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Graphical Abstract

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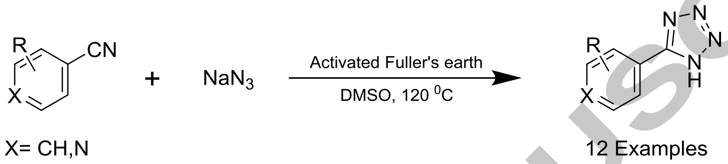

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Activated Fuller's earth as an inexpensive, eco-friendly, efficient catalyst for the synthesis of 5-Aryl 1-*H*- tetrazole *via* [3+2] cycloaddition of nitriles and sodium azide

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ABSTRACT

A simple and efficient method for the preparation of 5-aryl 1-*H*-tetrazoles was developed from various aryl nitriles and sodium azide (NaN_3) *via* [3+2] cycloaddition reaction using activated Fuller's earth as an efficient heterogeneous catalyst. This catalyst has advantageous of cost, stability, recovery, reusability, and ecological benefits along with high product yield, and mild protocol.

Nowadays chemistry of heterocycles has acquired enormous importance.[1] Tetrazoles which belongs to the heterocyclic class has attracted considerable importance because of wide usefulness [2, 3] and applications as heterocyclic ligands in coordination chemistry, material sciences, pharmaceuticals, explosives, photography [4-8] as well as plant growth regulators.[9] A well-known tetrazole, dimethyl thiazolyl diphenyl tetrazolium bromide (MTT) is used in the MTT cell proliferation assay.[10] Biphenyl tetrazoles are intermediates to synthesize sartan drugs (Figure 1). Tetrazoles have been extensively used as a bioisostere of carboxylic acids in molecular design,[4] and also used in the preparation of imidoylazides[11]. Tetrazoles containing molecules possess various biological activities *viz.* antiulcer, [12] anticonvulsant,[13] antiviral, antibacterial, antifungal, anti-inflammatory, [14] antihistaminics,[15] and antitubercular.[16]

The usual method for preparation of tetrazole is through the addition of azide ion to organic nitrile.[17,18-21] Various methods have been reported for the preparation of 5-aryl 1-*H*-tetrazoles; however, most of the methods have certain boundaries with regard to scope and reaction conditions; e.g. cost of synthesis, harsher reaction conditions, longer reaction time, lower yields, and the use of expensive, explosive and toxic reagents.[22] In order to overcome these limitations, Sharpless and co-workers reported a relatively simple, convenient, and safe procedure for the synthesis of tetrazole by the addition of sodium azide to nitriles catalyzed by (50 mol %) Zn (II) salts.[23, 24] In spite of the advantages of homogeneous catalysts, this procedure hinders its use in the industry due to difficulty in recovery of Zn (II) salts. Several catalyst have been reported for the addition of sodium azide to nitriles such as mesoporous ZnS,[25] silica sulfuric acid,[26] $FeCl_3$-SiO_2,[27] $NaHSO_4$-SiO_2,[28] chitosan derived magnetic ionic liquid,[29] $AgNO_3$,[30]CoY zeolite,[31] CAN-HY-zeolite,[32] Zn/Al hydrotalcite,[33] Zn hydroxyapatite,[34] $AlCl_3$,[35] $Et_3N{\cdot}HCl$,[22] TBAF,[36] $Pd(PPh_3)_4$,[37] ZnO,[38] Zn-Cu alloy,[39] $Ln(OTf)_3$–SiO_2.[47]

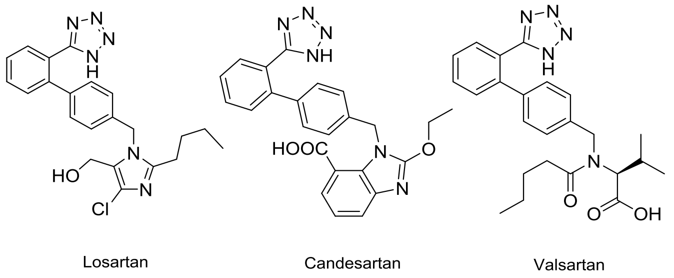

Figure 1. Drugs of sartan series.

The reported catalytic methods are time consuming, with the stringent conditions, and utilizing costly, air sensitive, non-recoverable, toxic metal catalysts (e.g., $Pd(PPh_3)_4$). Therefore, the development of a more efficient, convenient, scalable catalyst that addresses these limitations.

Recent reports revealed that the clay or silica based solid acid catalysts played a pivotal role under heterogeneous conditions by catalyzing organic transformations.[40] This is due to tangible benefits like non-corrosiveness, ease of preparation, handling, regeneration, low cost, and insolubility in most of the organic solvents. The catalytic activity of clays is due to their Bronsted as well as Lewis acidic characters in their natural form.[41-43] Fuller's earth is a commercially available, non-toxic, eco-friendly, economic material. These qualities of Fuller's earth makes it safer and suitable for both laboratories as well as industrial processes. Fuller's earth has been used to analyze color

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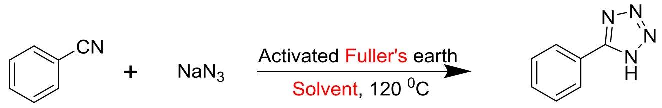
additives in food products and as an adsorbent in pharmaceutical & cosmetics. However, to the best of our knowledge, the applications of Fuller's earth for organic transformation have seldomly reported. Fuller's earth was reported as a catalyst for synthesizing bis(indolyl)methanes.[44] This inspired us to develop a new, eco-friendly activated Fuller's earth as a catalyst. In continuation of our efforts towards the development of eco-friendly green catalytic methodology, we herein report an alternative, simple, and heterogeneous catalyst for the synthesis of 5-aryl 1-*H*-tetrazole.

The Fuller's earth clay was treated with 5% HCl, at 100 °C for 4 h to activate, cooled to room temperature. Insoluble solid was filtered, wash with distilled water till free from acid, dried at 100 °C till constant weight.[48] This treatment increases its adsorption capacity, specific surface area, and pore volume.[45, 46]

The catalyst was characterized by various analytical techniques such as Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), scanning electron microscopy (SEM), and energy dispersive X-ray spectroscopy (EDAX) (Figure 2). FTIR spectrum of the catalyst was recorded to ascertain the functional groups. The catalyst exhibited characteristic absorption bands at 3398 and 1656 cm^{-1} that could be assigned to the OH stretching and bending of the free OH groups, which can be regarded as ''Bronsted active sites'' of the catalyst. The bands at 1026 cm^{-1} correspond to Si-O-Si stretching of silicates and at 1118 cm^{-1} for Al-OH stretching. Stretching at 987 cm^{-1} represents Al-OH-Al deformation vibration. The surface morphology of catalyst in the SEM image clearly indicated that the catalyst is amorphous nature with aggregates of particles in µm range. Powder XRD pattern of catalyst showed the significant peak around 25.02^0, and 26.21^0 which indicated an amorphous nature.

Table 1.
Solvent optimization studies for the synthesis of 5-aryl 1-*H*-tetrazole.



Entry	Catalyst by wt %	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1.	10	No solvent	120	12	0
2.	10	Acetonitrile	reflux	6	0
3.	10	Tetrahydrofuran	reflux	6	0
4.	10	Water	reflux	6	18
5.	10	Ethanol	reflux	6	30
6.	10	DMF	120	1.5	78
7.	**10**	**DMSO**	**120**	**1.5**	**91**

[a] Isolated yield.

The average elemental distribution mapping of the catalyst by EDAX showed silicon: aluminum: oxygen: in the ratio of 34.94: 3.63: 46.11 wt % over different areas.

Initially, our study was aimed to determine the suitability of the catalyst under different reaction conditions. For the preliminary experiment, a mixture of benzonitrile, a representative substrate and sodium azide (1:1.5 equiv.) were used to synthesize 5-phenyl 1-*H*-tetrazole. The results are summarized in Table 1.

The effect of solvents on product yield was studied. Solvent played a prominent role on the yield of the product (Table 1, entries 2-7). In acetonitrile, THF, and under solvent-free condition reactions were fruitless even in the presence of a catalyst (Table 1, entries 1-3).

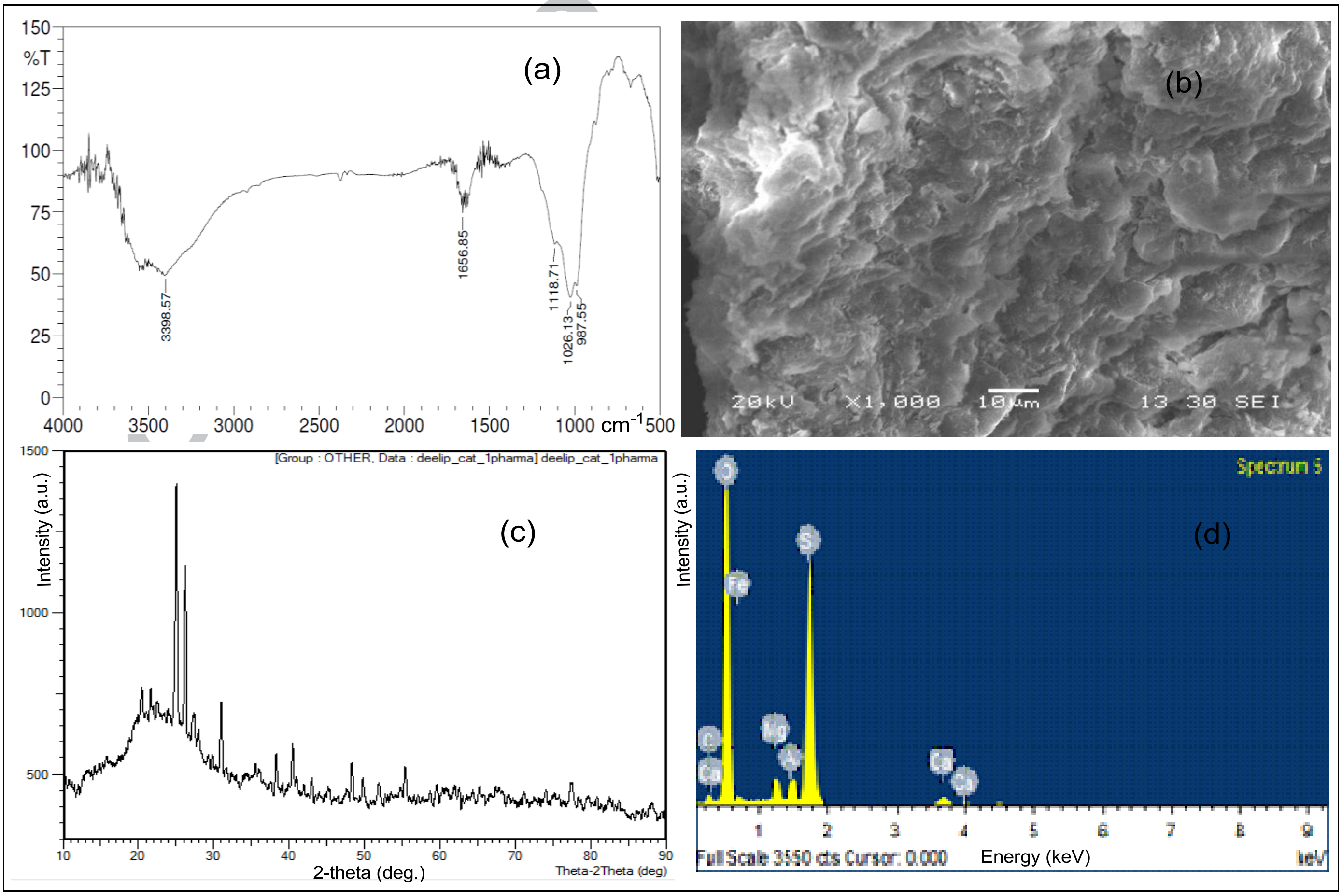


Figure 2. (a) FTIR spectrum; (b) SEM image; (c) XRD pattern; (d) EDAX.

Table 2.
Catalyst loading and temperature optimization study for the synthesis of 5-phenyl 1-*H*-tetrazole.

Entry	Catalyst by wt %	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1.	0	DMSO	120	12	0
2.	5	DMSO	120	1.5	80
3.	10	DMSO	120	1.5	91
4.	20	DMSO	120	1.5	92
5.	30	DMSO	120	1.5	93
6.	10	DMSO	rt	6	20
7.	10	DMSO	80	1.5	56
8.	10	DMSO	100	1.5	84
9.	10	DMSO	150	1.5	87

[a] Isolated yield.

The yields were lower in polar protic solvents (Table 1, entries 4 and 5), while polar aprotic solvents gave good yields, and DMSO was best amongst two (Table 1, entries 6 and 7). The temperature optimization showed that at room and lower temperature, the reaction proceeded slowly with lower yields, while yield gradually increased with temperature till a plateau of 120 °C (Table 2, entries 3, 6- 8). In the absence of the catalyst at 120 °C, no reaction occurred in 12h (Table 2, entry 1). The catalyst loading of 10 wt % was found to be adequate for the maximum yield (Table 2, entries 1-5).

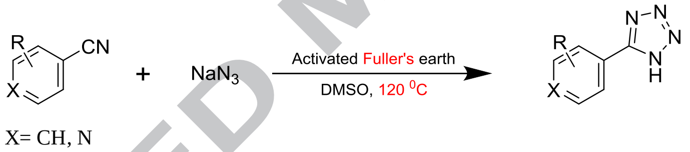
Table 3.
Comparison of the efficiency of activated Fuller's earth with literature reported catalysts for the synthesis of 5-phenyl 1-*H*-tetrazole.

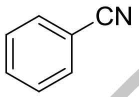
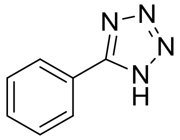
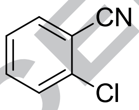
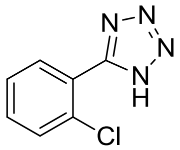
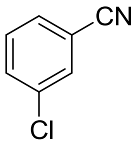
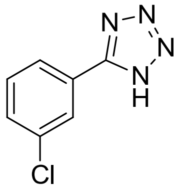
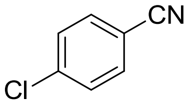
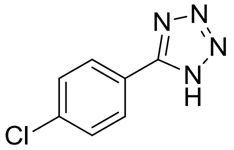
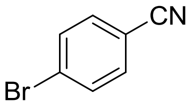
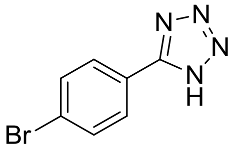
Entry	Catalysts	Condition	Time (h)	Yield[a] (%)	Ref.
1.	Activated Fuller's earth	DMSO/120 °C	1.5	91	This work
2.	CAN-HY-Zeolite	DMF/ 110 °C	4	93	33
3.	Silica sulfuric acid	DMF/reflux	5	88	27
4.	$Ln(OTf)_3$–SiO_2	DMF/MeOH/ 100 °C	7.5	88	47
5.	$NaHSO_4$- SiO_2	DMF/ 120 °C	10	91	29
6.	$FeCl_3$-SiO_2	DMF/ 120 °C	12	79	28
7.	Zn/Al hydrocalcite	DMF/ 120 °C	12	84	34
8.	Zn Hydroxyapatite	DMF/ 120 °C	12	78	35
9.	CoY Zeolite	DMF/ 120 °C	14	90	32

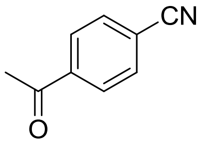
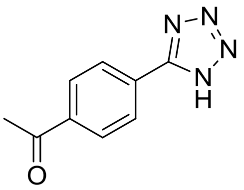
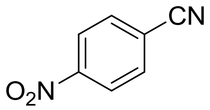
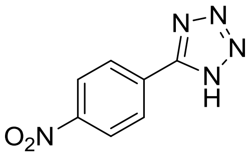
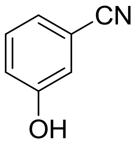
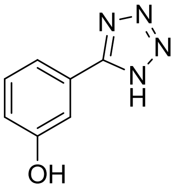
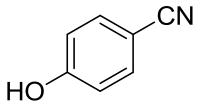
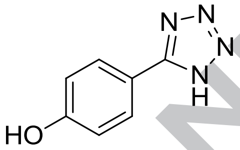
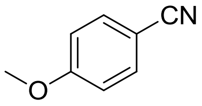
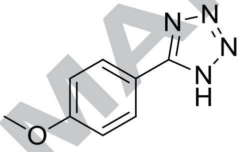
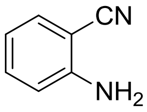
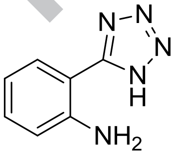
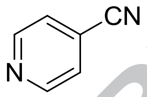
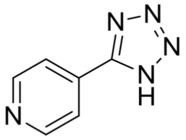
[a] Isolated yield

There are various catalysts reported for tetrazole synthesis. Here the present study is compared with other reported catalysts used for the synthesis of 5-phenyl 1-*H*-tetrazole which indicates that activated Fuller's earth has an advantage in many cases with respect to reaction conditions, time and yields (Table 3, entries 1-9).

Table 4.
Activated Fuller's earth catalyzed synthesis of 5-aryl 1-*H* –tetrazole.[49]



Entry	Substrate	Product	Time (h)	Yield[a] (%)
1.			1.5	91
2.			2.5	81
3.			2	85
4.			1.5	90
5.			2	89

Entry	Substrate	Product	Time (h)	Yield[a] (%)
6.			3	87
7.			3	88
8.			7	77
9.			6	80
10.			6	82
11.			8	78
12.			3	83

[a] Isolated yield.

To explore the scope and applicability of the catalyst, the optimal reaction conditions were applied to functionalized benzonitriles[49] and the results are summarized in Table 4. The reaction time and yields for aromatic nitriles bearing electron withdrawing and electron donating groups have a significant difference, apparently due to the electrophilic character of nitriles. The unsubstituted aromatic nitriles and those bearing electron withdrawing substituents at *ortho* and para position took shorter reaction time, and gave corresponding tetrazoles in higher yields (Table 4, entries 1–7), in contrast to this, those with electron donating groups at *ortho* and *para* position took a long time with lower yields (Table 4, entries 8 -11). Heteroaromatic nitrile gave moderate yield in comparable reaction time (Table 4, entry 12). We also attempted the reaction of aliphatic nitriles under optimized reaction condition without success.

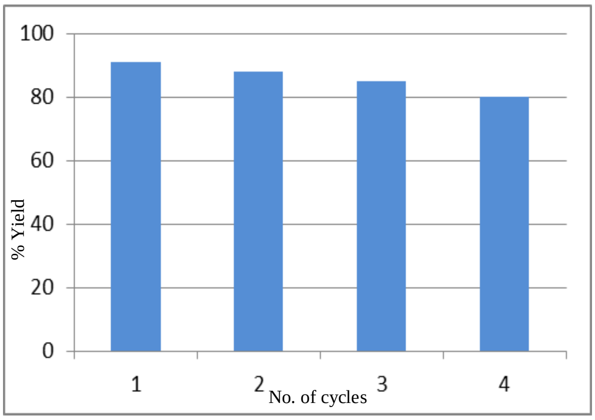


Figure 3. Recyclability of the catalyst.

Recyclability of the catalyst is an important attribute for the industrial suitability. Therefore, the reusability of the catalyst was investigated using benzonitrile as substrate (Table 3, entry 1) over four cycles. After completion of each cycle, the catalyst was separated by filtration and residue was washed with methanol to remove the organic traces. The catalyst was dried at 60 ^{0}C for 1h and used for successive cycles with no remarkable loss of yield

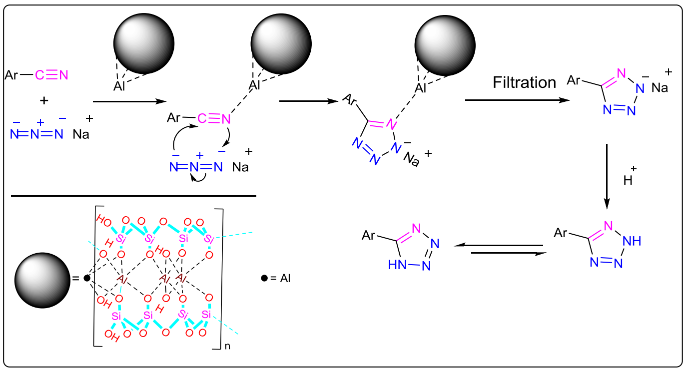


Figure 4. A possible mechanism of 5-Aryl 1-H-tetrazole synthesis by Activated Fuller's earth.

and produced a pure product comparable to fresh catalyst (Figure, 3).

The possible mechanism of synthesis of 5-aryl 1-*H*-tetrazole is depicted in Figure 4. We strongly believe that the Lewis acid character of Al present on the surface of the catalyst activates nitrile towards the [3+2] cycloaddition *via* coordination bond with the lone pair of electrons of the nitrogen of nitriles. Hence, the Lewis acidity is responsible for the catalysis.

Conclusion

In conclusion, the activated Fuller's earth is an inexpensive, eco-friendly, efficient heterogeneous catalyst for the [3+2] cycloaddition of sodium azide and a wide variety of nitriles to form 5-aryl 1-*H*-tetrazoles with excellent to good yields. The catalyst can be easily prepared, used, recovered and recycled with no loss of catalytic activity.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/00.0000/

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48. *Preparation of activated Fuller's earth catalyst:* Fuller's earth (commercial) 10 g was stirred with 100 ml of distilled water to separate water soluble material if any. The suspended solid was filtered, washed with distilled water, and dried in an oven at 100 °C for 1h. In a 250 ml round bottom flask containing 50 ml of 5% HCl solution, added 5 g of solid obtained from above treatment. The mixture was heated at 100 °C for 4 h, cool to room temperature, and filtered; the residue was washed with distilled water till neutrality. Resultant activated fuller's earth was dried at 100 °C till constant weight.
49. *General procedure for the synthesis* of *5-aryl 1-H -tetrazoles*: To a DMSO (3 ml) solution of nitrile (1 mmol), and sodium azide (1.5 mmol), was added catalyst (10 wt %). The reaction mixture was stirred to 120 ^{0}C in an oil bath. The reaction was monitored by TLC. After completion of the reaction, the mixture was filtered to separate the catalyst. The filtrate was quenched with water (30 ml), acidified with 5N HCl (20 ml) to precipitate the product, extracted with ethyl acetate (2 X 20 ml). The combined organic layers were washed with water, dried over sodium sulphate and evaporated under reduced pressure to give the product.

Highlights:

- Simple, efficient and green method for preparation of 5-aryl 1-*H*-tetrazoles.
- Preparation, characterization and application of activated Fuller's earth.
- Recyclable catalyst with no significant loss in activity.
- Method tolerates a variety of functional groups.