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$(NH_4)_2Ce(NO_3)_6$ as an inexpensive, eco-friendly, efficient catalyst for the synthesis of 5-substituted 1-*H* tetrazoles from nitriles

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ABSTRACT

Ceric ammonium nitrate (CAN) is found to be a suitable, inexpensive, and effective non-toxic catalyst for a smooth (3+2) cycloaddition of organic nitriles with NaN_3 to afford 5-substituted 1*H*-tetrazoles in excellent yields. Shorter reaction times, easy work-up, and substantial and pure product formation are the key advantages of the present method.

Tetrazoles are nitrogen containing heterocyclic compounds, which are generally not found in nature. Over the last two decades, applications of tetrazole-based pharmacophore have increased rapidly, and are currently under thorough review owing to their wide range of applications.[1] The 5-substituted-1*H*-tetrazole fragment has been used in a number of clinical drugs, such as antihypertensive sartan family drugs (Valsartan I, Losartan II, Fig. 1).[2] In addition to this, they are also used for different applications such as coordination chemistry as ligands,[3] agriculture,[4] photography,[5] information recording systems in materials,[6] explosives[7] among others. Further, due to their similarity in acidity and planarity, they can function as lipophilic spacers and carboxylic acid substitutes[8] in pharmaceuticals. Finnegan's invention for the synthesis of tetrazoles came long time back and since then a number of reports followed with the combination of myriad of the new catalysts. The conventional method of synthesizing tetrazoles is based on the addition of azide ions to organic nitriles in suitable solvent in the presence of catalyst. Majority of these catalysts are based on metals such as cadmium[9] ($CdCl_2$), copper[10] (CuI, Cu_2O, $CuFe_2O_4$ nano particles, $CuSO_4{\cdot}5H_2O$, CuO, copper triflates), iron[11] ($FeCl_3$–SiO_2, $Fe(OAc)_2$, Fe_3O_4/ZnS Hollow Nanospheres) palladium[12] ($Pd(PPh_3)_4$), aluminum[13] ($AlCl_3$, $Al(HSO_4)_3$, $(Me)_3Al$), zinc[14] (mesoporous ZnS nanospheres, $ZnBr_2$, $ZnCl_2$), zinc copper alloy,[15] Zn/Al hydrotalcite,[16] silver[17] (silver benzoate), titanium[18] (TiO_2), tungstates[19] (MWO_4 M = Ba, Ca, Zn, Cd, Cu, Na, H) as well as recently used lanthanides as triflates[20] ($Yb(OTf)_3{\cdot}xH_2O$) among others. In addition to this, some other heterogeneous catalysts, such as COY zeolites[21] and acid catalysts[22] (silica sulfuric acid, $NaHSO_4{\cdot}SiO_2$) are also applied for the synthesis of tetrazole via cycloaddition. Sharpless[23] used Zn(II) salt in water for tetrazole synthesis in a widely accepted approach. However, it is found that sterically hindered aromatic nitrile requires high temperatures (140–170 °C) and in the case of the aliphatic nitriles low yield of conversion is also mentioned.

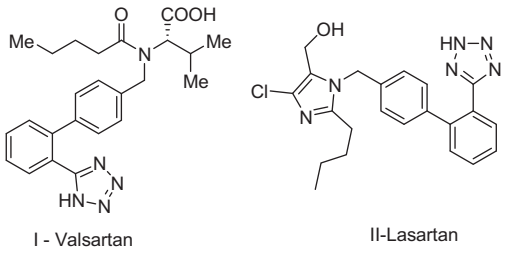

Figure 1. 5-Substituted-1*H*-tetrazole fragment in clinical drugs.

Similarly, many of the aforementioned procedures are found inefficient for the synthesis of aliphatic tetrazoles or excluded from the study. Currently, a number of above mentioned methods of tetrazole synthesis are in use but some of these known methods have potential limitations such as low yields, drastic reaction conditions, use of expensive water sensitive reagents, toxic metal catalysts,

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tedious work-up, complex isolation, and recovery procedures, which emphasize the need of new methods devoid of aforementioned limitations. Therefore, researchers in this area are exploring the potential of other catalysts for the synthesis of substituted 1-*H* tetrazole for combating the issues related to the tetrazole synthesis.

Ceric ammonium nitrate (CAN) is a commercially available, non-toxic, eco-friendly,[24] and extensively used catalyst, and due to these advantages, it is found safer and suitable for both laboratory as well as industry. CAN has been widely used as wonderful catalyst in numerous reactions such as nitration,[25] oxidation,[26] opening of epoxies,[27] cycloaddition,[28] esterification,[29] regioselective iodination,[30] 1,4-additon,[31] epoxide to β-nitro alcohol,[32] synthesis of 3,4-dihydropyrimidin-2(1*H*)-one,[33] unsymmetrical bis (indolyl)alkanes,[34] in aza-Michael reaction,[35] thiocyanation of alkenes,[36] 2-phenylquinazolines,[37] C—C bond formation,[38] deprotection of triisopropylsilyl group,[39] and many more.

Our research group is focused on the design and synthesis of antimicrobial agents.[40–42] Recently, we reported new catalysts for the synthesis of tetrazoles[43] using Ag (nanoparticles) and $AgNO_3$. In continuation to search new and efficient economically viable catalyst, we selected ceric ammonium nitrate for its efficacy in the synthesis of tetrazoles via (3+2) cycloaddition.

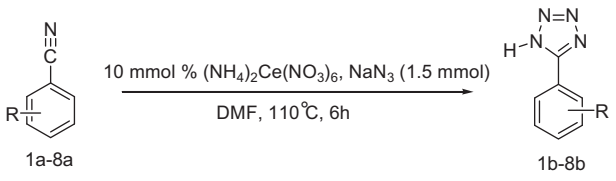
Choice of appropriate reaction medium, efficient eco-friendly catalyst, and optimum reaction temperature plays a key role in obtaining higher yield of title compounds. On investigating the literature, it is observed that currently many rare earth metal based compounds are exploited for their catalytic profile. Lewis acidity of Ce(IV) in CAN supports its use in the (3+2) cycloaddition reaction. In the present case, the coordination capacity of Ce(IV) with π electrons of the nitrile group ease cycloaddition via activation of the nitrile entity which approves the addition of the dipolar azide group. This leads the reaction to get an added selectivity and eventually leads to the formation of a particular product only.

In this Letter, we report the synthesis of 5-substituted 1-*H* tetrazoles via (3+2) cycloaddition using different organic nitriles (**1a**–**14a**) with sodium azide and CAN as catalyst (Schemes 1 and 2). In an effort to develop a better catalytic system, the protocol was standardized by carrying out reaction between benzonitrile and sodium azide as the model and the results are summarized in Table 1. Further, the solvent for reaction medium was optimized (Table 1, entries 10–16). DMF was found to be the most suitable solvent giving a maximum yield of 97%, whereas DMSO, NMP, and toluene prove to be other good solvents and gave 66%, 60%, and 58% yields, respectively (Table 1, entries 12, 13 and 15). Although, other solvents such as acetonitrile, EtOH, $CHCl_3$, dichloromethane, 1,4-dioxane, acetone, and H_2O, were also tested for their efficiency as solvent in the synthesis, they were found not suitable for the synthesis due to either low yield or no reaction. This limits the choice to DMF, DMSO, toluene, and NMP. The DMF was selected over DMSO as a reaction solvent due to some advantages over others like the ease of removal in vacuum and convenient work-up procedure. Further, we investigated the effect of catalyst (CAN) loading and temperature over the formation and yield of substituted 1-*H* tetrazoles by performing various reactions (Table 1, entries 1–11). It is evident that the small loading of catalyst (5 mmol %) would require longer reaction time to perform cyclization, with poor yield of final compound (Table 1, entries 1 and 2). Interestingly, higher ratio of catalyst (15 mmol % and 20 mmol %) neither reduces the reaction time nor significantly improves the yield of tetrazoles (Table 1, entries 7 and 8). Keeping these results in mind, we set up the optimized reaction conditions for cyclization between benzonitriles, sodium azide in DMF, and CAN as catalyst, at 110 °C. The optimized reaction conditions are represented by Scheme 1 (Table 1 entry 4). This optimized protocol (1 mmol nitrile, 1.5 mmol NaN_3, and 10 mmol % of CAN in DMF at 110 °C)[44] yielded persistently considerable amount of products in all cases (Table 2).

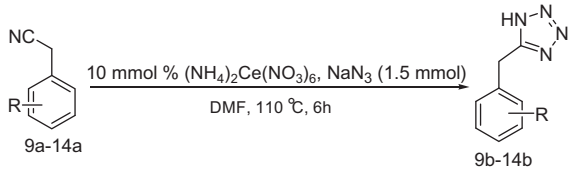
Table 1
Effect of $(NH_4)_2Ce(NO_3)_6$ as catalyst, solvents, temperature, and time on the synthesis of tetrazole **1b** from nitrile **1a**

Entry	Catalyst $(NH_4)_2Ce(NO_3)_6$ (mmol %)	Solvent	Temp (°C)	Time (h)	Yield **1b** (%)
1	5	DMF	110	8.0	70
2	5	DMF	110	24	75
3	10	DMF	110	2.0	50
4*	10	DMF	110	6.0	97
5	10	DMF	110	8.0	97
6	0.0	DMF	110	6.0	0.0
7	15	DMF	110	6.0	98
8	20	DMF	110	6.0	98
9	10	DMF	20.0	12.0	00
10	10	DMF	80.0	12.0	50
11	10	DMF	90.0	12.0	70
12	10	DMSO	110	8.0	66
13	10	NMP	110	10	60
14	15	NMP	110	15	60
15	10	Toluene	110	8.0	58
16	10	CH_3CN	81	22	0
17	10	EtOH	78	12	5
18	10	$CHCl_3$	60	24	0
19	10	DCM	38	24	0
20	10	1,4-Dioxane	100	24	0
21	10	Acetone	56	24	0
22	10	Water	80	24	0

*optimized protocol.



Scheme 1. Reaction of benzonitrile (aromatic nitrile) with sodium azide in DMF.



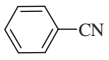
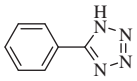
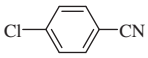
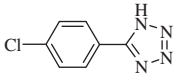
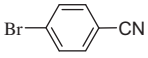
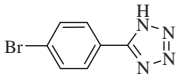
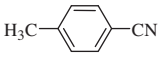
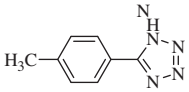
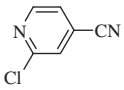
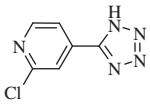
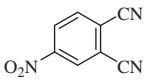
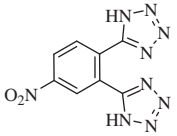
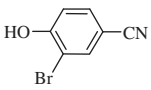
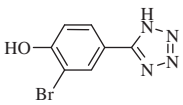
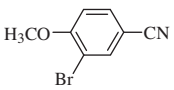
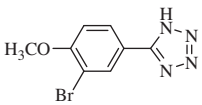
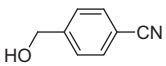
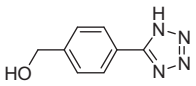
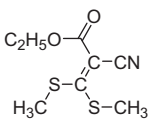
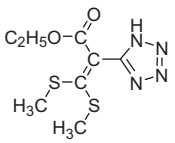
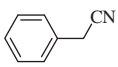
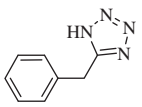
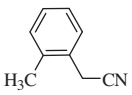
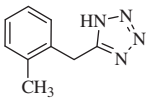
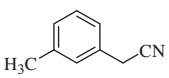
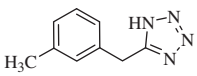
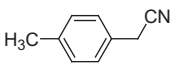
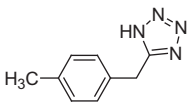
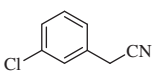
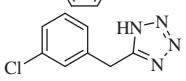
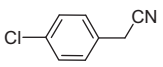
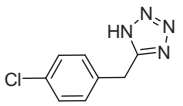
Scheme 2. Reaction of benzylnitrile (aliphatic nitrile) with sodium azide in DMF.

In addition to this, reaction was also performed in standardized conditions without CAN but no product formation was observed (Table 1, entry 6).

This process is found significantly useful for various tetrazole syntheses such as aromatic and aliphatic nitrile transformations. We achieved >95% yield in all aromatic tetrazole syntheses irrespective of the groups (Table 2, entries 1–9). One of the most attractive conversions in this series is the ditetrazole synthesis from their respective dicyano derivatives (Table 2, entry 6). In addition to this, aliphatic nitriles gave slightly lower yields (82–94%) irrespective of the functional group (Table 2, entries 10–16). It is interesting to note that, benzyl alcohol (Table 2, entry 9b), thioether, ester (Table 2, entry 10b), and ether (Table 2, entry 8b) functional groups are compatible with the CAN catalyst in the tetrazole synthesis.

The comparative overviews of present approach along with a few previously known methods are summarized in Table 3.

Table 2
$(NH_4)Ce(NO_3)_6$ catalyzed synthesis of aromatic/aliphatic 5-substituted 1*H*-tetrazoles (**1b**–**16b**)

S. No.	Nitriles[a]	Tetrazoles[b]	Compound	Time (h)	Yields[b] (%)
1[a]			**1b**	6.0	97
2			**2b**	6.0	99
3			**3b**	6.0	98
4			**4b**	6.0	95
5			**5b**	6.0	98
6[c]			**6b**	6.0	97
7			**7b**	6.0	96
8			**8b**	6.0	96
9			**9b**	6.0	97
10			**10b**	6.0	94
11			**11b**	6.0	87
12			**12b**	6.0	82
13			**13b**	6.0	86
14			**14b**	6.0	86
15			**15b**	6.0	89
16			**16b**	6.0	90

[a] Reaction of nitriles **1** with NaN_3 (1.5 mmol) was conducted in DMF in the presence of 10 mmol % $(NH_4)_2Ce(NO_3)_6$ at 110 °C as shown in Table 2.
[b] Experimental yield.
[c] Reaction of nitrile **6a** with NaN_3 (3.0 mmol) was conducted in DMF in the presence of 20 mmol % of $(NH_4)_2Ce(NO_3)_6$ at 110 °C as shown in Table 2.

Table 3
Comparative overview of the present method with few previously known methods

S. No.	Tetrazoles[b]	Catalyst	Temp (°C)	Time (h)	% Yields
1	**4b**	Cu_2O[10]	120	12	77.0 (79.0)
2	**4b**	$(NH_4)_2Ce(NO_3)_6$	110	6.0	95
3	**1b**	$Fe(OAc)_2$[11]	80	24	55.0 (56)
4	**1b**	TiO_2[18]	120	14	79.0 (82.0)
5	**1b**	$ZnCl_2$[23]	Reflux	24	66.0 (76.0)
6	**1b**	$(NH_4)_2Ce(NO_3)_6$	110	6.0	97
7	**11b**	Cu_2O[10]	120	24	66.0 (66.0)
8	**11b**	$Fe(OAc)_2$	80	28	0.0
9	**11b**	TiO_2[18]	120	24	74.0 (74.0)
10	**11b**	$(NH_4)_2Ce(NO_3)_6$	110	6.0	87

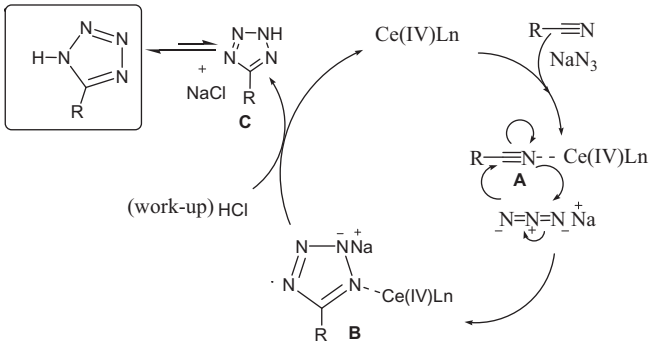
Entries 1–10 represent aromatic and aliphatic tetrazole synthesis, respectively. Parentheses show reported yield.

Aliphatic nitrile fails to give tetrazole on use of catalyst, $Fe(OAc)_2$[11] (Table 3, entry 8) while CAN gave 87% tetrazoles with aliphatic substrate. (Table 3, entry 10). Further, $ZnCl_2$ is used as a catalyst for the aliphatic tetrazole synthesis but requires drastic conditions (170 °C, 24–48 h).[23] Hence, CAN is a better catalyst for both aliphatic and aromatic tetrazole synthesis.

This study reveals that the above (3+2) cycloaddition reaction bears an ample range of substituents, irrespective of their electronic behavior, position, and independent of the type of aromatic/heteroaromatic/aliphatic ring involved in transformation.

A plausible mechanism is presented through Scheme 3. It is proposed that initially, Ce(IV) attaches with π-electron-cloud of the nitrile moiety of given starting molecule which, in turn reacts with NaN_3 for transformation into respective tetrazole. In fact, the coordination of Ce(IV) assists to activate C-N functionality to form intermediate [**A**] for nucleophilic addition of NaN_3 which, in turn generates the intermediate [**B**]. The reaction proceeds via (3+2) cycloaddition pattern. The complex [**B**] on protonolysis by 35% HCl (pH of solution was adjusted in between 2 and 3) gives [**C**], which rearranges to produce more stable desired product, 5-substituted 1*H*-tetrazole.

In conclusion, we report a competent economic and eco-friendly CAN catalyst for the synthesis of 5-substituted 1*H*-tetrazoles via (3+2) cycloaddition in significantly quantitative yields irrespective of the nature of nitrile (aliphatic/aromatic) used. In addition to this, the effects of various substituents are also studied and procedure was found useful and tolerant with a wide range of substituents without potentially affecting the yield and nature of substituent, for example, alcohol, ether, thioether, ester, and alkyl groups



Scheme 3. Plausible mechanism for the synthesis of tetrazole from nitrile by using $(NH_4)_2Ce(NO_3)_6$ as catalyst.

remain intact. The CAN catalyst already has considerable importance in industry sector for various applications. Use of CAN in tetrazole synthesis is another new additional application. The other noteworthy advantages of this methodology comprise simple work-up procedure, easy handling of the catalyst, elimination of hazardous and unsafe hydrazoic acid formation, and no requirement of column chromatography at the end.

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Supplementary data

The spectroscopic data of all compounds are found as supplementary, and crystallographic data for the compound **13b** have been deposited with the Cambridge Crystallographic Data Centre (995816). Data can be obtained free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.-cam.ac.Uk).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.010.

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44. *Experimental condition for 5-substituted 1-H tetrazoles (**1b**–**16b**):* The representative tetrazole **1b** was synthesized via following procedure: sodium azide (1.5 mmol) was added to a magnetically stirred solution of nitrile **1a** (1 mmol) in anhydrous DMF and the CAN (10 mmol %) was added. The reaction mixture was constantly stirred for another 6 h at 110 °C under nitrogen atmosphere. After the completion of reaction as seen by TLC, the reaction mixture was brought to room temperature and the solvent was evaporated under vacuum. The crude thus obtained, was dissolved in ethyl acetate (20 mL) and solution was washed with acidified water (4 M HCl, 15 mL) twice. Separated organic layer was washed with brine solution dried over anhydrous Na_2SO_4, and solvent was removed under high vacuum to obtain tetrazole **1b** as a white crystalline solid in 97% yield.