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Silica molybdic acid catalysed eco-friendly three component synthesis of functionalised tetrazole derivatives under microwave irradiation in water

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Abstract

The catalytic multicomponent reaction between different aldehydes, malonitrile and sodium azide, for the synthesis of functionalised tetrazoles in pure water was performed by using silica molybdic acid as an acidic catalyst under microwave irradiation at ambient temperature. The catalyst showed remarkable activity by decreasing the time period of the reaction from 24 hrs (without catalyst) to 15 min under microwave irradiation. The catalyst successfully tolerated different aromatic and heterocyclic aldehydes furnishing the desired products in excellent yields. The major advantages of this protocol are recyclable catalyst, water as a green solvent, excellent yields, very short reaction times, use of microwaves and high TOF of the catalyst.

Key words: Tetrazoles, Silica molybdic acid, Microwaves, Water, Green.

Introduction

Application of clean technologies in chemical synthesis has currently been the major area of focus in green chemistry. The eco-friendly and reusable heterogeneous catalysts have till now been the leaders in providing such clean technologies. The promising applications shown by such catalysts have in turn been exploited by industries and presently there are more than 100 industrial transformations being catalysed by over 103 solid acid catalysts. [1-4] Due to rapid advances in medicinal chemistry, ever increasing attention has been paid towards the development of novel clean processes employing nontoxic reagents, catalysts and solvents as a majority of drug-like compounds and natural products contain a heterocyclic nucleus at their core. [5-9]

Among various heterocycles tetrazoles and their derivatives represent an important class of N-containing heterocycles. The close similarity between the acidity of tetrazole group and carboxylic group has led to their development as potential medicinal agents [10] and compounds like Lasortan, Irbesartan, Tomelukast, and PTZ (2) (Fig 1), which have been developed into drugs, have proven to be successful bioisosteric replacements for carboxylic acid groups. Moreover, 5-substituted tetrazoles are reported to possess biological profiles like potential drugs against schizophrenia and cerebral ischemia, [11] antidiabetic, [12] antiviral, [13] antibacterial [14] and antihypertensive activities. [15] Also, the role of tetrazoles as important synthons in synthetic organic chemistry, [16] as ligands in coordination chemistry and applications in material chemistry [17, 18] has led to the development of various efficient protocols for their synthesis.

Many available methods for the synthesis of tetrazoles include [3 + 2] cycloaddition of azide to nitriles, [19] reaction of primary amines with NaN_3 and triethyl orthoformate, [20] nucleophilic substitution by an azide anion [21] and addition of $NaNO_2$ to aminoguanidine. [22] But [3+2]

cycloaddition still remains the most employed method for the synthesis of 5-substituted tetrazoles. New efforts to develop multicomponent protocols for the synthesis of 5-substituted tetrazoles have led to the utilization of 2-benzylidenemalononitrile and sodium azide. [23] Water is the most abundant and environmentally benign solvent in nature, but due to low solubility of organic compounds in water, its application in organic synthesis is currently limited. [24] Recently a great deal of interest has been placed towards the reactions of water insoluble substrates that take place in aqueous suspensions because of their high efficiency and straightforward synthetic protocols. It is believed that the generation of internal pressure due to hydrophobic effects of water promotes the association of reactants in solvent cavities and thus, accelerates the reactions. [25, 26] Although the reported protocol has merits like the use of water as solvent and good yields but long reaction times such as 24 hours, hampers its practical applicability. So there is lot of scope for the development of this protocol to make it practically more attractive and also extend it to the medicinally important heterocyclic substrates. Moreover, it is a well-established fact that the combination of heterogeneous catalysts and microwaves have led to the development of effective, rapid and environmentally benign synthetic methods. [27] Keeping in view the environmental concerns and practical applicability of the synthetic methods, we herein, report the synthesis of novel silica molybdic acid (SMA) and its application for the synthesis of novel functionalized tetrazoles via three component addition of aldehydes, malononitrile and sodium azide in water using microwaves.

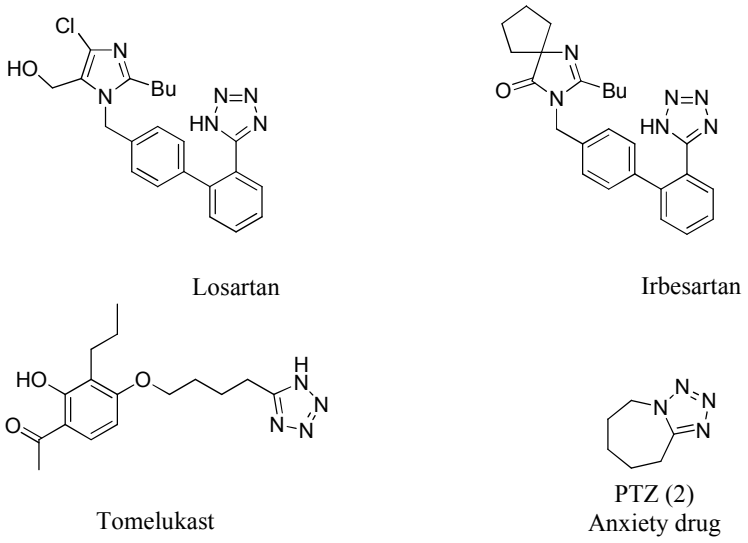


Figure 1: Representative drugs based on tetrazoles.

Experimental

General

Melting points of all the synthesized compounds were taken in a Riechert Thermover instrument and are uncorrected. The IR spectra were recorded on Perkin Elmer RXI spectrometer using KBr pellets. WD-XRF data was obtained from Bruker, S8-Tiger spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO-*d6*/$CDCl_3$ as solvent. Mass spectra were recorded on Micromass Quattro II (ESI) spectrometer. Elemental analyses (C, H and N) were conducted using the Elemental vario EL III elemental analyser and their results were found to be in agreement with the calculated values. TGA data was obtained with DSC-60 Shimadzu instrument and the analysis was performed in the temperature range of 0 – 800 °C at a constant heating rate of 20 °C /min in the nitrogen atmosphere. X-ray diffractograms (XRD) of the catalyst were recorded in the 2θ range of 5-80° with scan rate of 4°/ min on a Rigaku Minifax X-ray diffractometer with Ni-filtered Cu Kα radiation at a wavelength of 1.54060 A°. The SEM-EDX characterization of the catalyst

was performed on a JEOL JSM-6510 scanning electron microscope equipped with energy dispersive X-ray spectrometer operating at 20 kV. The microwave synthesis was performed in Anton Paar, Monowave 300 microwave synthesiser. All reagents were purchased from Merck and Sigma-Aldrich and were used without further purification. Silica gel (for column chromatography) used for the synthesis of catalyst was purchased from Merck. The purity of compounds was checked by thin layer chromatography (TLC) on glass plates coated with silica gel G254 (E. Merck) using chloroform-methanol (3:1) mixture as mobile phase and visualised by iodine vapours and alcoholic ferric chloride.

Synthesis of silica chloride [28]

A mixture of silica–gel (10 g) and thionyl chloride (40 mL) was refluxed for 48 h in a round bottomed flask (250 mL) equipped with a condenser and a drying tube ($CaCl_2$ as a drying agent). The resulting white-greyish powder was filtered and stored in a tightly capped bottle.

Synthesis of silica molybdic acid (SMA)

A mixture of silica chloride and sodium molybdate in n-hexane (10 mL) was stirred under refluxing conditions for 3.5 h. The reaction mixture was then filtered, washed with distilled water and dried at 120 °C in an oven for 6h. The resulting mixture was then further stirred in 0.1N HCl solution (40 mL) for 1 h, filtered, washed with distilled water and dried in an oven at 120 °C for 6h to finally obtain the catalyst.

General procedure for the synthesis of tetrazoles under thermal condition:

A mixture of aldehyde (2 mmol), malononitrile (2 mmol), sodium azide (3 mmol) and catalyst (200 mg) in 10 mL water was stirred at 50 °C for appropriate period of time. After completion of reaction (monitored by TLC), the reaction mixture was allowed to cool and added 10 mL of 2N HCl solution with vigorous stirring. The precipitate obtained was extracted by ethyl acetate, washed with water (3 × 10 mL), dried over anhydrous Na_2SO_4 and

evaporated under reduced pressure to obtain the product. The remaining solid catalyst was separated by filtration, washed with ethyl acetate (3 x 10 mL) and reused for further catalytic cycles. The crude product was recrystallized to afford the pure product.

General procedure for the synthesis of tetrazoles under microwave irradiation:

A mixture of aldehyde (2 mmol), malononitrile (2 mmol), sodium azide (2 mmol) and catalyst (200 mg) in 10 mL water was taken in a G30 vial and irradiated using microwaves with continuous stirring at 50 °C for 15 min. After completion of reaction (monitored by TLC), the reaction mixture was allowed to cool and added 10 mL of 2N HCl solution with vigorous stirring. The precipitate obtained was extracted by ethyl acetate, washed with water (3 × 10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to obtain the product. The remaining insoluble solid catalyst in aqueous phase was separated by filtration, washed with ethyl acetate (3 x 10 mL) and reused for further catalytic cycles. The crude product was recrystallized to afford the pure product.

Spectral data of synthesised compounds

3a *3-(5-chloro-3-methyl-1-phenylpyrazol-4-yl)-2-(1H-tetrazol-5-yl) acrylonitrile*

M.p. 125-130° C. IR (KBr, cm^{-1}): 3435 (NH), 2227 (CN), 1676 (C=C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.51-7.59 (m, Ar-region, 5H), 3.34 (s, 1H, NH), 2.52 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$):159.71, 155.48, 149.29, 137.53, 134.32, 129.17, 127.62, 123.98, 118.13, 116.49, 114.21, 15.14. Anal. Calcd. ($C_{14}H_{10}ClN_7$) C, 53.94; H, 3.23; N, 31.45. Anal. Found ($C_{14}H_{10}ClN_7$) C, 53.88; H, 3.28; N, 31.51. ESI-MS m/z 312.1 (M^++1).

3b *3-(4-oxo-4H-[1]benzopyran-3-yl)-2-(1H-tetrazol-5-yl) acrylonitrile*

M.p. 255-260° C. IR (KBr, cm^{-1}): 3462 (NH), 2228 (CN), 1653 (C=O), 1605 (C=C). ^1H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.18-8.11 (m, Ar-region, 4H), 6.79 (s,1H, Chromone),

4.08 (s, NH, overlap with solvent). ^{13}C NMR (100 MHz, DMSO-d_6): 185.64, 164.39, 150.38, 147.12, 146.49, 135.77, 129.52, 128.51, 127.28, 119.02, 117.13, 114.57, 112.28. Anal. Calcd. ($C_{13}H_7N_5O_2$) C, 58.87; H, 2.66; N, 26.41. Anal. Found. ($C_{13}H_7N_5O_2$) C, 58.81; H, 2.70; N, 26.45. ESI-MS m/z 266.2 (M^++1).

3c *3-(6-Methyl-4-oxo-4H-[1]benzopyran-3-yl)-2-(1H-tetrazol-5-yl) acrylonitrile*

M.p. 260-265° C. IR (KBr, cm^{-1}): 3414 (NH), 2229 (CN), 1659 (C=O), 1598 (C=C).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (s, 1H), 7.26-8.15 (m, Ar-region, 3H), 6.88 (s,1H, Chromone), 4.10 (s, NH, overlap with solvent), 2.27 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): 188.21, 162.54, 151.22, 147.36, 145.91, 137.44, 135.18, 129.11, 128.34, 121.09, 118.22, 113.63, 111.79, 25.38. Anal. Calcd. ($C_{14}H_9N_5O_2$) C, 60.21; H, 3.25; N, 25.08. Anal. Found ($C_{14}H_9N_5O_2$) C, 60.25; H, 3.31; N, 25.03. ESI-MS m/z 280.1 (M^++1).

3d *3-(6-chloro-4-oxo-4H-[1]benzopyran-3-yl)-2-(1H-tetrazol-5-yl) acrylonitrile*

M.p. 263-268° C. IR (KBr, cm^{-1}): 3423 (NH), 2225 (CN), 1665 (C=O), 1585 (C=C).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1H), 7.25-8.23 (m, Ar-region, 3H), 6.73 (s, 1H, Chromone), 3.90 (s, NH, overlap with solvent). ^{13}C NMR (100 MHz, DMSO-d_6): 183.51, 163.22, 150.57, 146.88, 144.91, 136.22, 131.27, 130.17, 126.22, 120.55, 119.86, 114.18, 112.54. Anal. Calcd. ($C_{13}H_6ClN_5O_2$) C, 52.10; H, 2.02; N, 23.37. Anal. Found ($C_{13}H_6ClN_5O_2$) C, 52.16; H, 1.95; N, 23.42. ESI-MS m/z 300.1 (M^++1).

3e *3-(4-chloro-2-oxo-2H-[1]benzopyran-3-yl)-2-(1H-tetrazol-5-yl) acrylonitrile*

M.p. 230-235° C. IR (KBr, cm^{-1}): 3441 (NH), 2219 (CN), 1642 (C=O), 1591 (C=C).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 7.38-7.77 (m, Ar-region, 4H), 3.28 (s, NH, overlap with solvent). ^{13}C NMR (100 MHz, DMSO-d_6): 167.23, 158.56, 151.18, 148.54, 142.71, 138.44, 131.52, 129.76, 127.94, 126.33, 121.41, 119.92, 110.55. Anal. Calcd. ($C_{13}H_6ClN_5O_2$)

C, 52.10; H, 2.02; N, 23.37. Anal. Found ($C_{13}H_6ClN_5O_2$) C, 52.07; H, 2.07; N, 23.41. ESI-MS m/z 300.1 (M^++1).

3f *3-(2-chloro-4quinolinyl)-2-(1H-tetrazol-5-yl) acrylonitrile*

M.p. 240-245° C. IR (KBr, cm^{-1}): 3432 (NH), 2220(CN), 1588(C=C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (s, 1H), 7.24-7.80 (m, Ar-region, 5H), 3.30 (s, NH, overlap with solvent). ^{13}C NMR (100 MHz, DMSO-d_6): 157.56, 154.05, 149.33, 146.68, 136.88, 130.07, 129.17, 128.62, 127.58, 126.96, 117.49, 115.29. Anal. Calcd. ($C_{13}H_7ClN_6$) C, 55.23; H, 2.50; N, 29.73. Anal. Found ($C_{13}H_7ClN_6$) C, 55.19; H, 2.55; N, 29.77. ESI-MS m/z 283.1 (M^++1).

3g *3-(thiophen-2-yl)-2-(1H-tetrazol-5-yl) acrylonitrile*

M.p. 132-137° C. IR (KBr, cm^{-1}): 3456 (NH), 2223(CN), 1571(C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.72 (d, 1H, CH), 6.97 (d, 1H, CH), 3.34 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 151.22, 145.67, 142.51, 133.76, 132.41, 127.87, 118.58, 112.09. Anal. Calcd. ($C_8H_5N_5S$) C, 47.28; H, 2.48; N, 34.46. Anal. Found ($C_8H_5N_5S$) C, 47.33; H, 2.43; N, 34.50. ESI-MS m/z 204.1 (M^++1).

3h *3-(5-methyl-thiophen-2-yl)-2-(1H-tetrazol-5-yl) acrylonitrile*

M.p. 135-140° C. IR (KBr, cm^{-1}): 3439 (NH), 2220 (CN), 1575 (C=O). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.75 (d, 1H, CH), 7.04 (d, 1H, CH), 3.33 (s, 1H, NH), 2.63 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 151.72, 146.45, 142.12, 134.71, 132.13, 125.53, 119.18, 114.23, 15.27. Anal. Calcd. ($C_9H_7N_5S$) C, 49.76; H, 3.25; N, 32.24. Anal. Found ($C_9H_7N_5S$) C, 49.82; H, 3.21; N, 32.27. ESI-MS m/z 218.1 (M^++1).

3i *3-(4-methoxyphenyl)-2-(1H-tetrazol-5-yl) acrylonitrile*

M.p. 156-160° C. IR (KBr, cm^{-1}): 3433 (NH), 2219 (CN), 1566 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.10-8.00 (m, Ar-region, 4H), 3.90 (s, 3H, OCH_3), 3.33 (s, 1H, NH).

^{13}C NMR (100 MHz, $CDCl_3$): 163.04, 151.52, 141.97, 132.25, 126.18, 120.11, 119.44, 100.37. 59.88. Anal. Calcd. ($C_{11}H_9N_5O$) C, 58.14; H, 3.99; N, 30.82. Anal. Found ($C_{11}H_9N_5O$) C, 58.19; H, 3.94; N, 30.87. ESI-MS m/z 228.1 (M^++1).

3j 3-*(4-chlorophenyl)-2-(1H-tetrazol-5-yl) acrylonitrile*

M.p. 165-168° C. IR (KBr, cm^{-1}): 3434 (NH), 2224 (CN), 1580 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ8.32(s, 1H), 7.15-8.21 (m, Ar-region, 4H), 3.35 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 165.18, 152.26, 143.71, 134.21, 125.07, 121.81, 119.13, 101.56. Anal. Calcd. ($C_{10}H_6ClN_5$) C, 51.85; H, 2.61; N, 30.23. Anal. Found ($C_{10}H_6ClN_5$) C, 51.79; H, 2.66; N, 30.27. ESI-MS m/z 232.1 (M^++1).

3k *3-(4-hydroxy-3-methoxyphenyl)-2-(1H-tetrazol-5-yl) acrylonitrile*

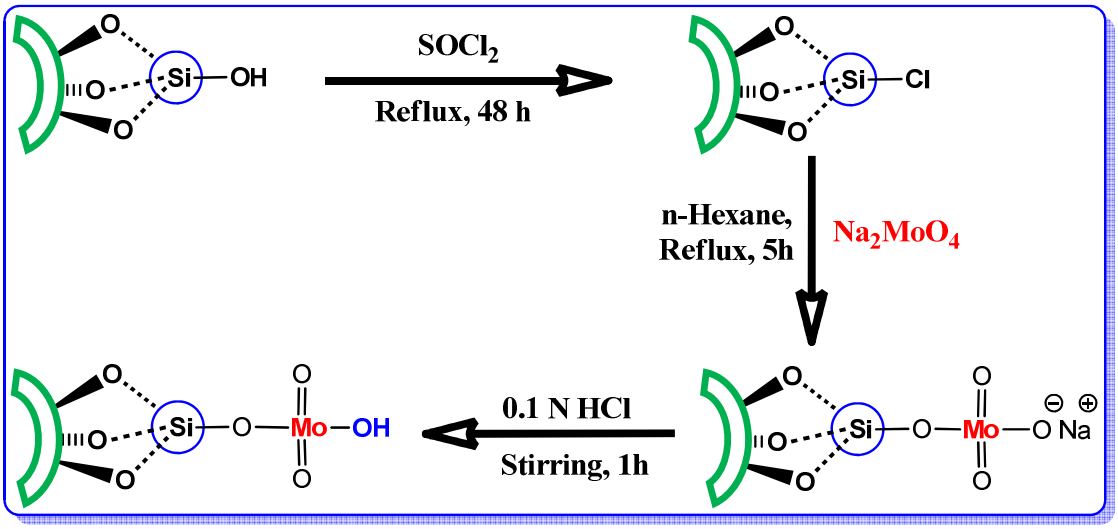
M.p. 164-169° C. IR (KBr, cm^{-1}): 3441 (NH), 3122(OH), 2220 (CN), 1588 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 6.79-7.52 (m, Ar-region, 3H), 10.21 (s, 1H, OH), 3.98 (s, 3H, OCH_3), 3.31 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 168.05, 154.22, 140.54, 131.31, 130.89, 130.17, 129.58, 127.19, 119.55, 102.28, 54.25. Anal. Calcd. ($C_{11}H_9N_5O_2$) C, 54.32; H, 3.73; N, 28.79. Anal. Found ($C_{11}H_9N_5O_2$) C, 54.36; H, 3.68; N, 28.81. ESI-MS m/z 244.1 (M^++1).

3l *3-(3-nitrophenyl)-2-(1H-tetrazol-5-yl) acrylonitrile*

M.p. 159-163° C. IR (KBr, cm^{-1}): 3430 (NH), 2219 (CN), 1575 (C=C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.86-8.18 (m, Ar-region, 4H), 3.34 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 157.23, 149.17, 146.38, 140.27, 136.71, 130.88, 127.27, 125.35, 119.88, 102.72. Anal. Calcd. ($C_{10}H_6N_6O_2$) C, 49.59; H, 2.50; N, 34.70. Anal. Found. ($C_{10}H_6N_6O_2$) C, 49.63; H, 2.56; N, 34.67. ESI-MS m/z 243.1 (M^++1).

Results and discussion

The route for the preparation of the catalyst is schematically illustrated in Scheme 1. The silica molybdic acid (SMA) was initially prepared by the reaction of silica with $SOCl_2$ to produce silica chloride which was then successively functionalised by molybdate groups via nucleophilic substitution at silicon by sodium molybdate followed by stirring in 0.1N HCl solution. The amount of H^+ was determined by back titration of weighed amount of catalyst with standard 0.01N NaOH solution and was found to be equal to 0.23 meq/gm of the catalyst.



Scheme 1: Schematic representation of the synthesis of silica molybdic acid (SMA)

The successful incorporation of molybdate moieties on silica surface was evaluated by analysing the respective spectra of sodium molybdate and SMA. FT-IR spectra of sodium molybdate (Fig. 2a) shows characteristic Mo−O stretching frequencies at 865 and 912 cm^{-1}. [29] The FT-IR spectra of SMA (Fig. 2b) showed characteristic frequencies of both silica and molybdate groups. The absorption peaks at 873 and 975 cm^{-1} were attributed to the Mo−O stretching frequency in $[MoO4]^{2-}$ species and the broad peak from 1000-1200 cm^{-1} was attributed to antisymmetric Si-O−Si stretching. The symmetric Si−O−Si stretching vibration

was obtained at 803 cm^{-1}. The IR spectra, thus, shows successful functionalization of molybdate groups on silica surface.

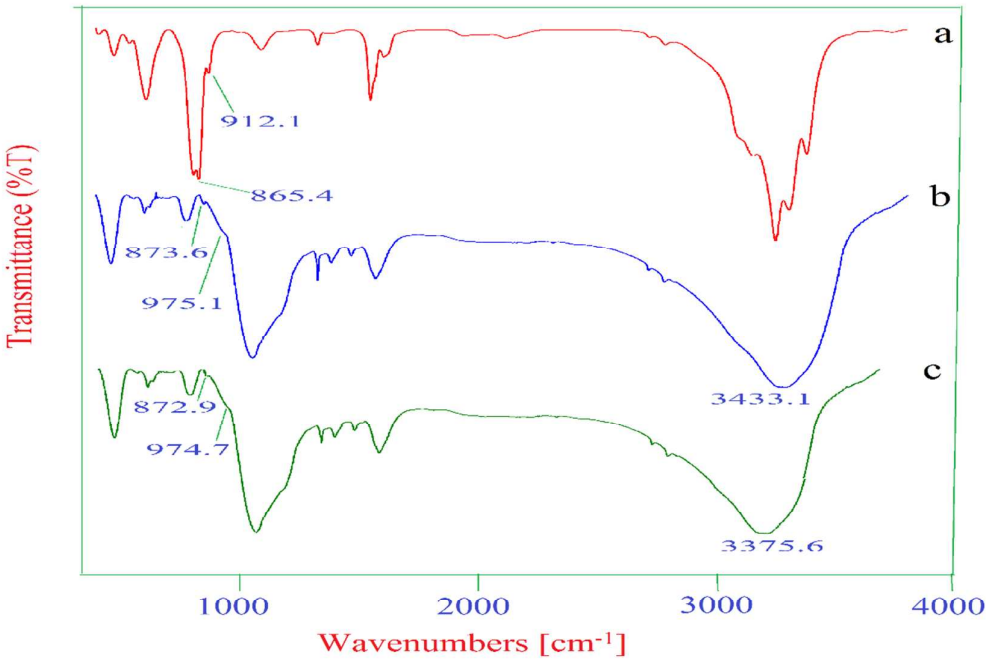


Figure 2: FT-IR spectral analysis (a) of sodium molybdate, (b) of silica molybdic acid and (c) of recycled silica molybdic acid.

The actual composition of the catalyst was determined by XRF analysis (Table 1). The analysis confirmed the presence of molybdate groups on the surface of silica. The actual composition of the catalyst was found as 84.60 (%W/W) SiO_2 (Entry 1) and 1.58 (%W/W) MoO_4 (Entry 2).

Table 1: XRF data of Silica Molybdic acid

Entry	Compound	Concentration
1	SiO_2	84.60%
2	MoO_4	1.58%
3	V_2O_5	0.34%

4	Cl	0.04%
5	SO_3	0.04%
6	CaO	0.03%
7	Al_2O_3	0.02%
8	Fe_2O_3	0.02%
9	TiO_2	0.02%
10	Others + LOI*	13.25%
*LOI= Loss on ignition		

The XRD analysis (Fig. 3a) exhibited similar XRD pattern of the catalyst to that of support (Fig. 3b). The MoO_4 group exhibits peaks in the range of 2θ 20-35° which merge with the broad peak shown by SiO_2 in the range of 2θ 20-30°. [30] The presence of MoO_4 groups was further confirmed by comparing the data with PDF#852405. The peaks obtained at 24.086, 25.921, 27.672 and 29.558 denoted the presence of molybdate groups on the silica surface.

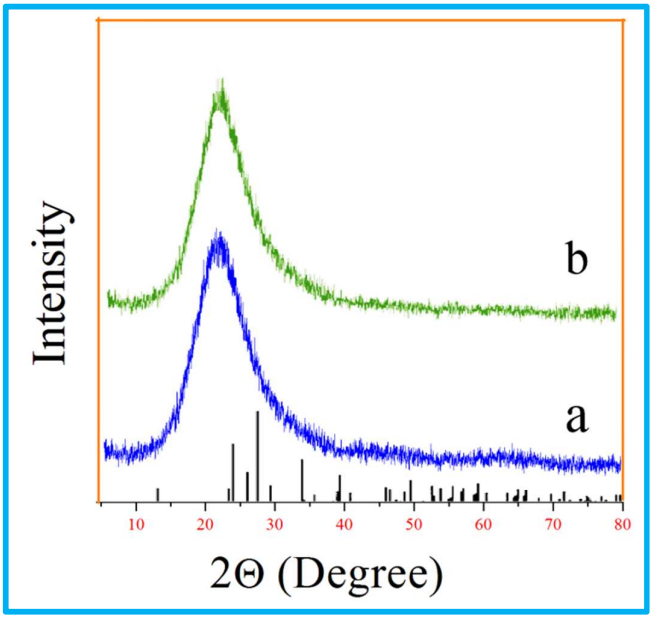


Figure 3: XRD analysis (a) of fresh SMA and (b) of silica.

The stability of the catalyst and the amount of molybdate groups functionalised on silica surface was determined by TG analysis (Fig. 4). The first weight loss of 15.09% shown by TG curve up to 200 °C can be attributed to loss of physically adsorbed water molecules. The TG curve then shows another weight loss of 5.12% in the range 301 °C - 579 °C which can be attributed to the loss of molybdate groups covalently bound to silica surface. Thus, it can be concluded that the catalyst is stable up to 300 °C.

The amount of molybdate groups bound to silica surface was also calculated by TG analysis. The weight loss of 5.12 % corresponded to 0.051gm of molybdate in 1 gm of catalyst, which, therefore, amounted to loading of 0.21mmol/gm of the catalyst, as also confirmed by back titration analysis.

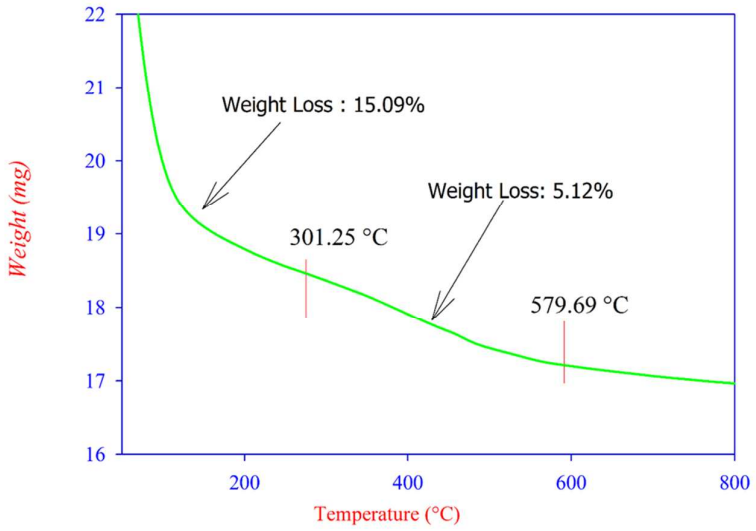


Figure 4: TG analysis of SMA.

The SEM image (Fig. 5b) shows the surface morphology of the catalyst. The image shows the change in surface morphology of the silica (Fig. 5a) after functionalization with molybdate groups. The successful incorporation of molybdate groups was also confirmed by EDX analysis (fig. 6), which showed the presence of Mo in addition to O and Si elements.

The elemental mapping analysis (Fig 7) showed the uniform distribution of molybate groups on the surface of the silica.

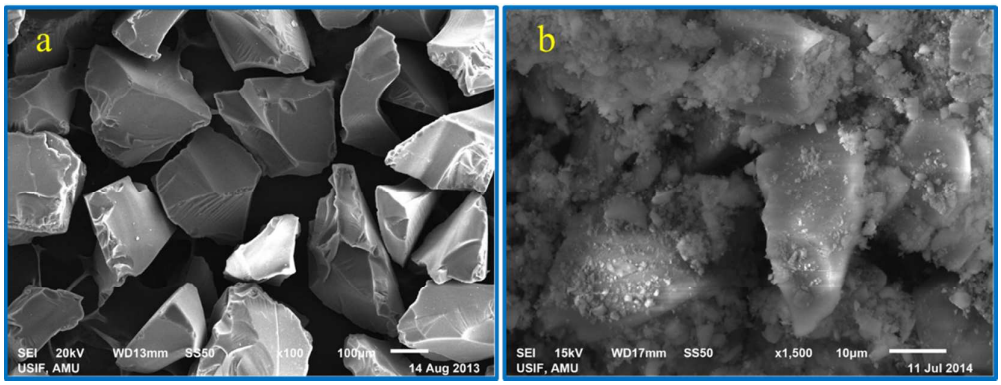


Figure 5: SEM images (a) of silica and (b) of silica molybdic acid (SMA).

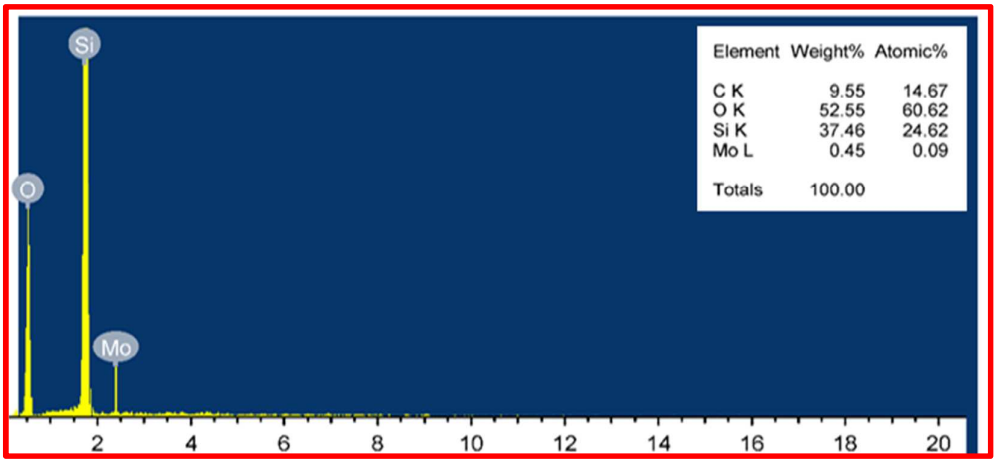


Figure 6: EDX analysis of SMA showing presence of Mo in addition to Si and O.

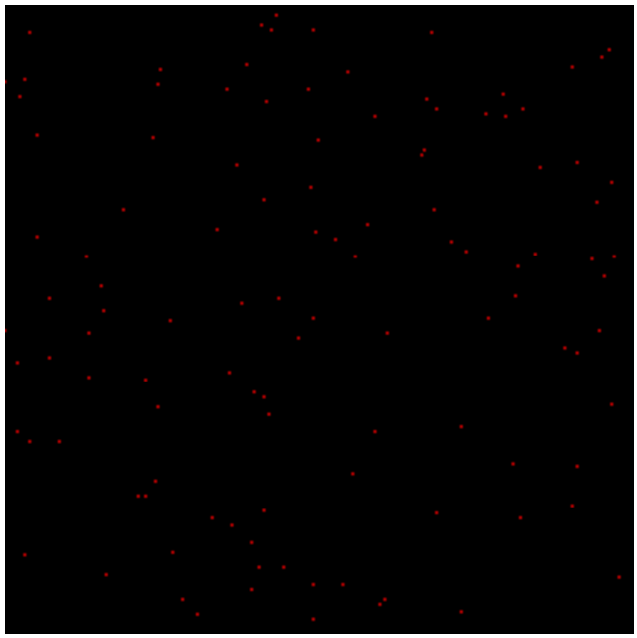


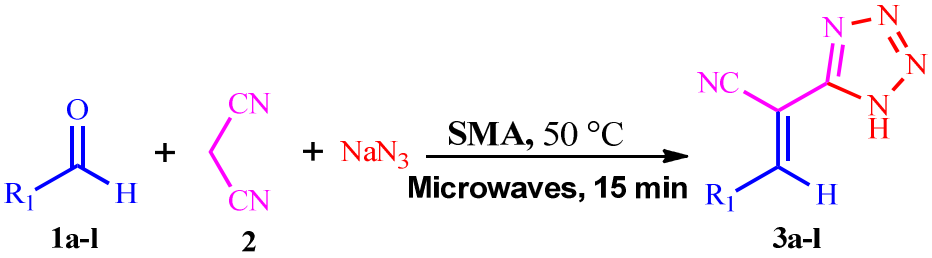
Figure 7: Elemental mapping showing distribution of Mo on the surface of silica.

Optimization of reaction conditions

Our initial study was focused on the development of the optimal reaction conditions for this transformation and included screening of catalysts, solvents and the influence of the catalyst amount. Initially, the reaction between thiophene-2-carboxaldehyde, malononitrile and sodium azide (Scheme 2) was investigated using different catalysts in water at 50 °C. The reaction without any catalyst afforded the product with moderate yield in 24h. Silica gel and silica chloride as catalysts could not show promising catalytic effects (Table 2, entries 2&3). When the reaction was tried with $FeCl_3$ and $AlCl_3$ as catalysts, the product was obtained in moderate yield in longer time period (entries 4&5). With protic acid such as AcOH as catalyst, again the product was obtained in low yield (entry 6). H_2MoO_4 catalysed reaction gave good yield of the product in 6.1h (entry 7). However, when the reaction was tried using SMA as a catalyst, the results obtained were very satisfactory as good yield of the product (85%) was obtained in 3.5h only (entry 8). Taking SMA as a catalyst for this reaction the reaction conditions were further optimized by the screening of different solvents at 50 °C.

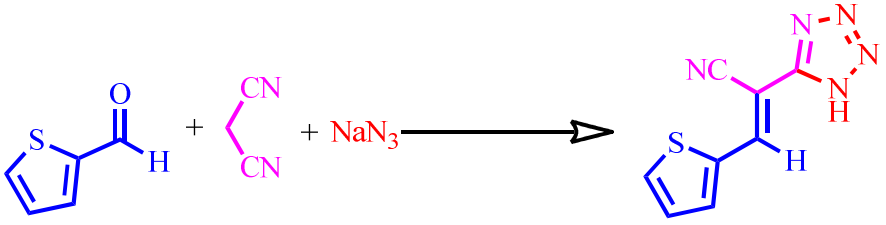
Various solvents like ethanol, methanol, toluene, benzene, Ethylene glycol, PEG-200 and water were screened to test the efficiency of the catalyst and the results are summarized in Table 2 (entries 9-14). The results clearly indicated the superiority of water over the other solvents. The increased reactivity in water can be attributed to the development of hydrogen bonding between the water and the azide ion, which stabilizes the intermediate structures during the formation of products. The hydrophobic effects generated by water also help in increasing the rate of reaction by decreasing the hydrocarbon–water interfacial area.

In order to further improve the protocol to make it more energy efficient we introduced microwaves. The use of microwaves improved the protocol remarkably as visualised and very high yield of the product was obtained in very short time period (Table 2, entry 15). The enhancement can be due to the combined effect of the efficient interaction of molecules in reaction mixture with generated electromagnetic waves and good potential of water (polar nature) to absorb microwaves and convert them into heat energy.



Scheme 2: General scheme for the synthesis of tetrazole deriatives.

Table 2: Effect of different reaction media on model reaction



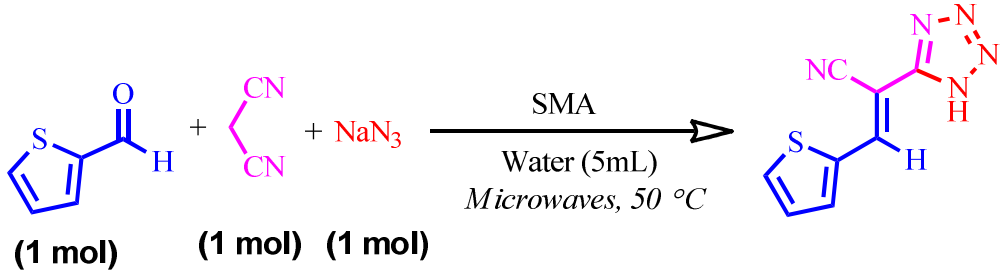
Entry	Solvent	Condition	Time [a]	Yield% [b]
1	Water (5ml)	50 °C, Heat, without catalyst	24 h	76
2	Water (5mL)	50 °C, Heat, Silica gel (100 mg)	19h	72
3	Water (5mL)	50 °C, Heat, Silica Chloride(100 mg)	22h	69
4	Water (5mL)	50 °C, Heat, $FeCl_3$ (10 mol%)	6.4h	77
5	Water (5mL)	50 °C, Heat, $AlCl_3$ (10 mol%)	6.2h	73
6	Water (5mL)	50 °C, Heat, AcOH (10 mol%)	7.6h	69
7	Water (5mL)	50 °C, Heat, H_2MoO_4 (100 mg)	6.1h	77
8	Water (5mL)	50 °C, Heat, SMA (100 mg)	4.5 h	85
9	Ethanol (5mL)	50 °C, Heat , SMA (100 mg)	6 h	65
10	Methanol (5mL)	50 °C, Heat, SMA (100 mg)	6.5 h	61
11	Toluene (5mL)	50 °C, Heat, SMA (100 mg)	9 h	25
12	Benzene (5mL)	50 °C, Heat, SMA (100 mg)	9 h	23
13	Ethylene glycol (5mL)	50 °C, Heat, SMA (100 mg)	10 h	33
14	PEG-200 (5mL)	50 °C, Heat, SMA (100 mg)	8.5 h	35
15	Water (5ml)	50 °C, Microwaves, SMA (100 mg)	15 min	93

[a] Reaction progress monitored by TLC.

[b] Isolated yield.

In order to further optimize the reaction conditions we investigated the effect of the catalyst loading on the model reaction (Table 3). It was found that 0.1 g of the catalyst was sufficient to get the optimum yield. Decreasing the amount of catalyst to 0.05 g and 0.03 g decreased the yields with increase in time period for completion of the reaction. Increasing the catalyst amount to 0.15 g and 0.20 g did not have any effect on the reaction. Therefore, 0.1 g of the catalyst was used for further studies.

Table 3: Effect of catalyst loading



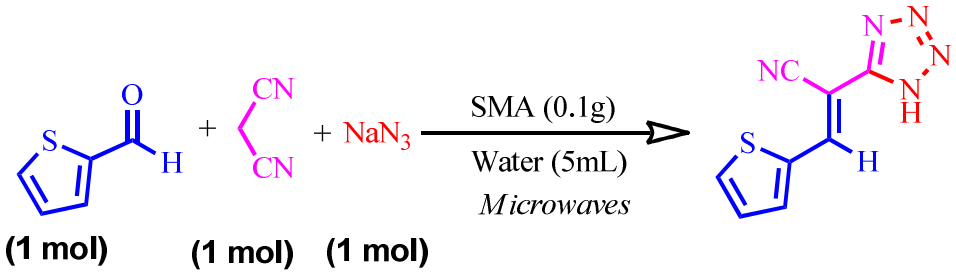
Entry	Catalyst loading (g)	Time(min) [a]	Yield (%) [b]
1	0.03	35	71
2	0.05	20	87
3	0.10	15	93
4	0.15	15	93
5	0.20	15	91

[a] Reaction progress monitored by TLC.

[b] Isolated yield.

The study of the effect of temperature revealed that the reaction was strongly influenced by the temperature (Table 4). At room temperature the reaction completed in 75 min with poor yield of the product. With the increase in temperature to 40 °C the reaction completed in 35 min with improved product yield. At 50 °C the reaction produced best results of 93 % product yield in 15 min. Further increase in temperature did not have any effect on the reaction. Therefore, 50 °C was chosen as the optimum temperature for the reaction.

Table 4: Effect of reaction temperature



(1 mol) (1 mol) (1 mol)

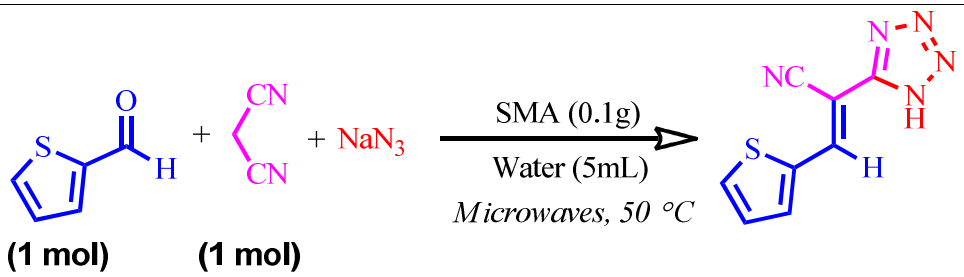
Entry	Temperature (°C)	Time(min) [a]	Yield (%) [b]
1	Room Temp.	75	25
2	40	35	66
3	50	15	93
4	70	15	90

[a] Reaction progress monitored by TLC.

[b] Isolated yield.

The effect of the amount of the NaN_3 on the product formation (Table 5) was also evaluated and it was observed that under the optimium thermal reaction conditions, without any catalyst, 2 mmols of NaN_3 were required for the satisfactory product formation. With the use of 0.1g of SMA as a catalyst, 1.5 mmol NaN_3 was needed to obtain good yield of the product. With the introduction of microwaves, under the optimum conditions, it was observed that 1 mmol of NaN_3 was enough to give excellent product yield. More than 1 mmol of the NaN_3 does not have any effect on the product formation. Thus, the use of microwaves further added to greenness of the procedure by making the reaction more economical.

Table 5: Effect of the amount of NaN_3



(1 mol) (1 mol)

Entry	Condition	NaN_3 (mmol)	Yield (%) [a,b]
1	50 °C, Stirring	1	57
2	50 °C, Stirring	2	79
3	50 °C, Stirring, SMA (0.1g)	1	73
4	50 °C, Stirring, SMA (0.1g)	1.5	85
5	50 °C, Microwaves, SMA (0.1g)	1	93
6	50 °C, Microwaves, SMA(0.1g)	1.25	93

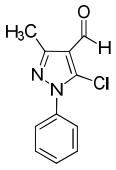
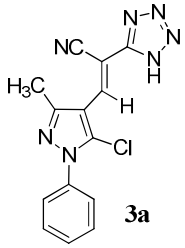
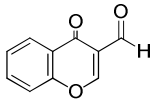
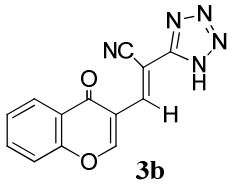
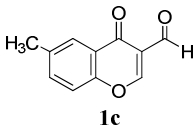
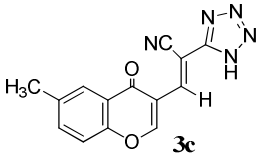
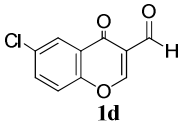
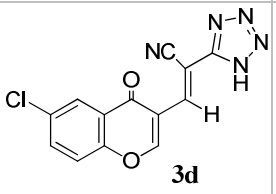
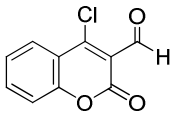
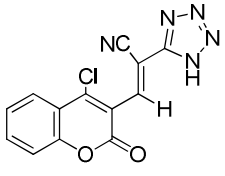
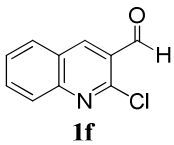
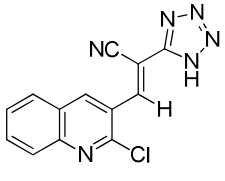
[a] Reaction progress monitored by TLC, [b] Isolated yield.

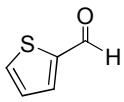
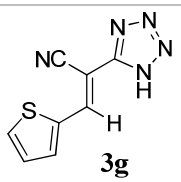
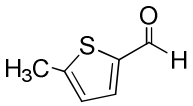
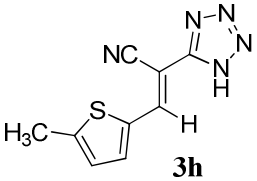
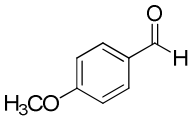
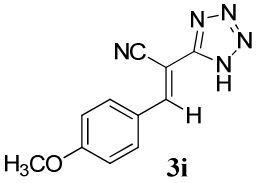
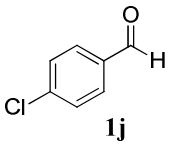
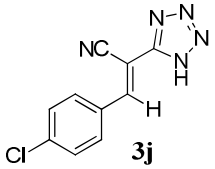
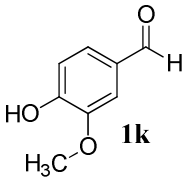
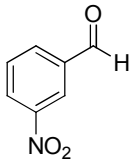
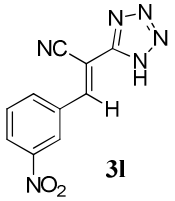
Catalytic reaction

After optimization of the reaction conditions, the substrate scope of SMA catalyzed system was examined under the optimized reaction conditions using both conventional and microwave heating. As shown in Table 6, a wide variety of aldehydes containing electron-withdrawing and electron-donating groups reacted with malononitrile and sodium azide to afford the corresponding tetrazoles in excellent yields. The aldehydes containing heterocyclic substituents like chromones, quinolines and thiophene took part in the reaction smoothly affording the expected products in good to excellent yields. Though, the catalyst showed good efficiency under conventional heating giving the products in 5-6 h, however, excellent product yield in 15 min was obtained under microwave irradiation. Moreover, the high turnover frequency (TOF) of the catalyst (154-165) under microwave irradiation denoted the high efficiency of our catalytic system. From the above results, it is obvious that SMA is an

efficient catalyst for the preparation of large spectrum of substituted tetrazoles in very high yields under aqueous conditions.

Table 6: Synthesis of tetrazole derivatives

Entry	Aldehyde	Product	Conventional method		Microwave Irradiation		
			Time (h) [a]	Yield % [b]	Time (min) [a]	Yield % [b]	TOF [c]
1	 1a	 3a	4.5	81	15	92	160
2	 1b	 3b	4	78	15	89	154.78
3	 1c	 3c	4	80	15	91	158.26
4	 1d	 3d	4	81	15	90	156.52
5	 1e	 3e	3.5	77	15	91	158.26
6	 1f	 3f	3.5	79	15	90	156.52

7	 **1g**	 **3g**	4.5	85	15	93	161.73
8	 **1h**	 **3h**	4.5	85	15	94	163.47
9	 **1i**	 **3i**	5	88	15	95	165.21
10	 **1j**	 **3j**	5	87	15	93	161.73
11	 **1k**	 **3k**	5.5	83	15	91	158.26
12	 **1l**	 **3l**	5.5	86	15	92	160

[a] Reaction progress monitored by TLC.

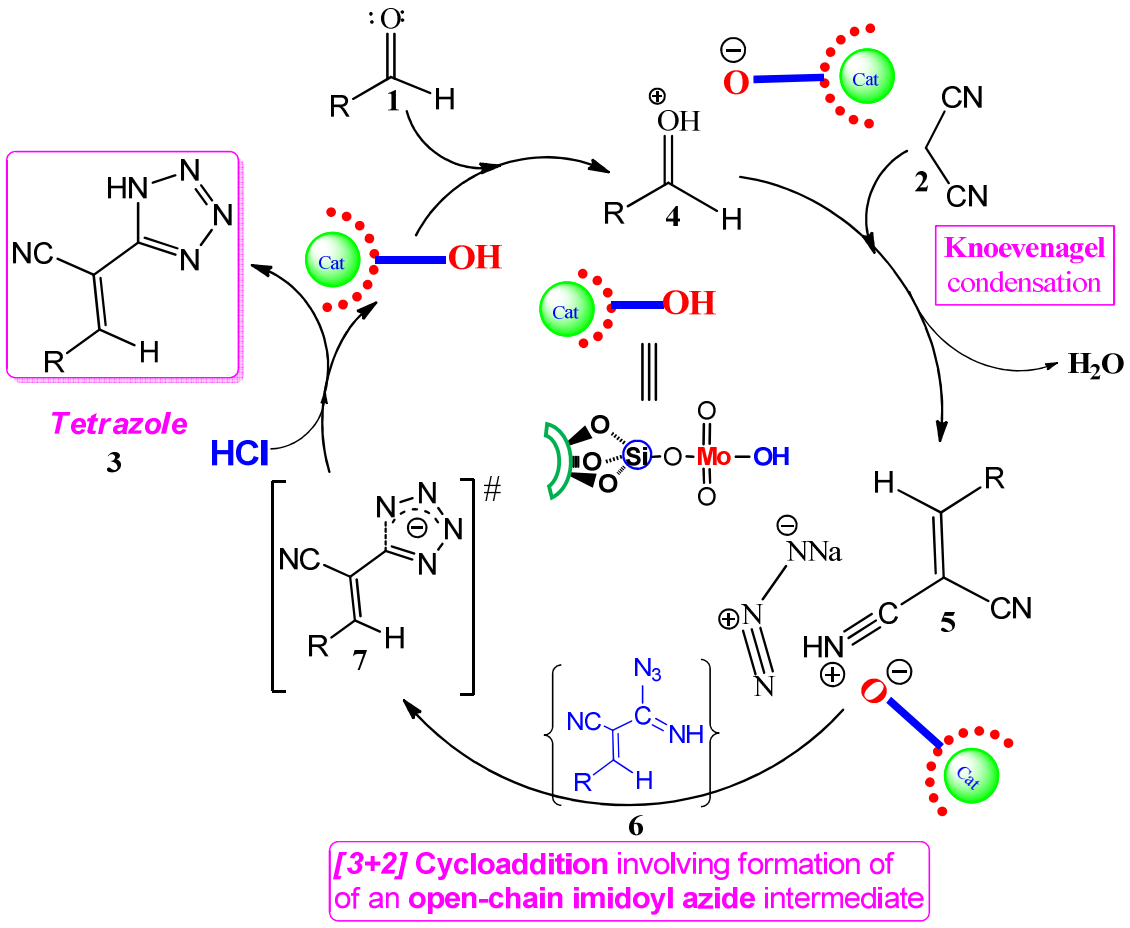
[b] Isolated yield.

[c]TOF= TON/reaction time (h); TON= No. of moles of the starting materials being converted per mole of active site of the catalyst.

Reaction mechanism

Experimentally it was found that the reaction is strongly accelerated by the catalyst. Initially the reaction is initiated by protonation of aldehyde **1** by the catalyst to generate the active

species **4** which then undergoes knoevenagel condensation reaction to form aryl/heteroarylidenemalononitrile **5**. The further protonation of the nitrile group of this intermediate activates it towards the attack of the azide ion. The attack of the azide ion then leads to the formation of an open imidoyl azide intermediate **6** which subsequently cyclises to intermediate **7** via [3+2] cycloaddition reaction. Addition of HCl finally, generates the tetrazole derivative **3**. [31]



Scheme 3: Plausible reaction mechanism for the formation of tetrazoles.

Recyclability:

In order to explore the extent of recyclability of our catalyst system, the catalyst was recovered by extracting the mixture with ethyl acetate followed by filtration. The catalyst was

then reused for subsequent cycles and was found to retain its activity for a minimum of seven reaction cycles in water. The catalyst displayed almost high catalytic performance with over 85 % conversion of the substrate. The FT-IR spectra of the catalyst after seven runs (Figure 2c) showed the same spectral fingerprint of the freshly prepared catalyst indicating the stability of the catalyst throughout the recycling experiment.

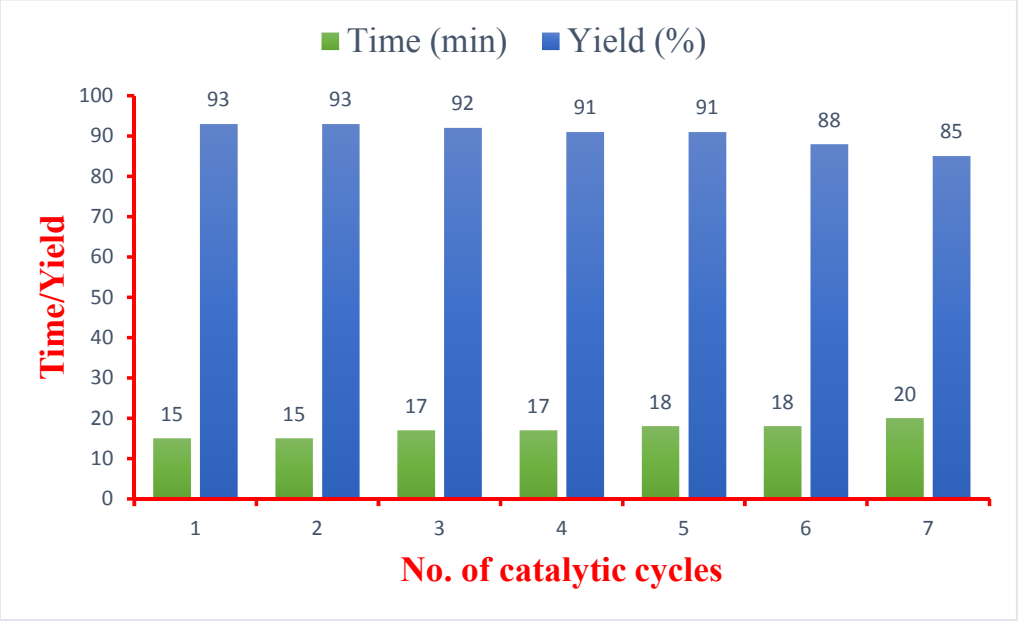


Figure 8: Recycling data of SMA

Conclusion

In conclusion, we have developed a novel SMA catalysed, water compatible, green protocol for the multicomponent synthesis of tetrazole derivatives using microwave irradiation. The catalyst is easily preparable and can be recycled up to seven cycles without any significant loss in catalytic activity. The presented protocol tolerates a wide range of aromatic and heterocyclic aldehydes giving the corresponding tetrazoles in good to excellent yields. Salient features of the presented protocol are the use of microwaves at low temperature, water as a green solvent, low reaction times, recyclable catalyst and excellent yields of the products.

Acknowledgments

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