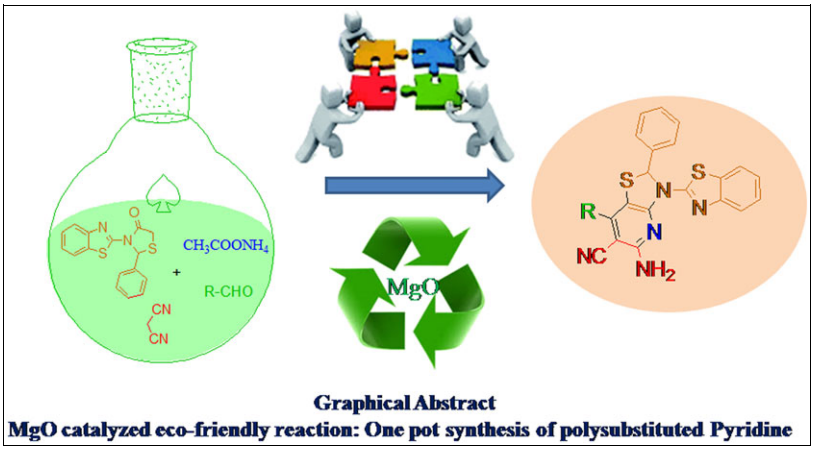
MgO NPs Catalyzed Eco-friendly Reaction: A Highly Effective and Green Approach for the Multicomponent One-pot Synthesis of Polysubstituted Pyridines using 2-Aminobenzothiazole

Divyani Gandhi and Shikha Agarwal*

Synthetic Organic Chemistry Laboratory, Department of Chemistry, Mohanlal Sukhadia University, Udaipur 313001, Rajasthan, India
*E-mail: shikha_urj@yahoo.com
Received July 2, 2018
DOI 10.1002/jhet.3384
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).



A one-pot multicomponent green and environmentally friendly synthesis of 5-amino-3-benzothiazol-2-yl-7-(phenyl)-2-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridine-6-carbonitrile via Knoevenagel condensation followed by Michael addition has been described in the presence of a green, low-cost, mild, and efficient magnesium oxide as the heterogeneous base catalyst. The present methodology has attractive features such as excellent product yields, environmentally benign milder reaction conditions, use of nontoxic organic solvents, and easily recoverable and reusable nanocatalyst. The synthesized compounds have been confirmed by spectral analysis (Fourier transform infrared, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry).

INTRODUCTION

Multicomponent reactions (MCR) have gained tremendous importance in the synthetic organic chemistry. MCR are fruitful to diversity based on combinatorial library of molecules, legible for discovery of new drugs [1]. They offer several features to synthetic organic reactions, namely, simple and fast implementation, energy and time saving, eco-friendly, high atom economy, building blocks with diverse range of complexity, and very few by-products, that is, less waste production [2]. In today's chemistry, design of highly efficient reactions with structural complexity along with few synthetic steps is the alarming need, and for the purpose, environmental benign reactions using nanoparticles seemed to be highly efficient for a number of organic transformations.

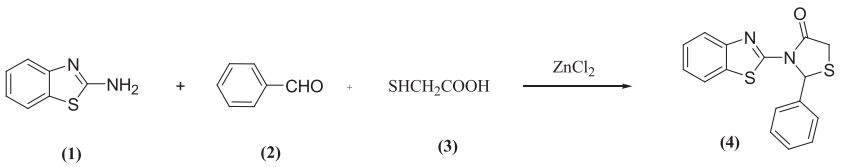
Nowadays, researchers have developed nano sized catalyst to progress the unique and tunable properties in synthetic organic chemistry. Magnesium oxide (MgO) NPs have been recently known as highly effective heterogeneous base catalyst for Michael addition and Knoevenagel condensation [3,4]. The acidic Mg^{2+} site and aldehyde complexes with an activated methylene compound on a nearby Lewis basic site O^{2-} in the field of catalysis have a large number of promising applications in toxic waste remediation, additive in refractory and paints, etc. This prompted us to find MgO NPs as convenient catalyst for the synthesis of novel pyridine derivatives via MCR.

Benzothiazoles are well established biologically important heterocycles that have received devastating response in consequence of its diversified molecular design and astonishing biological properties like anticancer [5,6], anticonvulsant [7,8], antibacterial [9], anti-HIV [10], antidiabetic [11], antimalarial [12], diuretic [13], antifungal [14], antileishmanial [15], antitubercular [16], anti-inflammatory [17], anthelmintic activity [18], and DNA minor groove binding agents [19]. Commercially available drug compounds such as riluzole, thioflavin, Pittsburgh compound B, ethoxzolamine, pramipexole, dimazole, flutemetamol, and dithiazanine iodide are some typical examples of drug compounds containing benzothiazole as core nucleus. Thiazolidine derivatives have been studied broadly and found to

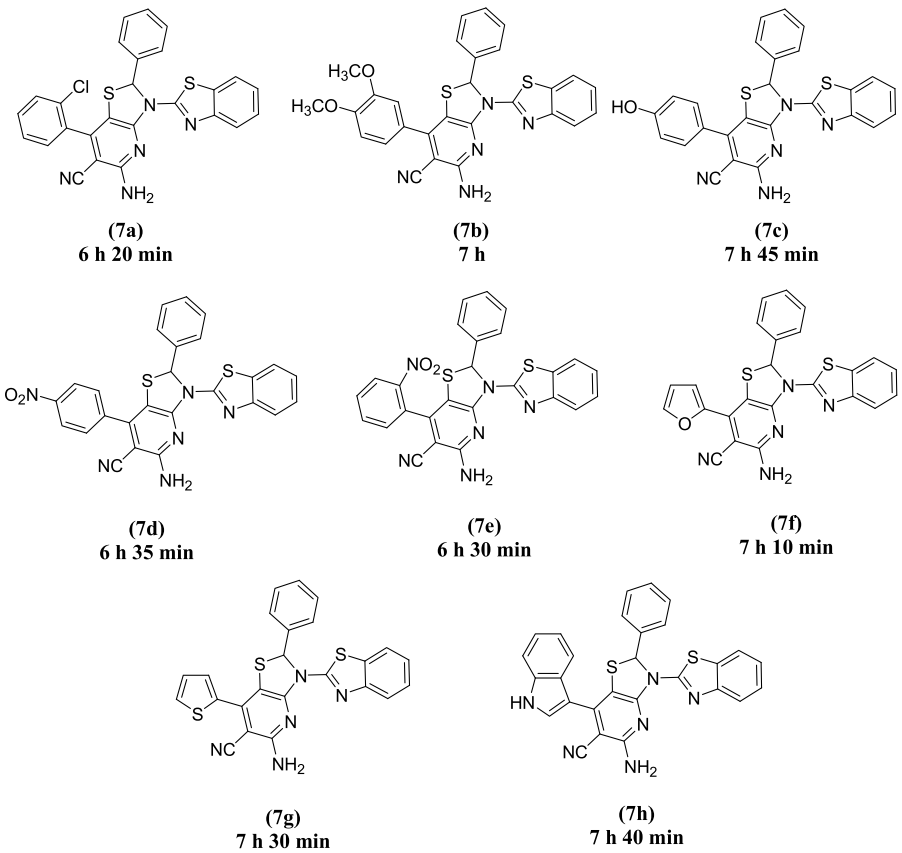
have miscellaneous chemical reactivities and broad spectrum of biological activities as antimicrobial [20,21], anti-inflammatory [22], antioxidant [23], anti-YFV (yellow fever virus) activity [24], antitubercular [25], anti HIV [26], anticancer [27–29], antidiabetic [30], anticonvulsant [31], antiparasitc [32], antimalarial [33], antihyperlipidemic [34] activity, etc. Similarly, pyridines also constitute a versatile class of bioactive molecules, which are present in a number of natural products and biologically active materials and in materials with interesting physical–chemical properties. They are known to have a broad variation in biological properties [35] such as antitubercular [36], anticancer [37], antimicrobial [38], antihypertensive [39], phytotoxic [40], anti-Alzheimer [41], and vasorelaxant [42] activities.

In continuation of our laboratory research, which aims at developing green and environmental friendly synthetic methodologies for organic reactions, we herein report for the first time highly efficient ecobenign approach for the one-pot multicomponent synthesis of thiazolo[4,5-b] pyridine-6-carbonitrile derivatives via MgO nanoparticles. To the best of our knowledge, there have been no discussions regarding synthesis of thiazolo[4,5-b] pyridine-6-carbonitrile derivatives (**7a**–**h**) using MgO nanoparticles as catalyst with MCR approach.

Scheme 1. Synthesis of 3-benzothiazol-2-yl-2-phenyl-thiazolidin-4-one.



(1) (2) (3) (4)



(7a) **6 h 20 min**

(7b) **7 h**

(7c) **7 h 45 min**

(7d) **6 h 35 min**

(7e) **6 h 30 min**

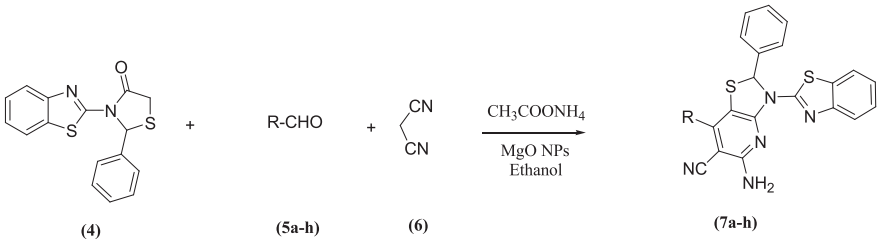
(7f) **7 h 10 min**

(7g) **7 h 30 min**

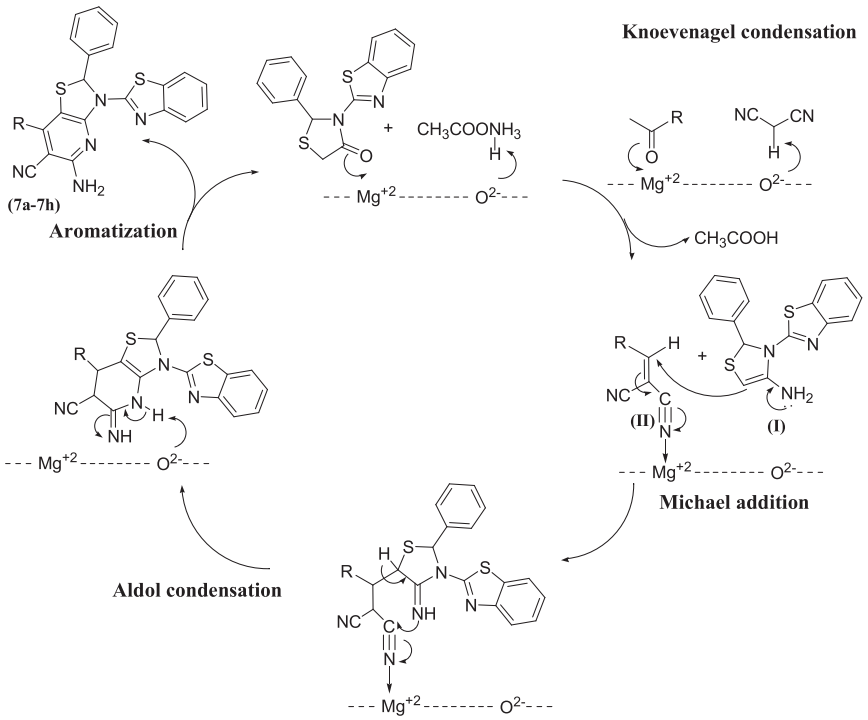
(7h) **7 h 40 min**

Figure 1. Library of synthesized compounds (**7a**–**h**).

Scheme 2. Synthesis of 5-amino-3-benzothiazol-2-yl-7-(phenyl)-2-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridine-6-carbonitrile derivatives.



Scheme 3. Plausible mechanistic pathway of reaction.



RESULTS AND DISCUSSION

As a part of our continued interest in catalysis by nanoparticles, we found excellent selectivity of heterogenous nanocrystalline MgO NPs for MCR leading to synthesis of thiazolo[4,5-b]pyridine-6-carbonitrile derivatives in high yields. This method has attracted interest because of high yield of products and easy experimental workup, and the reactivated catalyst was reused for four consecutive cycles without any significant loss in catalytic activity from environmental and economic point of view. MgO NPs were prepared by using magnesium nitrate as a precursor. The preliminary characterizations of MgO were performed by using IR, thermogravimetric analysis (TGA), differential thermal analysis (DTA), and X-ray diffraction (XRD).

Our present investigation involved synthesis of thiazolidin-4-one (**4**) (Scheme 1) as precursor for the design of thiazolo[4,5-b]pyridine-6-carbonitrile derivatives using malononitrile, substituted aromatic aldehydes, and ammonium acetate in ethanol using MgO NPs as catalyst (Fig. 1, Scheme 2). It was assumed that MgO nanoparticles activated the carbonyl carbon of 3-benzothiazol-2-yl-2-phenyl-thiazolidin-4-one (Scheme 1) and promoted the formation of imine (I) by the reaction of the 3-benzothiazol-2-yl-2-phenyl-thiazolidin-4-one and ammonium acetate followed by simultaneous formation of arylidene (II) by Knoevenagel condensation of the substituted aromatic aldehyde and malononitrile in the initial step. This further underwent Michael addition of imine (I) (nucleophilic endocyclic carbon of thiazolidinone) to the activated double bond of the arylidene intermediate. The adduct formed was then cyclized intramolecularly through aldol condensation and subsequent oxidation and aromatization provided target compounds, 5-amino-3-benzothiazol-2-yl-7-(phenyl)-2-phenyl-2,3-dihydro-thiazolo

Table 1

Effect of solvents and catalyst on the model reaction.

S. no.	Catalyst	Solvent	Time	Yield (%)
1	No catalyst	Ethanol	24 h	65
2	MgO NPs	THF	8 h 30 min	77
3	MgO NPs	Toluene	10 h 45 min	78
4	MgO NPs	$CHCl_3$	9 h 15 min	76
5	MgO NPs	DMSO	8 h	80
6	MgO NPs	Ethanol	6 h 20 min	92

[4,5-b]pyridine-6-carbonitrile (**7a**–**h**) (Schemes 2 and 3). The structures of the desired compounds (**7a**–**h**) were established by means of their Fourier transform infrared (FTIR), ^{1}H-NMR, ^{13}C-NMR, mass, and elemental data.

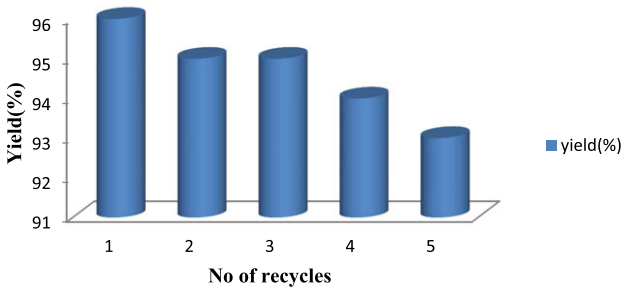


Figure 2. Recyclability and reusability of magnesium oxide NPs. [Color figure can be viewed at wileyonlinelibrary.com]

The band appeared in the region 3320–3367 and 2218–2262 cm^{-1} for compounds were attributed to NH_2-stretching and CN-stretching vibrations, respectively. The absorption bands occurred in the region 3072, 3055, 1614 cm^{-1} were attributed to the aromatic ring. The ^{1}H-NMR spectra of target compounds have displayed downfield singlet at δ 8.18–8.68 ppm due to NH_2 proton. The signals at δ 115.0–116.8 ppm and δ 121.07–136.95 ppm in ^{13}C-NMR spectra confirm the presence of CN and aromatic ring in the structure.

Based on the literature studies, this work has not been reported till date. In the absence of catalyst, the product was obtained in poor yields on refluxing for more than 24 h. Based on literature studies and our experimental work (Table 1), we found that MgO was the most effective catalyst in our work giving 80–92% product yield in about 6–8 h in ethanol. Basically, MgO enhanced the efficiency of synthesized compounds because of its basic properties and binding of substrate to active sites.

SCREENING AND REUSABILITY OF CATALYST

For the screening and reusability of catalyst, the control experiments were performed for the one-pot three-component condensation in order to demonstrate high catalytic activity generated from MgO in the synthesis of thiazolo[4,5-b]pyridine-6-carbonitrile derivatives (**7a**–**h**).

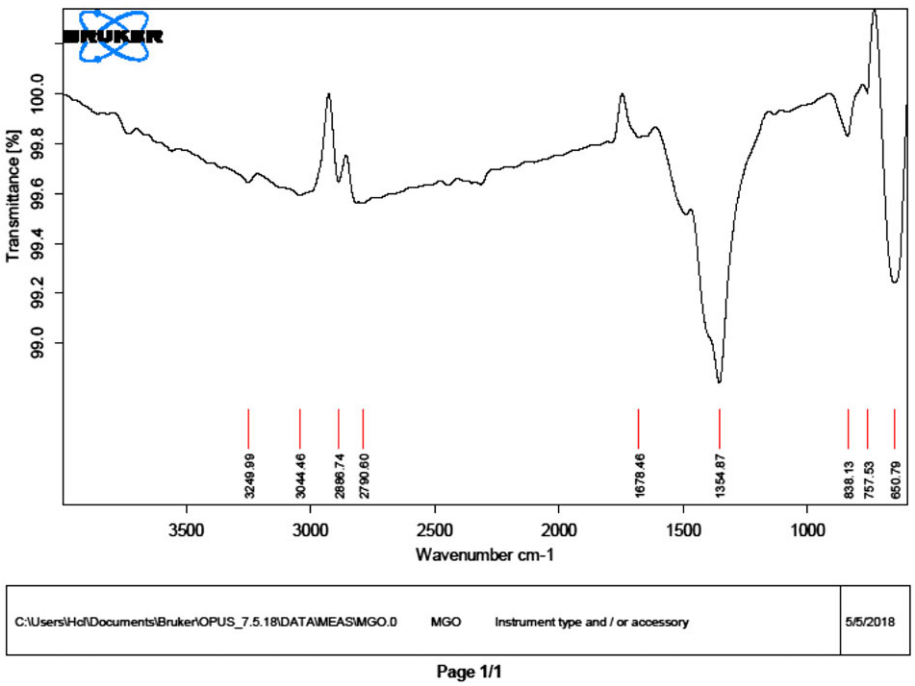


Figure 3. IR spectrum of nanocrystalline magnesium oxide. [Color figure can be viewed at wileyonlinelibrary.com]

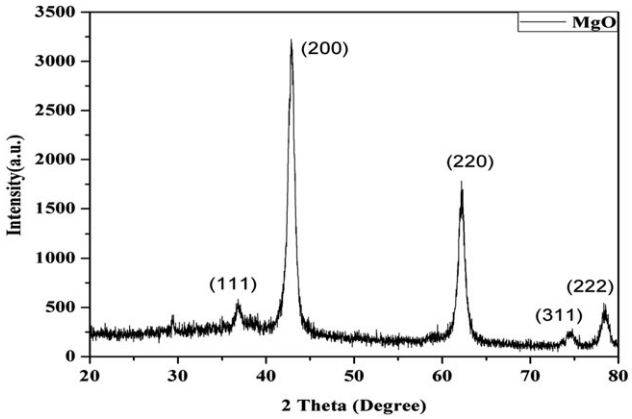


Figure 4. Powder X-ray diffraction pattern of magnesium oxide nanoparticles.

Table 2

Crystal data and structural parameters from the X-ray diffraction pattern of magnesium oxide NPs.

2θ	FWHM (β)	Miller indices	Grain size (D) (nm)
36.88	0.7845	111	14.44
42.77	0.8512	200	14.72
62.12	0.8722	220	16.00
74.90	0.9458	311	17.26
78.25	0.9740	222	17.66

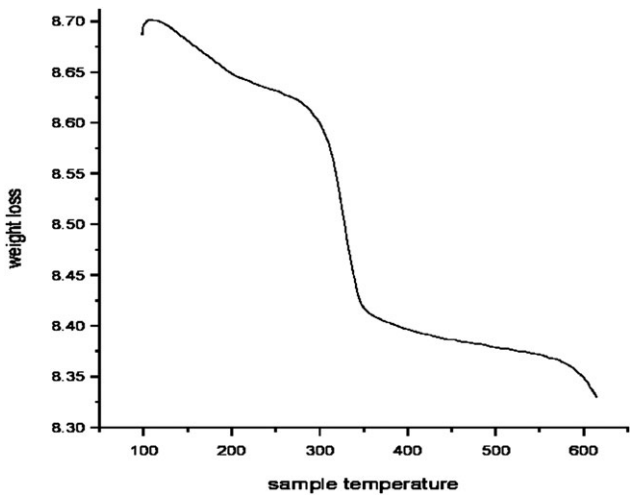


Figure 5. Thermogravimetric analysis profile of prepared Mg $(OH)_2$.

Being insoluble in reaction mixture, the catalyst is easily recovered by simple filtration. The recovered catalyst was washed with ethanol and dried at room temperature and reused directly for subsequent reaction without any further purification. Thus, the catalyst was recycled and reused for four times without significant loss in its activity (Fig. 2).

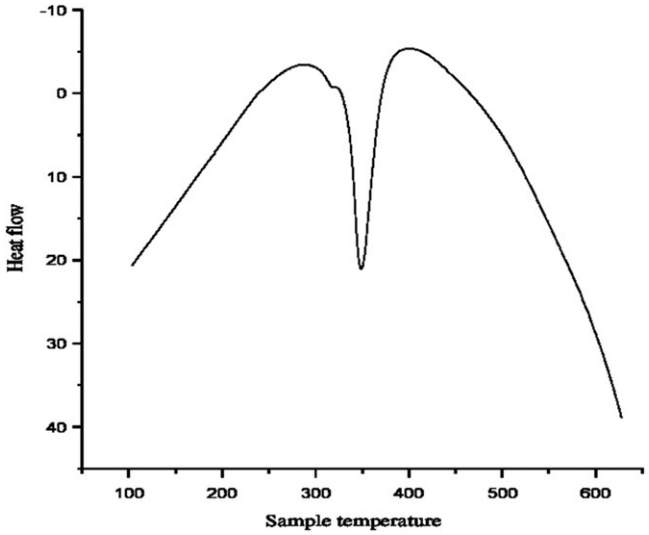


Figure 6. Differential thermal analysis profile of prepared Mg $(OH)_2$.

CONCLUSION

In this study, MgO NPs, being heterogeneous and recyclable catalyst, were found to be very efficient for the synthesis of thiazolo[4,5-b]pyridine-6-carbonitrile by one-pot MCR under conventional conditions. The synthesis of catalyst was very simple and easily recovered and reused for successive cycles. The eco-friendly and green approach made the reaction very facile and high yielding. In the future, these MgO NPs shall be used for more combinational synthesis and for the high throughput screening in medicinal chemistry.

EXPERIMENTAL

Chemistry. All the chemicals required for synthesis were commercially procured from Merck Ltd., Sigma-Aldrich and Hi-Media and used without further purification. The melting points were determined in open capillary tubes and are uncorrected. The FTIR spectra were recorded on Bruker FTIR Spectrometer. The ^{1}H-NMR and ^{13}C-CMR spectra were scanned on a Bruker Avance II (400 MHz) spectrometer using tetramethylsilane as internal standard and $CDCl_3$ as a solvent, and the chemical shifts are expressed in δ, ppm. The mass spectra were recorded on Waters Xevo G2-S QTof with UPLC spectrometer. XRD analysis was performed with an X-ray diffractometer (Bruker AXS D8 Advance) of CuKa radiation in the 2θ range from 20° to 80° TGA/DTA was performed with a Perkin Elmer STA-6000. The spectral facilities were carried out by Sophisticated Analytical Instrumentation Facility,

Chandigarh, India. The purity of the each synthesized compounds were checked by thin-layer chromatography using silica gel "G" as adsorbent in developing solvent hexane/ethylacetate, and visualization was accomplished by UV light or an iodine; the compounds were purified by column chromatography using hexane/ethylacetate as solvent system.

Spectral and analytical data. ***Synthesis of MgO nanoparticles.*** MgO nanoparticles are prepared by co-precipitation method [43] using magnesium nitrate and sodium hydroxide as precursors. In this process, (0.2 M) NaOH solution was prepared and added slowly dropwise into magnesium nitrate (0.1 M) solution with vigorous stirring. The pH was maintained at 10.5 by controlled addition of NaOH solution. The mixture was stirred at room temperature for 1–2 h after complete precipitation. A white precipitate of Mg $(OH)_2$ was obtained, which was washed thoroughly with distilled water and centrifuged at 4000 rpm for 15 min. The procedure was repeated several times until the precipitate was free from any trace of impurities. The precipitate was dried at 100°C, followed by calcination at 400°C resulting in the formation of MgO NPs.

Characterization of MgO nanoparticles. ***FTIR analysis.*** An FTIR spectrum for synthesized and calcined MgO nanoparticles is shown in (Fig. 3). The spectrum shows bands at 3249, 2139, 1678, 1354, 838, 757, and 650 cm^{-1}. The broad infrared band at 3249 cm^{-1} is associated with the OH-stretching vibrations of surface-adsorbed water molecules, while those at 1678 and 838 cm^{-1} are associated with their bending vibrations. A broad band at around 650–838 cm^{-1} is assigned to the metal–oxygen bending vibration of Mg–O–Mg bonding.

XRD spectral analysis. X-ray diffraction (XRD) analysis was analyzed to investigate the phase and crystallographic structure of MgO NPs (Fig. 4). All the major peaks appeared in 2θ: 36.88°, 42.77°, 62.12°, 74.26°, and 78.66° are corresponding with the MgO plane of (111), (200), (220), (311), and (222), respectively, (JCPDF 450946). Analysis of XRD profile using the Scherrer equation allowed the determination of particle sizes. The crystallite sizes determined by XRD were between 14.44 and 17.66 nm indicative of the nanocrystalline structure of the prepared MgO. A definite line broadening of the direction peaks is an indication that the synthesized materials are in nanometer range. The particles are in cubic phase with average crystalline size of about 14.72 nm. The crystallite size was calculated from Scherrer formula applied to major peaks and was found to be around 30 nm. The lattice parameters calculated are in accordance with the reported value. Average grain size was calculated using Debye–Scherrer formula [44] and is tabulated in Table 2.

$$D = \frac{K\lambda}{\beta\cos\theta}$$

where K: Constant 0.89 λ: Wavelength of employed X-ray 1.54 Å θ: Angle of the Bragg diffraction peak β: Full width at half maximum of the peak intensity D: Grain size (nm)

TGA/DTA analysis of the catalyst. Thermogravimetric analysis (TGA) was used to determine the minimum temperature required to calcine the dried precursor from the change in mass and thermal properties in relation to temperature. The thermal properties of MgO nanoparticles were investigated using TGA/DTA, and the observed results are shown in (Figs 5 and 6). The TGA curve shows slight weight loss probably due to vaporization of water or other volatile impurities that were physically adsorbed at the particle surface. The MgO nanoparticles were relatively stable in air and somewhat decomposed. The TGA curve shows one major degradation of the water in the weight loss started from 200°C to 600°C, which is attributed to dehydration of the hydroxide Mg $(OH)_2$ that occurs as the material transitions to the oxide form of MgO. A strong peak (endothermic) observed at 350–400°C in DTA curve might be attributed to decomposition of Mg $(OH)_2$ to MgO.

$$Mg(OH)_2 \rightarrow 2MgO + H_2O$$

Synthesis and spectral data of 3-benzothiazol-2-yl-2-phenyl-thiazolidin-4-one (4). Compound (**4**) as starting material was synthesized by the reported method [45].

Yield: 85%; Sticky light yellow; FTIR (KBr, cm^{-1}): 3072 (C-H Str., Ar), 3055 (C-H Str., CH_2), 1718 (CO Str.), 1608 (C=C, Ar). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.68 (d, 1H), 3.97 (d, 1H), 6.41 (s, 1H, NCHS), 7.18–7.79 (m, 9H, ArH). ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 34.25, 68.51, 119.76, 121.07, 124.96, 126.46, 128.2, 128.2, 128.60, 128.60, 128.92, 130.72, 139.25, 150.10, 165.63, 170.87. *Anal*. Calcd for $C_{16}H_{12}N_2OS_2$; C, 61.51; H, 3.87; N, 8.97; Found; C, 61.67; H, 3.92; N, 8.56; MS (EI): m/z 312.04 [M+].

General procedure for the preparation of 5-amino-3-benzothiazol-2-yl-7-(phenyl)-2-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridine-6-carbonitrile (7a–h). To a mixture of 3-benzothiazol-2-yl-2-phenyl-thiazolidin-4-one **4** (1 mmol), aromatic aldehyde (1 mmol) and malononitrile (1 mmol), ammonium acetate, and nanocatalyst MgO (0.16 g) were added and heated at 80°C in ethanol (5 mL) for 6–8 h. Completion of the reaction was indicated by thin-layer chromatography. The mixture was filtered to remove the solid catalyst, and the filtrate was concentrated under reduced pressure and was poured into ice cold water; the crude product obtained was further purified by column

chromatography (7:3) to afford the pure product. The catalyst was separated, dried, washed with ethanol, and reused for subsequent runs.

5-Amino-3-benzothiazol-2-yl-7-(2-chloro-phenyl)-2-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridine-6-carbonitrile (7a). Yield: 92%; Brown; m.p. 180–182°C; FTIR (KBr, cm^{-1}): 3364 (N-H Str., NH_2), 3072 (C-H Str., Ar), 2992 (C-H Str., thiazolidine), 2200 (-CN Str.), 1614 (C=C, Ar). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.89 (s, 1H, NCHS), 7.19–7.65 (m, 13H, ArH), 8.18 (s, 2H, NH_2). ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 66.24, 83.51, 115.48, 119.76, 121.15, 124.64, 126.13, 127.16, 128.20, 128.19, 128.64, 128.70, 128.89, 128.92, 130.55, 130.66, 130.72, 130.74, 132.34, 134.44, 134.75, 136.95, 151.10, 155.57, 159.45, 165.63. *Anal*. Calcd for $C_{26}H_{16}ClN_5S_2$; C, 62.70; H, 3.24; N, 14.06; Found; C, 62.73; H, 3.28; N, 14.12; MS (EI): m/z 497.05 [M+], 499.05 [M + 2].

5-Amino-3-benzothiazol-2-yl-7-(3,4-dimethoxy-phenyl)-2-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridine-6-carbonitrile (7b). Yield: 88%; Brick red; m.p. 174–176°C; FTIR (KBr, cm^{-1}): 3335 (N-H Str., NH_2), 3045 (C-H Str., Ar), 2983 (C-H Str., CH_3), 2933 (C-H Str., thiazolidine), 2243 (-CN Str.), 1627 (C=C, Ar). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 3.79 (s, 3H), 3.86 (s, 3H), 4.24 (s, 1H, NCHS), 6.95–7.65 (m, 12H, ArH), 8.37 (s, 2H, NH_2). ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 56.15, 56.88, 64.76, 84.34, 111.02, 112.24, 115.05, 119.39, 121.26, 124.88, 127.56, 128.22, 128.44, 128.60, 128.83, 128.90, 128.92, 130.52, 130.77, 134.40, 136.91, 139.15, 148.31, 149.17, 152.75, 154.16, 159.80, 165.59. *Anal*. Calcd for $C_{28}H_{21}N_5O_2S_2$; C, 64.22; H, 4.04; N, 13.37; Found; C, 64.45; H, 4.20; N, 13.43; MS (EI): m/z 523.11 [M+].

5-Amino-3-benzothiazol-2-yl-7-(4-hydroxy-phenyl)-2-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridine-6-carbonitrile (7c). Yield: 92%; Brown; m.p. 202–204°C; FTIR (KBr, cm^{-1}): 3420 (OH Str.), 3358 (N-H Str., NH_2), 3,066 (C-H Str., Ar), 2922 (C-H Str., thiazolidine), 2228 (-CN Str.), 1612 (C=C, Ar). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.66 (s, 1H, NCHS), 6.95–7.65 (m, 13H, ArH), 8.45 (s, 2H, NH_2). ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 66.52, 83.68, 115.24, 119.76, 121.17, 124.52, 126.66, 127.16, 128.21, 128.47, 128.54, 128.60, 128.84, 128.92, 130.55, 130.64, 130.72, 130.74, 132.34, 132.90, 134.46, 136.90, 150.14, 156.25, 159.12, 166.83. *Anal*. Calcd for $C_{26}H_{17}N_5OS_2$; C, 65.12; H, 3.57; N, 14.60; Found; C, 65.16; H, 3.61; N, 14.65; MS (EI): m/z 479.09 [M+].

5-Amino-3-benzothiazol-2-yl-7-(4-nitro-phenyl)-2-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridine-6-carbonitrile (7d). Yield: 85%; Dark Coffee; m.p. 212–214°C; FTIR (KBr, cm^{-1}): 3385 (N-H Str., NH_2), 3098 (C-H Str., Ar), 2967 (C-H Str., thiazolidine), 2249 (-CN Str.), 1627 (C=C, Ar). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.95 (s, 1H, NCHS), 7.19–8.24 (m, 13H, ArH), 8.63 (s, 2H, NH_2). ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 65.83, 86.22, 116.56, 117.29, 118.14, 119.76, 121.11, 124.36, 125.45, 126.11, 126.46, 128.60, 128.79, 128.86, 128.90, 128.92, 130.66, 131.42, 134.43, 136.97, 139.15, 140.47, 151.11, 153.99, 159.16, 166.18. *Anal*. Calcd for $C_{26}H_{16}N_6O_2S_2$; C, 61.40; H, 3.17; N, 16.52; Found; C, 61.47; H, 3.22; N, 16.58; MS (EI): m/z 508.08 [M+].

5-Amino-3-benzothiazol-2-yl-7-(2-nitro-phenyl)-2-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridine-6-carbonitrile (7e). Yield: 80%; Mustard Brown; m.p. 232–234°C; FTIR (KBr, cm^{-1}): 3380 (N-H Str., NH_2), 3078 (C-H Str., Ar), 2983 (C-H Str., thiazolidine), 2262 (-CN Str.), 1634 (C=C, Ar). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.91 (s, 1H, NCHS), 7.19–8.15 (m, 13H, ArH), 8.68 (s, 2H, NH_2). ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 67.42, 84.93, 114.68, 119.76, 120.85, 121.99, 124.28, 126.91, 126.46, 126.71, 128.16, 128.33, 129.39, 128.59, 128.60, 128.64, 128.92, 130.64, 130.72, 134.46, 136.94, 148.37, 151.30, 153.78, 159.00, 164.34. *Anal*. Calcd for $C_{26}H_{16}N_6O_2S_2$; C, 61.40; H, 3.17; N, 16.52; Found; C, 61.51; H, 3.19; N, 16.64; MS (EI): m/z 508.08 [M+].

5-Amino-3-benzothiazol-2-yl-7-furan-2-yl-2-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridine-6-carbonitrile (7f). Yield: 91%; Red Violet; m.p. 154–156°C; FTIR (KBr, cm^{-1}): 3353 (N-H Str., NH_2), 3045 (C-H Str., Ar), 2936 (C-H Str., thiazolidine), 2227 (-CN Str.), 1608 (C=C, Ar). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.63 (s, 1H, NCHS), 6.50 (dd, 1H, J = 3.4, 1.8 Hz), 6.78 (dd, 1H, J = 3.4, 0.9 Hz), 7.20–7.62 (m, 9H, ArH), 7.90 (dd, 1H, J = 1.8, 0.9 Hz), 8.52 (s, 2H, NH_2). ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 66.06, 83.01, 106.8, 111.36, 115.19, 119.76, 120.19, 125.12, 126.44, 128.10, 128.29, 128.60, 128.77, 128.92, 130.61, 130.73, 134.42, 136.93, 142.28, 152.10, 152.50, 154.85, 159.43, 166.67. *Anal*. Calcd for $C_{24}H_{15}N_5OS_2$; C, 63.56; H, 3.33; N, 15.44; Found; C, 63.59; H, 3.38; N, 15.46; MS (EI): m/z 453.07 [M+].

5-Amino-3-benzothiazol-2-yl-2-phenyl-7-thiophen-2-yl-2,3-dihydro-thiazolo[4,5-b]pyridine-6-carbonitrile (7g). Yield: 93%; Red brown; m.p. 176–178°C; FTIR (KBr, cm^{-1}): 3367 (N-H Str., NH_2), 3088 (C-H Str., Ar), 2974 (C-H Str., thiazolidine), 2218 (-CN Str.), 1626 (C=C, Ar). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.68 (s, 1H, NCHS), 7.06 (dd, 1H, J = 7.9, 5.9 Hz), 7.19–7.42 (m, 9H, ArH), 7.47 (dd, 1H, J = 7.9, 1.2 Hz), 7.75 (dd, 1H, J = 5.9, 1.2 Hz), 8.22 (s, 2H, NH_2). ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 65.18, 83.77, 116.72, 119.76, 122.34, 124.06, 125.49, 125.97, 127.78, 128.20, 128.22, 128.57, 128.60, 128.63, 128.92, 130.16, 130.72, 134.45, 136.75, 142.69, 150.09, 155.19, 159.69, 165.76. *Anal*. Calcd for $C_{24}H_{15}N_5S_3$; C, 61.38; H, 3.22; N, 14.91; Found; C, 61.43; H, 3.26; N, 14.98; MS (EI): m/z 469.05 [M+].

5-Amino-3-benzothiazol-2-yl-7-(1H-indol-3-yl)-2-phenyl-2,3-dihydro-thiazolo[4,5-b]pyridine-6-carbonitrile (7h). Yield: 89%; Brown; m.p. 243–245°C; FTIR (KBr, cm^{-1}): 3410, 3285 (N-H Str., in NH indole, NH_2), 3040 (C-H Str., Ar), 2925 (C-H Str., thiazolidine), 2232 (-CN Str.), 1665

(C=C, Ar). ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 4.76 (s, 1H, NCHS), 6.80–8.07 (m, 14H, ArH), 8.37 (s, 2H, NH_2) 9.07 (s, 1H, NH), ^{13}C-NMR (400 MHz, $CDCl_3$) δ (ppm): 66.49, 83.85, 111.62, 114.21, 118.16, 119.20, 120.76, 120.18, 121.07, 121.30, 122.20, 124.17, 125.10, 125.55, 128.26, 128.60, 128.60, 128.83, 128.92, 130.67, 130.72, 134.41, 135.76, 136.95, 152.70, 156.21, 159.95, 166.47. *Anal*. Calcd for $C_{28}H_{18}N_6S_2$; C, 66.91; H, 3.61; N, 16.72; Found; C, 66.98; H, 3.74; N, 16.76; MS (EI): m/z 502.10 [M+].

Acknowledgments. The authors are thankful to Head, Department of Chemistry for providing necessary laboratory facilities. The Department of Physics, University College of science, MLSU, Udaipur is duly acknowledged for TGA, DTA, and XRD analysis. The authors would also like to acknowledge Sophisticated Analytical Instrumentation Facility, Chandigarh, India, for providing spectral data.

REFERENCES AND NOTES

[1] Ganem, B. Acc Chem Res 2009, 42, 463.
[2] Bastug, G.; Eviolitte, C.; Marko, I. E. Org Lett 2012, 14, 3502.
[3] Dummer, N. F.; Joyce, L.; Ellicotta, H.; Jiangc, Y. Cat Sci Technol 2016, 6, 1903.
[4] Calatayud, M.; Markovits, A.; Menetrey, M.; Mguig, B.; Minot, C. Catal Today 2003, 85, 125.
[5] Kaur, N.; Kaur, K.; Raj, T.; Kaur, G.; Singh, A.; Aree, T.; Park, S. J.; Kim, T. J.; Singh, N.; Jang, D. O. Tetrahedron 2015, 71, 332.
[6] Cui, J.; Qi, B.; Gan, C.; Liu, Z.; Huang, H.; Lin, Q.; Zhao, D.; Huang, Y. Mar Drugs 2015, 13, 2488.
[7] Siddiqui, N.; Rana, A.; Khan, S. A.; Haque, S. E.; Alam, M. S.; Ahsan, W.; Ahmed, S. J. Enz Inhib Med Chem 2009, 24, 1344.
[8] Liu, D. C.; Zhang, H. J.; Jin, C. M.; Quan, Z. S. Molecules 2016, 21, 164.
[9] Yardily, A.; Danie, V. A.; Rosy, B. A.; Reji, T. F. A. F. J. Saudi Chem Soc 2016, 20, 278.
[10] Nagarajan, S. R.; De Crescenzo, G. A.; Getman, D. P.; Lu, H. F.; Sikorski, J. A.; Walker, J. L.; Mc Donald, J. J.; Houseman, K. A.; Kocan, G. P.; Kishore, N.; Mehta, P. P.; Funkes-Shippy, C. L.; Blystone, L. Bioorg Med Chem 2003, 11, 4769.
[11] Kharbanda, C.; Alam, M. S.; Hamid, H.; Javed, K.; Bano, S.; Ali, Y.; Dhulap, A.; Alamc, P.; Pashac, M. A. Q. New J Chem 2016, 40, 6777.
[12] Takasu, K.; Inoue, H.; Kim, H.; Suzuki, M.; Shishido, T.; Wataya, Y.; Ihara, M. J Med Chem 2002, 45, 995.
[13] Yar, M. S.; Ansari, Z. H. Acta Pol Pharm Drug Res 2009, 66, 387.
[14] Kukreja, S.; Sidhu, A.; Sharma, V. K. Res Chem Intermed 2016, 42, 8329.
[15] Florence, D.; Antonio, A.; Carole, D. G.; Maxime, R.; Erik, D. C.; Pierre, T.; Jean-Pierre, G. Eur J Med Chem 2004, 39, 685.
[16] Patel, A. B.; Patel, R. V.; Kumari, P.; Rajani, D. P.; Chikhalia, K. H. Med Chem Res 2013, 22, 367.
[17] Oketani, K.; Nagakura, N.; Harada, K.; Inour, T. Eur J Pharmacol 2001, 422, 209.
[18] Munirajasekhar, D.; Himaja, M.; Mali, S. V. J Heterocyclic Chem 2014, 51, 459.
[19] Yang, M. L.; Zhang, H.; Wang, W. W.; Wang, X. J. J Heterocyclic Chem 2018, 55, 360.
[20] Liu, H. L.; Li, Z.; Anthonsen, T. Molecules 2000, 5, 1055.
[21] Stana, A.; Tiperciuc, B.; Duma, M.; Vlase, L.; Crişan, O.; Pîrnău, A.; Oniga, O. J Heterocyclic Chem 2014, 51, 411.
[22] Manojkumar, P.; Subbuchettiar, G. Acta Pharm 2009, 59, 159.
[23] Gurupadyya, B. M.; Gopal, M.; Padmashali, B.; Manohara, Y. N. Indian J Pharm Sci 2008, 70, 572.
[24] Sriram, D.; Yogeeshwari, P.; Ashok Kumar, T. G. J Pharm Sci 2005, 8, 426.
[25] Visagaperumal, D.; Kumar, R. J.; Vijayaraj, R.; Anbalgan, N. Int J Chem Tech Res 2009, 1, 1048.
[26] Rawal, R. K.; Prabhakar, Y. S.; Katti, S. B.; Clercq, D. Bioorg Med Chem 2005, 13, 6771.
[27] Voss, M. E.; Cartwer, P. H.; Tebben, A. J.; Scherle, P. A.; Brown, G. D.; Lorin, A.; Xu, M.; Lo, Y. C.; Yang, G.; Liu, R. Q.; Strzemienski, P.; Everlof, J. G.; Trzaskos, J. M.; Decicco, C. P. Bioorg Med Chem Lett 2003, 13, 533.
[28] Aly, A. A.; Brown, A. B.; Aziz, M. A.; El-Din, G.; Abuo-Rahma, A. A.; Radwan, M. F.; Ramadan, M.; Gamal-Eldeen, A. M. J Heterocyclic Chem 2012, 49, 726.
[29] Chen, E. M.; Lu, P. J.; Shaw, A. Y. J Heterocyclic Chem 2012, 49, 792.
[30] Yu, M.; Tsuyoshi, M.; Tohru, Y.; Mitsuru, K.; Hiroyuki, O.; Hitoshi, I.; Takashi, S. J Med Chem 2002, 45, 1518.
[31] Solomon, V. R.; Haq, W.; Srivastava, K.; Puri, S. K.; Katti, S. B. J Med Chem 2007, 50, 394.
[32] Agarwal, A.; Lata, S.; Saxena, K. K.; Srivastava, V. K.; Kumar, A. Eur J Med Chem 2006, 41, 1223.
[33] Seebacher, W.; Belaj, F.; Saf, R.; Brun, R.; Weis, R. Monatshef Chem 2003, 134, 1623.
[34] Patel, H. M.; Noolvi, M. N.; Goyal, A.; Thippeswamy, B. S. Eur J Med Chem 2013, 65, 119.
[35] Altaf, A. A.; Shahzad, A.; Gul, Z.; Rasool, N.; Badshah, A.; Lal, B.; Khan, E. J. Drug Des Med Chem 2015, 1, 1.
[36] Chaudhari, K. S.; Patel, H. M.; Surana, S. J. Indian J Tuberc 2016, 64, 119. https://doi.org/10.1016/j.ijtb.2016.11.012.
[37] Ansari, F.; Idrees, D.; Hassan, M. I.; Ahmad, K.; Avecilla, F.; Azam, A. Eur J Med Chem 2018, 144, 544. https://doi.org/10.1016/j.ejmech.2017.12.049.
[38] Bhardwaj, V.; Noolvi, M. N.; Jalhan, S.; Patel, H. M. J. Saudi Chem Soc 2016, 20, S406.
[39] Kumbhare, R. M.; Kosurkar, U. B.; Bagul, P. K.; Kanwal, A.; Appalanaidu, K.; Dadmal, T. L.; Banerjee, S. K. Bioorg Med Chem 2014, 22, 5824.
[40] Demuner, A. J.; Valente, V. M.; Barbosa, L. C.; Rathi, A. H.; Donohoe, T. J.; Thompson, A. L. Molecules 2009, 14, 4973.
[41] Chanda, K.; Alsoghiera, H. M.; Chavesa, S.; Santos, M. A. J Inorg Biochem 2016, 163, 266.
[42] Hernandez, F.; Sanchez, A.; Vallejo, P. R.; Pacheco, C. M.; Alcaraz, Y.; Delgado, F.; Vazquez, M. A. Eur J Med Chem 2013, 70, 669.
[43] Krishnamoorthy, K.; Moon, J. Y.; Hyun, H. B.; Cho, S. K.; Kim, S. J. J Mater Chem 2012, 22, 24610.
[44] Patel, S. L.; Purohit, A.; Chander, S.; Kannan, M. D.; Dhaka, M. S. Curr Applied Phy 2018, 18, 803.
[45] Shah, P. M.; Patel, M. P. Indian J Chem 2011, 50B, 310.