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Amberlyst-15 catalyzed synthesis of 5-substituted 1-*H*-tetrazole via [3+2] cycloaddition of nitriles and sodium azide

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ABSTRACT

A mild and efficient method for the preparation of 5-substituted 1-*H*-tetrazole derivatives is reported using solid acidic resin Amberlyst-15 as an effective heterogeneous catalyst. This method is advantageous because of non-toxicity and stability of catalyst, high product yield, simple methodology, and easy work up. The catalyst was recovered by simple filtration and reused several times delivering moderate to good product yield.

Tetrazoles have a wide range of applications in pharmaceutical science. They possess antihypertensive, anti-allergic, antibiotic activity[1,2] and the amino substituted tetrazoles have anti-inflammatory,[3] antineoplastic,[4] antiviral, and receptor modulator[5] activities. Tetrazoles are also used as plant growth regulators, herbicides, and fungicides.[6] Tetrazole derivatives have potential for drug development for HIV or other immune diseases.[7,8] Additionally they have also application in photography[9] and specialty explosives.[10] They are resistant to metabolic degradation as well as to chemical oxidants.[11] Tetrazoles show greater lipophilicity and hence may serve as non-classical isosteres for the carboxylic acid moiety in biologically active molecules.[12,13] Example of a potential anti-HIV drug candidate is shown in Figure 1. Tetrazoles play an important role in organocatalysis, in coordination chemistry as a ligand with various coordination modes,[14] and in preparation of imidoylazides.[15]

This broad utility has prompted significant effort toward the tetrazole synthesis. The most convenient method for the preparation of 5-substituted 1-*H*-tetrazole is via [3+2] cycloaddition of azide to corresponding nitriles. Earlier reported methods for the synthesis of 5-substituted tetrazole suffer from some drawbacks such as use of strong Lewis acid, expensive and toxic metals, use of organic azide complexes such as tin or silicon organic azides and the in situ generated hydrazoic acid which is highly toxic, volatile and explosive.[16] Synthesis of tetrazole from sterically hindered aromatic or alkyl nitriles requires high temperatures and moisture free reaction conditions. In order to overcome these disadvantages, new pathways have been developed, such as the catalytic method using a stoichiometric amount of inorganic salts[17] and transition metal complexes as catalysts.[18] However, these homogeneous catalytic processes suffer from serious problems namely, the separation, recovery, and reusability of the catalyst. Therefore, the heterogeneous alternatives are highly desirable and have attracted much more attention. Several heterogeneous catalytic systems were reported using various catalysts, such as, nanocrystalline ZnO,[19a] Zn/Al hydrotalcite,[19b] Zn hydroxyapatite,[19c] Cu_2O,[19d] $AlCl_3$,[19e] Pd $(PPh_3)_4$,[19f] and TBAF.[19g] These solid acid catalysts play a prominent role in organic synthesis under heterogeneous conditions. Recently our group developed an efficient catalytic system[20] for the synthesis of tetrazole.

In continuation with this research work, we have tried to develop an alternative heterogeneous and simple catalytic system for the synthesis of tetrazole. Amberlyst-15 is non hazardous in nature

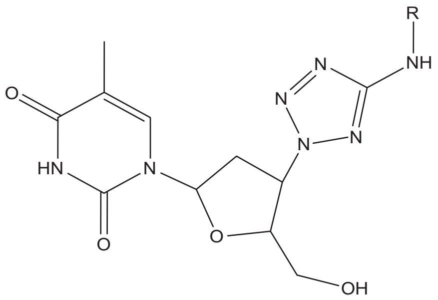

Figure 1. Potential anti HIV drug candidate.

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and easily separable from reaction mixture. Because of these features it is used in a variety of reactions.[21] Amberlyst-15 is a strongly acidic macro reticular polymeric resin based on cross linked styrene divinyl benzene co-polymers. Herein we report a new protocol for the preparation of 5-substituted 1-*H*-tetrazoles from a wide variety of nitriles using Amberlyst-15 as solid acid catalyst.

Benzonitrile was selected as the starting material to synthesize the corresponding tetrazoles. Various solid acid catalysts such as Amberlyst-15, Amberlite-120, montmorilonite, aluminium oxide, sulfated zirconia, and phosphated zirconia have been used for model reaction. The results are summarized in Table 1. Amberlyst-15 exhibits high catalytic activity with 91% product yield (Table 1, entry 1).

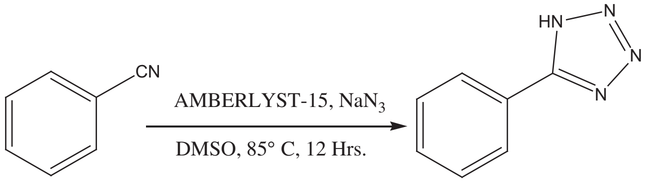
The most probable reason for its higher activity can be explained by its physical properties like high H^+ exchange capacity (4.2 meq/g) and surface area (42 m^2/g) (Table 1, entry 1). The Amberlite-120 gave a lower yield (Table 1, entry 2), even though the H^+ capacity and surface area are more or less similar to the Amberlyst-15. This happens because, the moisture content of Amberlyst-15 is 1.5–1.6% and that of Amberlite-120 is 53–58%. Since the reaction is in organic medium, the excess moisture content of Amberlite-120 may affect the yield of the product. Hence the Amberlyst-15 has superior catalytic activity. The data of H^+ exchange capacity and surface area are provided by the supplier.

The effect of different parameters such as solvents, temperatures, and catalyst concentrations was studied on model reaction (Scheme 1) and the results are summarized in Table 2. In order to get the optimal temperature we carried out the model reaction at various temperatures (Table 2, entries 1–5) and at 85 °C we get the maximum yield. The solvent has prominent influence on the yield of product (Table 2, entries 6–11). DMSO, DMF, and NMP are good solvents with 91%, 85%, and 80% yields, respectively, whereas IPA, ethanol, and water are not suitable for the reaction. 23 mol %, w/w catalyst concentration was sufficient to give maximum yield of the required product (Table 2, entries 12–16). In the absence of the catalyst at 85 °C, no reaction occurred even after 12 h (Table 2, entry 16).

Recyclability of the catalyst is important for the industrial applications. Therefore, the reusability of Amberlyst-15 was investigated for three cycles. The catalyst was recovered from reaction mixture by simple filtration, then washed with diethyl ether (2 × 10 mL) followed by treatment with 0.1 N HCl solution and dried at 60 °C for an hour. The recovered catalyst can be reused over three run cycles; only negligible loss of activity was observed (~5% per cycle) (Table 3, entry 1).

To understand the scope and applicability of the catalyst to cycloaddition reaction to form 5-substituted 1-*H*-tetrazole, different functionalized benzonitriles have been screened and the results are summarized in (Table 3).[23] The aromatic nitriles gave excellent yields (Table 3, entries 1–10). In case of aromatic nitriles, an electron-donating or electron-withdrawing property of the substituent has a significant influence on the product yield. The experimental results show that the electron-donating substituents at 4-position gave excellent yields. (Table 3, entries 2–6). Electron donating group at 2-position might have given comparatively lower yield due to steric effect (Table 3, entry 7). Electron-withdrawing effect is pronounced at 3-position than at 4-position which explains the lower yield of 3-nitrobenzonitrile. (Table 3, entries 8 and 9).

The heteroaromatic nitriles such as 2-pyridinylnitrile gave the corresponding tetrazole in moderate yield (Table 3, entry 10). Phenylacetonitrile and 4-chlorophenylacetonitrile provided moderate to good yield with same reaction time (Table 3, entries 11 and 12). We also explore the reactions of aliphatic nitriles with sodium azide under similar reaction conditions. The catalyst exhibited low activity for aliphatic nitriles in comparison with aromatic nitriles (Table 3, entries 13–14). The reaction was also scaled up by taking 10 mmol of starting material in which 79% yield of the product



Scheme 1. Reaction of benzonitrile and sodium azide with Amberlyst-15 is used as model reaction.

Table 2
Optimization of various reaction parameters for the preparation of 5-substituted 1-*H*-tetrazole[a]

Entry	Solvent	Catalyst	Cat. concn (mol %)	Temp (°C)	Yield[b] (%)
1	DMSO	Amberlyst-15	23	rt	30
2	DMSO	Amberlyst-15	23	60	39
3	DMSO	Amberlyst-15	23	80	84
4	DMSO	Amberlyst-15	23	90	87
5	DMSO	Amberlyst-15	23	100	79
6	DMSO	Amberlyst-15	23	85	91
7	DMF	Amberlyst-15	23	85	85
8	NMP	Amberlyst-15	23	85	80
9	IPA	Amberlyst-15	23	85	35
10	Ethanol	Amberlyst-15	23	85	30
11	Water	Amberlyst-15	23	85	<20
12	DMSO	Amberlyst-15	28	85	92
13	DMSO	Amberlyst-15	18	85	85
14	DMSO	Amberlyst-15	14	85	79
15	DMSO	Amberlyst-15	10	85	66
16	DMSO	—	00	85	00[c]

[a] Reaction and conditions: benzonitrile (1 mmol), NaN_3 (1.5 mmol), Amberlyst-15 (23 mol %, w/w), DMSO (3 mL), reaction time (12 h), and temperature (85 °C).
[b] Isolated Yield.
[c] In the absence of catalyst at 85 °C, no reaction occurred after 12 h.

Table 1
Characteristics of catalysts

Entry	Catalyst	H^+ Capacity	Surface area (m^2/g)	Particle size (mesh)	Yield[c] (%)
1	Amberlyst-15[a]	4.2 meq/g	42	20–50	91
2	Amberlite-120[a]	4.4 meq/g	45	16–50	69
3	Montmorilonite[a]	3.4 meq/g	220	<200	34
4	Aluminium oxide[a]	4.5 meq/g	200	150–300	28
5	Sulfate zirconia	—	85[b]	—	62
6	Phosphate zirconia	—	180[b]	—	56

[a] The H^+ capacity, surface area (m^2/g), and particle mesh size of the catalyst reported.[22]
[b] The surface area of sulfated and phosphated zirconia is determined by using BET method.
[c] Isolated yield.

Table 3
Amberlyst-15 catalyzed synthesis of 5-substituted 1-*H*-tetrazole[a]

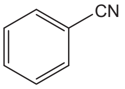
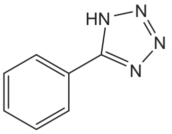
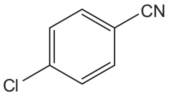
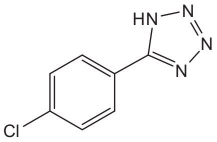
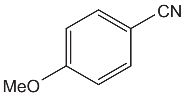
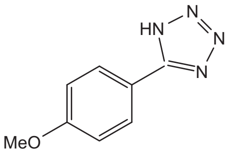
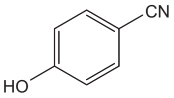
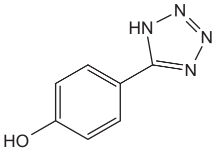
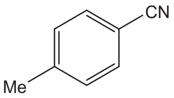
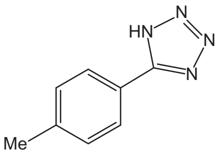
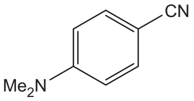
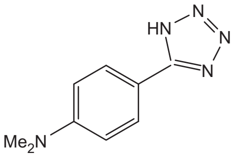
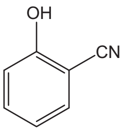
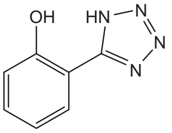
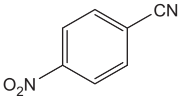
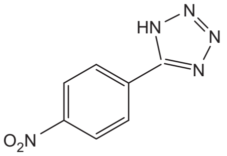
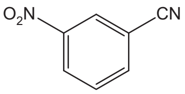
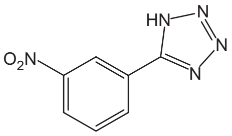
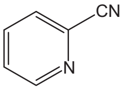
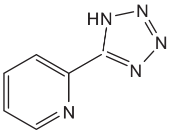
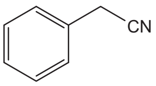
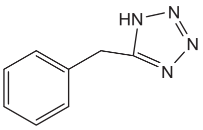
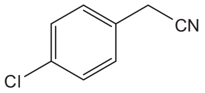
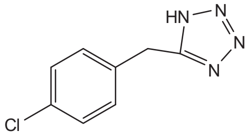
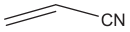
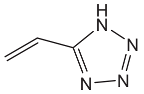
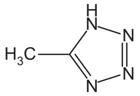
Entry	Substrate	Product	Yield[b] (%)
1			91, 88[c], 85[d], 80[e]
2			93
3			94
4			91
5			89
6			87
7			82
8			84
9			75
10			64
11			74

Table 3 (*continued*)

Entry	Substrate	Product	Yield[b] (%)
12			46
13			36
14	$H_3C{-}CN$		54

[a] Reaction and conditions: nitriles (1 mmol), NaN_3 (1.5 mmol), Amberlyst-15 (23 mol %, w/w), DMSO (3 mL), reaction time (12 h), and temperature (85 °C).
[b] Isolated yield.
[c] Yield after first cycle.
[d] Yield after second cycle.
[e] Yield after third cycle.

was obtained. This indicates that Amberlyst-15 can be used effectively as a catalyst for the large scale production of tetrazole.

Conclusion

In conclusion, we report that Amberlyst-15 is an effective heterogeneous catalyst for the [3+2] cycloaddition of sodium azide and a wide variety of nitriles to form 5-substituted 1-*H*-tetrazoles with excellent to good yields. The catalyst can be easily recovered and reused.

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22. Singh, A. S.; Bhanage, B. M.; Nagarkar, J. M. *Green Chem. Lett. Rev.* **2012**, *5*(1), 27–32.
23. *General procedure for the synthesis of Tetrazole.* A mixture of benzonitrile (103 mg, 1 mmol), sodium azide (97.5 mg, 1.5 mmol), and 3 mL DMSO solvent was added in a 25 mL round bottomed flask. Further (50 mg, 23 mol %, w/w) catalyst was added to the reaction mixture. The reaction mixture was heated to 85 °C for 12 h. After completion of the reaction (as monitored by TLC), the catalyst was separated by simple filtration, washed with diethyl ether and the filtrate was treated with ethyl acetate (30 mL) and 5 N HCl (20 mL) and stirred vigorously. The resultant organic layer was separated and the aqueous layer was again extracted with ethyl acetate (20 mL). The combined organic layers were washed with water and dried over anhydrous sodium sulfate and were evaporated under reduced pressure to give the product. The product was purified by the column chromatography. The structure was confirmed by spectral analysis (^{1}H NMR, mass and elemental analysis).
Characterization of 5-phenyl 1-H-tetrazole. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01–8.04 (m, 2H), 7.57–7.61 (m, 3H), 3.42 (m, 1H) MS (70 eV): *m/z* (%) = 146 (M+, 16.2%), 118 (100.0%), 103 (12.4%), 90.95 (47.1%), 77 (31.7%), 62.9 (24.4%) and 51 (12.3%). CHNS = Anal. Calcd for $C_7H_6N_4$: C, 57.53; H, 4.14; N, 38.34. Found C, 57.76; H, 4.74; N, 38.77.