of several efficient catalysts and different solvent conditions. Numbers of new catalysts have also been investigated till date and among those which serve the purpose are copper triflates,[9] $Fe(OAc)_2$,[10] zinc(II) salts,[11] Lewis acids such as $AlCl_3$,[12] BF_3–OEt_2,[13] $FeCl_3$,[14] TBAF,[15] heterogeneous catalysis COY zeolites,[16] mesoporous ZnS nanospheres,[17] Cu_2O,[18] and $CuFe_2O_4$ nano particles.[19a] Acid catalysts are also used for the synthesis of tetrazole via cycloaddition[19] Recently, many chemists have reported the use of transition elements and their salts as a catalyst. Sharpless and co-workers reported an innovative procedure for the preparation of 5-substituted-1*H*-tetrazoles from the corresponding nitriles and NaN_3 in the presence of a stoichiometric amount or 50 mol % of Zn(II) salts.[20] Shortly, an efficient method for the synthesis of tetrazoles was reported by the reaction of nitriles with $TMSN_3$ using 50 mol % of TBAF as catalyst.[21] (Table 1) More recently, efficient synthesis of tetrazoles by reaction of nitriles with NaN_3 using nano crystalline ZnO or zinc hydroxyapatite as the catalyst is reported at 120–130 °C.[22] These findings attracted the attention toward the chemistry of transition metal catalysis.

Table 1
Effect of catalyst and solvent on the formation of tetrazole **2a** from **1a**

Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield of **2a** (%)
1	$AgNO_3$ (5 mmol %)	DMF	120	5	42
2	$AgNO_3$ (10 mmol %)	DMF	120	5	83
3	$AgNO_3$ (20 mmol %)	DMF	120	5	94
4	$AgNO_3$ (10 mmol %)	DMSO	120	8	56
5	$AgNO_3$ (10 mmol %)	CH_3CN	80	22	13
6	$AgNO_3$ (10 mmol %)	EtOH	78	11	5
7	$AgNO_3$ (10 mmol %)	$CHCl_3$	60	24	0
8	$AgNO_3$ (10 mmol %)	1–4 Dioxane	100	24	0
9	$AgNO_3$ (10 mmol %)	Water	100	24	0

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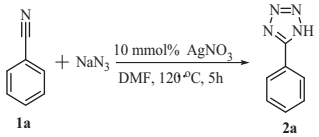
Table 2
Effect of temperature on the formation of tetrazole **2a** from **1a** in DMF with 10 mmol % $AgNO_3$

Entry	Temp (°C)	Time(h)	Catalyst	Yield (%)
1	25	12	$AgNO_3$ (10 mmol %)	0
2	50	12	$AgNO_3$ (10 mmol %)	28
3	100	12	$AgNO_3$ (10 mmol %)	49
4	120	5	$AgNO_3$ (10 mmol %)	83



Scheme 1. Reaction of Benzonitrile with sodium azide in DMF.

However, many of the above mentioned protocols have some disadvantages like use of toxic metals, strong Lewis acid, expensive reagents, low yield, harsh reaction conditions, water sensitivity, and the usual separation and toxicity problems associated with small alkyltin reagents. In addition to this in some cases formation of highly volatile and toxic hydrazoic acid as by product warrant the safety of the method.[23] Despite extensive researches on synthesis of tetrazoles, it is still an active research area which is in need to develop, and demands new synthetic methodologies, (Table 2) which simplifies the synthesis and minimizes the drawbacks.

The choice of a suitable catalyst for any reaction medium is of key importance to get good results. Last few decades, transition metal catalysis has drawn due attention of chemists due to their wide spectrum of utilities in numerous chemical conversions. The catalytic activities of such elements are mainly due to its ability of activation of a particular functionality via coordination toward a certain type of reaction.[24,25] This type of co-ordination/activation approves the other reagents/substrates to react with that functional group and thus the reaction attains an added

Table 3
$AgNO_3$-catalyzed synthesis of 5-substituted 1*H*-tetrazoles[a]

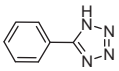
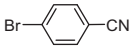
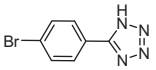
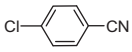
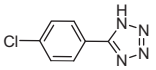
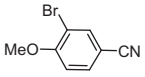
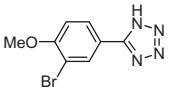
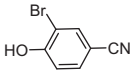
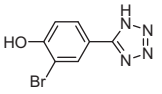
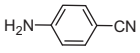
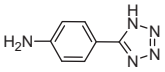
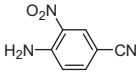
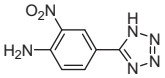
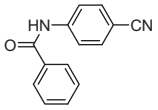
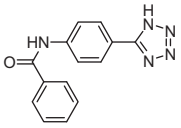
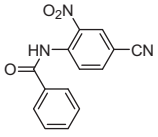
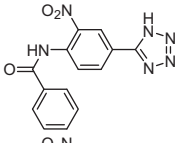
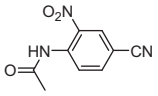
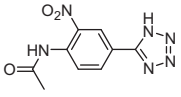
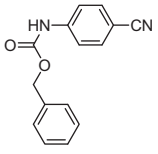
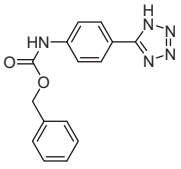
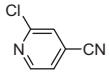
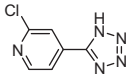
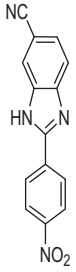
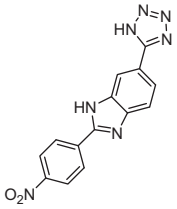
Sl. no	Substrate	1	Time (h)	Product	2	Yield[b] (%)
1		**1a**	5		**2a**	83
2		**1b**	5		**2b**	78
3		**1c**	5		**2c**	80
4		**1d**	5		**2d**	78
5		**1e**	5.5		**2e**	82
6		**1f**	5.5		**2f**	81
7		**1g**	5		**2g**	81
8		**1h**	5		**2h**	76
9		**1i**	5		**2i**	79
10		**1j**	5		**2j**[c]	87
11		**1k**	5		**2k**	84

Table 3 (*continued*)

Sl. no	Substrate	1	Time (h)	Product	2	Yield[b] (%)
12		**1l**	5		**2l**	83
13		**1m**	5		**2m**	83

[a] The reaction of nitriles 1 with NaN_3 (1.5 equiv) was conducted in DMF in the presence of 10 mmol % of $AgNO_3$ at 120 °C for the time shown in Table 3.
[b] Experimental yield.
[c] Figure 2.

selectivity and produces specific products only. As an example, in the present Letter, we wish to disclose our findings, which involve the activation of nitrile functionality of cyanobenzene by $AgNO_3$ catalyst which in situ gives AgN_3 by the action of sodium azide on it.[26] This silver azide thus formed perhaps coordinates the π-linkage of nitrile functionality of the substrate which results in the activation of the azide anion, and this promotes it to react with the nitrile functionality selectively, as a 1,3-dipole, to produce benzenetetrazoles. This is an extension of diversification of ongoing research work in our group.[27] In quest of the above approach we herein, report a simple and convenient, protocol for the synthesis of 5-substituted 1*H*-tetrazole (**2a**) by cycloaddition reaction between benzonitrile (**1a**) and sodium azide (NaN_3 1.5 equiv) in the presence of 10 mmol % of $AgNO_3$ in DMF as a solvent (Scheme 1).[28] The results of the [3+2] cycloaddition reaction of various nitriles 1 with NaN_3 are summarized in Table 3. The reactions of the arylnitriles **1b** and **1c**, bearing an electron-donating group at the *para*-position of the aromatic ring, with sodium azide were carried out in DMF at 120 °C in the presence of 10 mmol % $AgNO_3$. The reactions were completed in 5 h affording the corresponding tetrazoles **2b** and **2c** in 75% and 80% yields, respectively (entries 2 and 3).

Introduction of the nitro group at meta position shows improved yield (**2g**, 81%). The yield of tetrazoles further improved if we use protected amines (**2h** and **2k** in 76% and 84% respective yields). Nitro derivatives were also prepared in excellent yields (**2i** and **2j**) in 79% & 87%, respectively In addition to this heterocyclic based tetrazoles can also be prepared efficiently using $AgNO_3$ as a catalyst (Table 3, entry 12). The methodology was also found applicable with benzimidazole transformation to bear additional tetrazole moiety (Table 3, entry 12, yield 83%).

The above results specify that the tetrazole ring formation via [3+2] cycloaddition reaction tolerates a wide range of substituents irrespective of their electronic behavior, positions, and independent of the type of aromatic ring involved in conversion.

A plausible mechanism is shown in Figure 1. Initially, $AgNO_3$ reacts with NaN_3 to produce the AgN_3 catalytic species.[26] The [3+2] cycloaddition between the C–N bond of nitrile **1a** and AgN_3 takes place readily to form the intermediate **A**; pre-coordination of the nitrogen atom of the CN group of **1a** with silver azide to form complex **B** would accelerate this cyclization step. Figure 2 Protonolysis of the intermediate **B** by 2 N HCl to maintain pH of solution in between 2 and 3, affords the 5-substituted 1*H*-tetrazole **2a** and AgCl as white solid was recovered at the end of the reaction through filtration only.

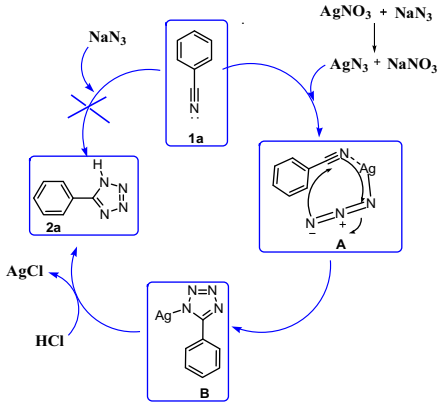


Figure 1. Proposed mechanism for the synthesis of tetrazole.

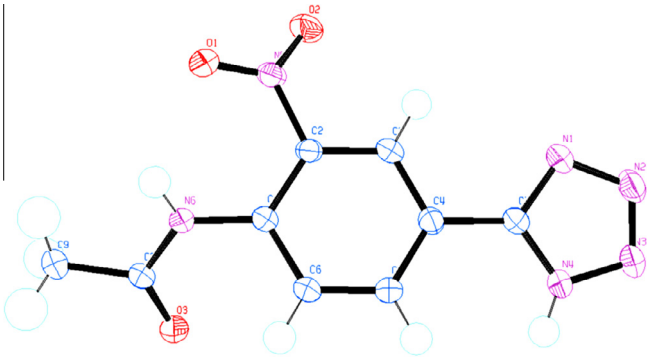


Figure 2. ORTEP diagram of compound **2j**.

The proposed mechanism is also supported by the experimental facts. For this we carried out the reaction of **1a** (1 equiv) with NaN_3 (1.5 equiv) in DMF at 50 to 120 °C for 12 h but the reaction did not proceed at all. This accounts for the absence of in situ generated AgN_3 catalyst required for the cycloaddition in tetrazole formation, further the starting material **1a** was recovered in 75% yield. These results clearly indicate that, AgN_3 is a key catalytic species which enables the [3+2] cycloaddition with **1a** to produce intermediate **A** and **B** followed by the formation of tetrazole salt which on protonolysis affords desired **2a** in good yield.

In the present study, we report silver nitrate as a highly efficient, one-pot, convenient catalyst for the synthesis of 5-substituted 1*H*-tetrazoles via the [3+2] cycloaddition involving various substituted nitriles and sodium azide in refluxing DMF in good to excellent yields. The reaction most likely proceeds through the in situ formation of a silver azide which acts as a catalytic species. The easy availability of catalyst, elimination of toxic hydrazoic acid, a simple work-up procedure, and better yields are significant advantages over other existing methods. Further, studies in this area are in progress to broaden the scope of the new catalyst.

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Supplementary data

Supplementary data (crystallographic data (excluding structure factors) for the structure in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication Nos. 977261. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.-cam.ac.Uk)) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.117.

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28. *The representative tetrazole* ***2a*** *was synthesized via following procedure:* Sodium azide (0.378 g, 0.046 mmol) was added to a solution of $AgNO_3$ (5 mg, 10 mmol) in DMF (5 ml) and reaction mixture was stirred for 5 min, to this stirred solution benzonitrile **1a** (0.4 ml, 0.033 mmol) was added dropwise over the period of 1 min at room temperature and stirring continued for 10 min at the same temperature and then heated at 120 °C for 5 h. After consumption of **1a**, the reaction mixture was cooled to room temperature and chilled by adding crushed ice into the reaction mixture followed by addition of 2 N HCl till reaction mixture reached the pH 2. The reaction mixture was then extracted with ethyl acetate. The organic layer was dried with anhydrous Na_2SO_4, and concentrated to obtain tetrazole **2a** in 83% yield as an off white solid (268 mg), mp = 215–217 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.6 (1H, s), 8.0 (3H, d), 7.1(1H, s), ^{13}C NMR (100 MHz, DMSO-d_6 δ (ppm); 147.77, 133.27, 129.97, 124.73, 120.69 IR(KBr)/cm^{-1}: 2932, 1601, 1438, 1270, 744. Some of the substituted tetrazole products **2** are known compounds and the spectral data and melting points are identical to those reported in the literatures.