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An efficient one pot three- component nanocatalyzed synthesis of spiroheterocycles using TiO₂ nanoparticles as heterogeneous catalyst.

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Abstract

An efficient and environmentally benign isocyanide based domino protocol has been presented for the synthesis of structurally diverse spiroheterocycles, spiroannulated with imidazothiazole and imidazothiadiazole, involving three component reaction of 2-aminobenzothiazole/2-amino-1,3,4-thiadiazole, cyclohexyl/tert.-butyl isocyanides and isatines/cyclic carbonyl compounds catalyzed by recyclable and reusable nanocrystalline TiO₂.

Keyword: Spirooxindoles; imidazothiazole; imidazothiadiazole, TiO₂ nanoparticles

Introduction

Modern drug discovery is faced with the challenges of designing chemical reactions that are highly capable of providing the target molecules with the structural diversity and molecular complexity involving minimum number of synthetic steps and avoiding the use of volatile organic solvents. The development of efficient and environmentally benign multicomponent domino reactions have attracted increasing interest in modern organic syntheses in view of growing environmental concern. The isocyanide based multicomponent reactions, in particular, combined with eco-compatibility find their significance especially in medicinal chemistry and drug discovery research for the syntheses of drug -like structurally diverse complex molecules in terms of lead finding and lead optimization [1,2]. Moreover, the use of low-cost, readily available and reusable catalysts also plays a significant role in organic syntheses and makes the synthetic methods economically-viable. The catalysis by nanoparticles (NPs) seems to be an attractive approach in organic syntheses due to their large reactive surfaces with higher potential for selectivity, which may enable the reactions to proceed efficiently under mild reaction conditions [3]. Moreover, the easier isolation of the products and possibility of reusing the catalyst are the additional advantages with the nanocatalyzed multicomponent reactions [4]. Recently, TiO₂ nanoparticles have emerged as efficient and inexpensive heterogeneous catalyst to

promote organic transformations [5]. Titanium dioxide (TiO₂) catalysis is considered very close to an ideal catalysis because of its sustainability and environmental concerns [6].

In recent years, the privileged structure-activity concept has been an emerging theme in medicinal chemistry and drug discovery research. Benzothiazole is privileged heterocyclic system and incorporated in marine and terrestrial bioactive natural products in addition to wide range of biopharmaceutical activities of its synthetic derivatives [7,8]. Benzothiazole derivatives have been evaluated as potential amyloid-binding diagnostic agents in neurodegenerative disease [9], selective fatty acid amide hydrolase inhibitors [10], inhibitors of stearylcoenzyme A δ -9 desaturase [11], LTD4 receptor antagonists [12], orexin receptor antagonists [13], and histamine H₂ antagonists [14].

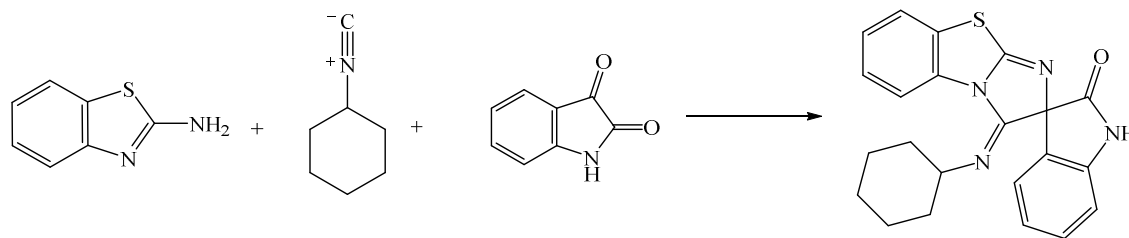
Imidazo[1,2-*b*]thiazoles have also attracted considerable interest in medicinal research in view of their uses as antitumor, antidiabetic, antitubercular, and anti-cardiovascular agents [15]. In addition, imidazo[2,1-*b*]benzothiazoles have been reported recently to exhibit antibacterial [16], antifungal [17], anti-inflammatory [18], anticancer [19] and analgesic activity [20]. Imidazo[2,1-*b*][1,3,4]thiadiazoles are also of considerable interest in chemical and medicinal research because of their structural characteristics: the presence of four heteroatoms and two condensed privileged heterocyclic systems with different π -conjugation and incorporation of the imidazothiadiazole ring system as structural framework of several bioactive natural products and synthetic pharmaceuticals [21]. Spirooxindoles, in particular, have emerged as attractive synthetic targets because of their prevalence in numerous clinical pharmaceuticals and natural alkaloids with their wide range of biopharmacological activities [22].

The synthetic methods reported in the literature for the synthesis of the imidazo[1,2-*b*]thiazoles, imidazo[1,2-*b*]thiadiazoles and related compounds involved many limitations in terms of the multi-step synthetic procedures, use of volatile organic solvents, expensive catalysts, higher energetic reaction conditions, lower product yields and longer reaction time [23,24]. Imidazo[1,2-*b*]thiazoles were synthesized also by isocyanide based multicomponent reaction using 2-aminobenzothiazole derivatives, quinoline-3-carbaldehyde/ 1*H*-indole-3-carbaldehyde and *p*-fluorophenyl isocyanide, but the reaction required 12 hrs for completion and provided 53-71 % yields of the products [25]. In view of the existing synthetic methods of imidazothiazoles, development of environmentally benign, diversity oriented, efficient and high-yielding synthetic protocol is highly desirable observing the concept of atom-economy and high convergence without isolation and purification of intermediates.

Encouraged by the promising biological activities of the heterocyclic privileged substructures and our continued research programme on the syntheses of therapeutically interesting heterocycles [26-29], we wish to report, for the first time, nanocrystalline TiO₂ catalyzed one-pot three-component isocyanide-based synthesis of spiro-heterocycles incorporating privileged heterocyclic substructures, imidazothiazole/imidazothiadiazole, in aqueous ethanol in excellent yields. Our main concern is to develop a sustainable synthetic methodology involving use of recyclable and reusable nanocatalyst with mild reaction conditions.

Results and discussion

In this context, we present highly efficient and convenient one-pot synthesis of spiroheterocycles incorporating medicinally privileged heterosystems involving the reaction of 2-aminobenzothiazole/2-amino-1,3,4-thiadiazole with cyclohexyl/tert.-butyl isocyanides and isatines/cyclic carbonyl compounds in the presence of reusable TiO₂ nanopowder as catalyst in aqueous ethanol. Initially, three-component reaction of 2-aminobenzothiazole, cyclohexyl isocyanides and isatin was selected as a simple model reaction to establish the feasibility of the present synthetic strategy and to optimize the reaction conditions using different catalysts (Scheme 1).



Scheme 1: Model reaction

Table 1: Optimization of reaction conditions^a

S.No.	Catalyst (mol %)	Solvent ^b	Time (hrs)	Yield (%) ^c
1.	Catalyst free	None	>10	Trace
2.	Boric acid (15 mol %)	Ethanol	7	45
3.	Sulfamic acid (15 mol %)	Ethanol	8	60
4.	<i>p</i> -TSA (15 mol %)	Ethanol	7	60
5.	Trifluoroacetic acid (15 mol %)	Ethanol	7	65
6.	ZnS NPs (15 mol %)	Ethanol	5	70
7.	Commercial TiO ₂ (15 mol %)	Ethanol	5	78, 80 ^d
8.	TiO ₂ NPs (10 mol %)	Ethanol	4	90
9.	TiO ₂ NPs (15 mol %)	Ethanol	4	92
10.	TiO ₂ NPs (20 mol %)	Ethanol	4	92
11.	TiO₂ NPs (15 mol %)	Ethanol:water (v/v:2:3)	3	94
12.	TiO ₂ NPs (15 mol %)	1,4-Dioxane	3.5	80
13.	TiO ₂ NPs (15 mol %)	Dichloromethane	4	84
14.	TiO ₂ NPs (15 mol %)	Tetrahydrofuran	4	85
15.	TiO ₂ NPs (15 mol %)	Methanol	3.5	89

Bold row indicates the optimization condition for the reaction.

^a 2-aminobenzothiazole (1 mmol), cyclohexyl isocyanides (1 mmol) and simple isatin (1 mmol) were stirred at 90°C till completion as indicated by TLC.

^b Solvents (2.0 mL).

^c Isolated yield after purification.

^d Isolated yield when commercial TiO₂ catalyst was finely grounded in a mortar/pestle prior to reaction.

It was observed that only a trace amount of product was obtained when the reaction was carried out in solvent free and catalyst free conditions (table 1, entry 1). The model reaction was also performed in various acid catalysts such as boric acid, *p*-TSA, sulfamic acid, and trifluoroacetic acid, but the desired product was obtained in moderate yield (table 1, entries 2-5). However, when the reaction was performed in the presence of ZnS nanoparticles as catalyst in ethanol as solvent, the yield of the desired product was good (table 1, entry 6). The reaction was also examined in the presence of commercial TiO₂ and TiO₂ nanoparticles as catalysts (table 1, entries 7-8). The results clearly indicate that when the reaction was catalyzed with TiO₂ nanoparticles in ethanol as solvent, the excellent yield of the desired product was obtained with high purity and in shorter reaction time than that obtained with the use of other catalysts. From the evaluation of screening results, it is clearly evident that TiO₂ nanoparticles exhibited the largest surface areas and hence the most reactive acidic sites due to its nano-sized nature and showed superior catalytic activity over the other catalysts. The effect of catalyst loading was also examined by varying the loading amount to 10%, 15%, 20% and observed that 15 mol % of TiO₂ NPs provided the maximum yield (table 1, entry 9). The solvent effect on the catalytic efficiency of TiO₂ nanoparticles was also examined employing various protic and aprotic solvents (table 1, entries 11-15) and observed that its catalytic efficiency was maximum in aqueous ethanol (ethanol:water: v/v:2:3) as compared with other solvents. The effect of temperature on catalytic activity of TiO₂

nanoparticles was also examined and it was observed that 90°C was optimum temperature for maximum catalytic efficiency of TiO₂ nanoparticles (Table 2).

Table 2: Effect of temperature^a

S.No.	Catalyst	Temp (°C)	Time (Hrs)	Yield (%) ^b
1.	TiO ₂ NPs (15 mol %)	50°C	4.5	80
2.	TiO ₂ NPs (15 mol %)	60°C	4.15	80
3.	TiO ₂ NPs (15 mol %)	80°C	3.5	82
4.	TiO₂ NPs (15 mol %)	90°C	3	94

^a Reaction conditions: 2-aminobenzothiazole (1 mmol), cyclohexyl isocyanides (1 mmol), and simple isatin (1 mmol); catalyst: TiO₂ NPs (15 mol %); Solvent: 2.0 mL aqueous ethanol (ethanol: water: v:v/2:3); at different temperatures.

^b Isolated yields after purification.

Additionally, catalytic recyclability and reusability was also investigated on the model reaction under optimized reaction conditions. The catalyst was easily recovered by the filtration after completion of the reaction. Then it was washed with diethyl ether and then first dried under vacuum followed by drying in the oven completely. Recovered TiO₂ could be used for five times without significant loss of its activity but after this, sudden decrease in yield was observed probably due to deactivation of the catalyst (Figure 1). However, post treatment of the catalyst by calcinations at 500°C for 1 h restored its catalytic activity and then further could be reused for three more reaction cycles (Figure 2). The reusability of the commercial TiO₂ was also observed and the results are presented in figure 3. Ultimately, synthesized acidic TiO₂ nanoparticles preserved its activity and thermal stability and showed superior behavior over commercial TiO₂ catalyst in terms of recyclability and reusability which is very important factor for large scale synthesis.

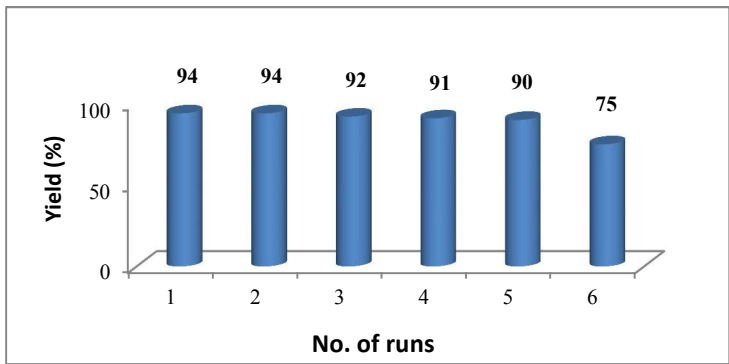


Figure 1: Recyclability and reusability of TiO₂ NPs.

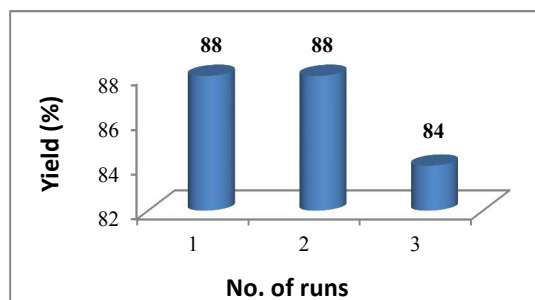


Figure 2: Reusability and reusability of catalyst after calcinations treatment.

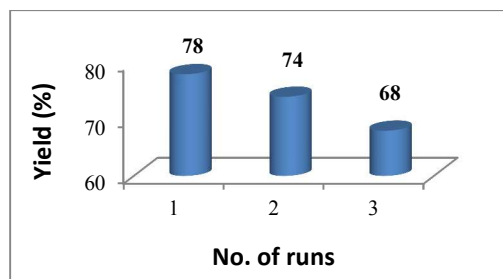


Figure 3: Reusability of and reusability commercial TiO_2 catalyst

Under the optimized reaction condition, this novel isocyanide based three component reaction was extended for the synthesis of structurally diverse spiroheterocycles to explore the scope and generality of reaction protocol. To our delight, the reaction proceeds smoothly and the structurally diverse spiroheterocycles were obtained in excellent yields. The results are summarized in table 5 and 6.

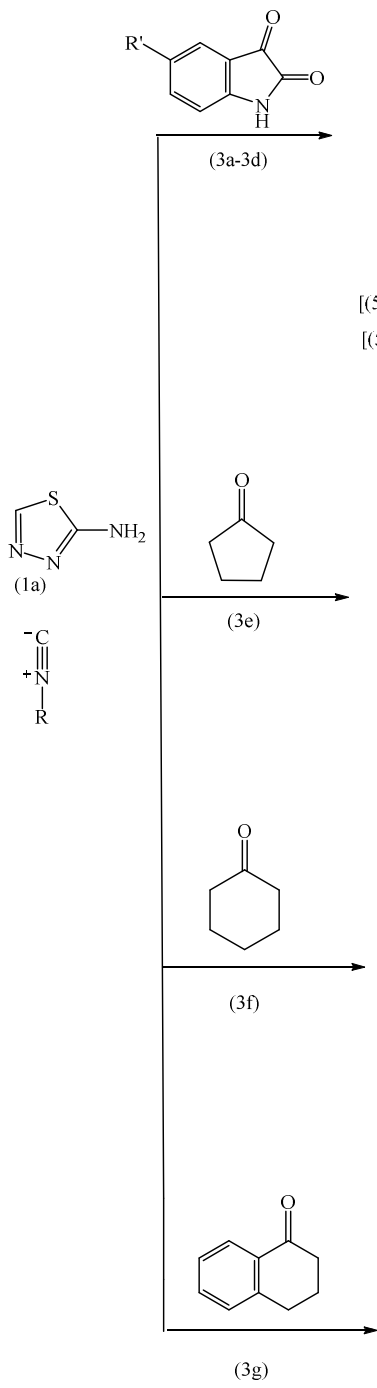
Table 5: Synthesis of spirooxindoles spiroannulated with imidazobenzothiazole^a

		Product	Time (Hrs)	Yield(%) ^b
<p>(1a)</p> <p>(3a-3d)</p> <p>[(4a-4d); R = C₆H₁₁-; R' = H, Br, F, NO₂] [(4e-4f); R = C₄H₉-; R' = H, Br, F, NO₂]</p>		4a	3	94
		4b	2.5	95
		4c	2.5	96
		4d	2	96
		4e	3.15	92
		4f	3	94
		4g	2.5	94
		4h	2	96
<p>(1a)</p> <p>(3e)</p> <p>[(4i); R = C₆H₁₁-] [(4j); R = C₄H₉-]</p>		4i	3.5	90
		4j	3.5	92
		4k	3.5	90
		4l	3.5	90
<p>(1a)</p> <p>(3f)</p> <p>[(4k); R = C₆H₁₁-] [(4l); R = C₄H₉-]</p>		4k	3.5	90
		4l	3.5	90
<p>(1a)</p> <p>(3g)</p> <p>[(4m); R = C₆H₁₁-] [(4n); R = C₄H₉-]</p>		4m	2.5	91
		4n	3	92

^a Reaction conditions: 2-aminobenzothiazole (1 mmol), cyclohexyl isocyanides (1 mmol), and simple isatin (1 mmol); catalyst: TiO₂ NPs (15 mol %); Solvent: 2.0 mL aqueous ethanol (ethanol: water: v:v/2:3); Temperature: 90°C.

^b Isolated yields after purification.

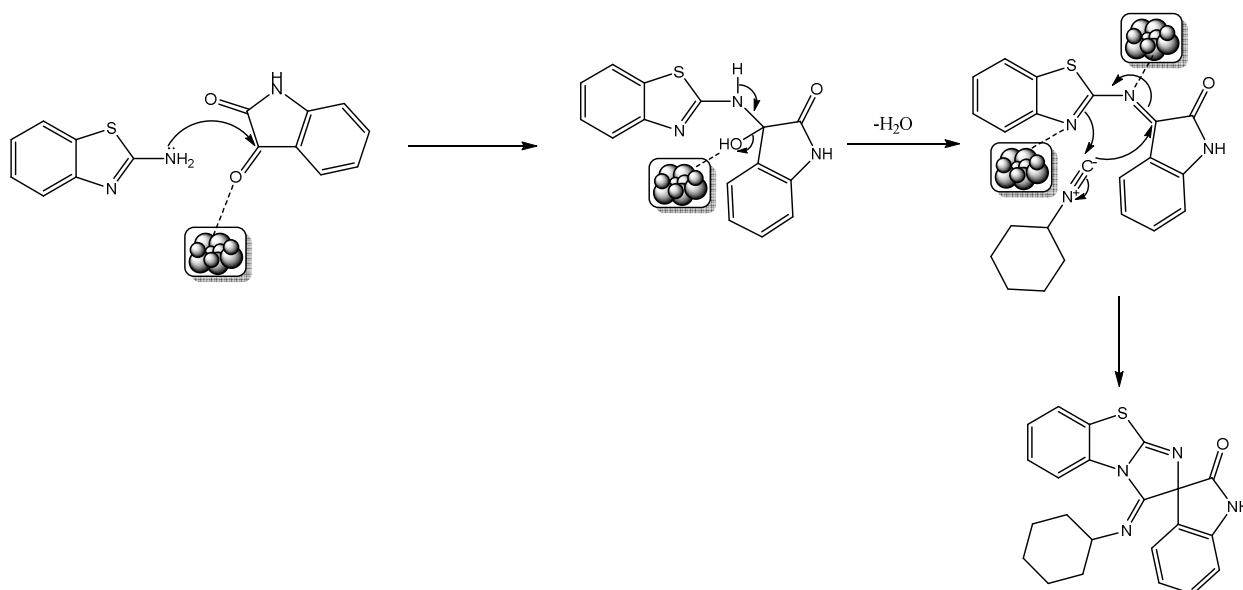
Table 6: Synthesis of spirooxindoles spiroannulated with imidazothiadiazole^a

		Product	Time (Hrs)	Yield
	(3a-3d)	5a	3.5	92
		5b	3	93
		5c	3	92
		5d	3	94
		5e	4	90
		5f	3.5	91
		5g	3	93
		5h	3	94
	(3e)	5i	4	88
		5j	4	90
	(3f)	5k	3.5	90
		5l	3.5	91
	(3g)	5m	3.15	92
		5n	3.5	93

^a Reaction conditions: 2-amino-1,3,4-thiadiazole (1 mmol), cyclohexyl isocyanides (1 mmol), and simple isatin (1 mmol); catalyst: TiO₂ NPs (15 mol %); Solvent: 2.0 mL aqueous ethanol (ethanol: water: v:v/2:3); Temperature: 90°C.

^b Isolated yields after purification.

A proposed mechanism for the formation of the products is presented in scheme 2. In the first step, nucleophilic attack of amino group of 2-aminobenzothiazole is facilitated on carbonyl carbon by coordination of TiO_2 nanoparticles with carbonyl oxygen of isatin with the formation of imine intermediate. Nucleophilic attack of endocyclic nitrogen of benzothiazole moiety on carbon of cyclohexyl nitrile group and simultaneous attack of cyclohexyl nitrile carbon on imino carbon of imine intermediate provides the desired product involving cyclization.



Scheme 2: Plausible mechanism

2 Experimental

2.1 General procedure

The melting points of all the synthesized compounds were determined on electric melting point apparatus and are uncorrected. 2-aminobenzothiazole/2-amino-1,3,4-thiadiazole, cyclohexyl/tertiary butyl isocyanides and isatines/cyclic carbonyl compounds used in the synthesis of complex heterocycles were purchased from the commercial sources and were used as such. The purity of all the synthesized compounds was checked by TLC. IR spectra were recorded on Shimadzu 8400S FTIR spectrometer. ^1H NMR and ^{13}C NMR were recorded on Bruker 300MHz and 75MHz NMR spectrometer, respectively. Analytical and spectral data of the synthesized heterocycles are also included.

2.2. Typical procedure for synthesis of TiO₂ Nanoparticles

TiO₂ nanoparticles were synthesized using chemical precipitation method. Titanium (III) chloride (TiCl₃) was mixed with ammonium hydroxide (NH₄OH) aqueous solution in 1:3 v/v ratio respectively. Resultant solution was stirred for 48 h at room temperature. White precipitate was formed. Precipitate was separated by centrifuging the solution. In order to remove side products precipitate was washed 3-4 times with isopropyl alcohol and dried at room temperature.

2.3. Typical procedure for synthesis of spiroquinazolinones

A mixture of 2-aminobenzothiazole/2-amino-1,3,4-thiadiazole (1mmol), cyclohexyl/tertiary butyl isocyanides (1mmol) and isatines/cyclic carbonyl compounds (1mmol) and TiO₂ nanoparticles (15 mol %) in 2.0 mL aqueous ethanol (ethanol: water: v:v/2:3) was stirred at 90°C for about 2 to 4 hrs. After the completion of the reaction (monitored by TLC), the catalyst was recovered by filtration. The synthesized compounds were purified by column chromatography (silica gel as stationary phase, hexane-ethyl acetate (7:3) as eluent). The catalyst was reused for the next reactions after washing it with diethyl ether.

The analytical and spectral data of representative compounds have been presented and the analytical and spectral data of all the synthesized compounds are included in the supplementary section of the paper.

Compounds names and spectral details

1. **3-(Cyclohexylimino)-3*H*-spiro[benzo[*d*]imidazo[2,1-*b*]thiazole-2,3'-indolin]-2'-one (4a).** M.p. 180-182°C. IR (KBr) (ν_{\max} cm⁻¹): 3350 (NH), 2930 (CH), 1670 (CO), 1655 (ArH), 1550 (ArH), 1225 (C-N). ¹H NMR (DMSO-*d*₆) δ (ppm): 1.45-1.92 (m, 10H, CH₂), 4.10-4.22 (m, 1H, CHN=C), 6.75-7.75 (m, 8H, ArH), 10.74 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ (ppm): 24.5, 25.6, 33.4, 58.6, 84.5, 116.3, 119.7, 122.2, 123.4, 124.7, 125.8, 127.1, 127.6, 128.4, 129.3, 142.3, 146.2, 158.9, 165.2, 169.6. Anal. calcd. For C₂₂H₂₀N₄OS: C 68.02, H 5.19, N 14.42%; found: C 67.94, H 5.11, N 14.36 %.

3-(Tert-butylimino)-3*H*-spiro[benzo[*d*]imidazo[2,1-*b*]thiazole-2,3'-indolin]-2'-one (4e). m.p. M.p. 175-177°C. IR (KBr) (ν_{\max} cm⁻¹): 3350 (NH), 2926 (CH), 1670 (CO), 1645 (ArH), 1550 (ArH), 1225 (C-N). ¹H NMR (DMSO-*d*₆) δ (ppm): 1.01 (s, 9H, CH₃), 6.56-7.65 (m, 8H, ArH), 10.74 (s, 1H, NH). ¹³C NMR (DMSO-*d*₆) δ (ppm): 30.6,

62.4, 84.9, 116.3, 119.8, 122.4, 123.4, 124.7, 125.8, 127.2, 127.8, 128.5, 129.3, 142.3, 146.2, 158.9, 165.4, 169.6.

Anal. calcd. For $C_{20}H_{18}N_4OS$: C 66.28, H 5.01, N 15.46 %; found: C 66.22, H 4.92, N 15.37 %.

3-(Cyclohexylimino)-3*H*-spiro[benzo[*d*]imidazo[2,1-*b*]thiazole-2,1'-cyclopentane]-(4i) M.p. 166-168°C. IR (KBr) (ν_{\max} cm^{-1}): 2845-2930, 1655, 1550. ^1H NMR (DMSO- d_6) δ (ppm): 1.45-1.92 (m, 18H, CH_2), 4.08-4.16 (m, 1H, $\text{CHN}=\text{C}$), 6.56-7.61 (m, 4H, ArH). ^{13}C NMR (DMSO- d_6) δ (ppm): 24.5, 25.6, 27.3, 33.4, 36.1, 59.4, 69.8, 120.2, 122.3, 123.6, 125.1, 127.5, 146.3, 158.9, 165.2. Anal. calcd. For $C_{19}H_{23}N_3S$: C 70.12, H 7.12, N 12.91 %; found: C 70.05, H 7.06, N 12.84.

3-(Cyclohexylimino)-3*H*-spiro[benzo[*d*]imidazo[2,1-*b*]thiazole-2,1'-cyclohexane]-(4k) M.p. 174-176°C. IR (KBr) (ν_{\max} cm^{-1}): 2848-2920, 1654, 1550. ^1H NMR (DMSO- d_6) δ (ppm): 1.45-1.92 (m, 20 H, CH_2), 4.08-4.20 (m, 1H, $\text{CHN}=\text{C}$), 6.56-7.61 (m, 4H, ArH). ^{13}C NMR (DMSO- d_6) δ (ppm): 24.3, 24.5, 25.6, 25.8, 32.7, 33.5, 59.1, 64.6, 120.3, 122.3, 123.5, 125.6, 127.4, 146.2, 158.8, 164.2. Anal. calcd. For $C_{20}H_{25}N_3S$: C 70.76, H 7.42, N 12.38 %; found: C 70.71, H 7.36, N 12.31.

3-(Cyclohexylimino)-3*H*-spiro[benzo[*d*]imidazo[2,1-*b*]thiazole-2,1'-tetrahydronaphthalene]-(4m) M.p. 187-189°C. IR (KBr) (ν_{\max} cm^{-1}): 2848-2920, 1655, 1550. ^1H NMR (DMSO- d_6) δ (ppm): 1.45-2.89 (m, 16 H, CH_2), 4.12-4.20 (m, 1H, $\text{CHN}=\text{C}$), 6.60-7.62 (m, 8H, ArH). ^{13}C NMR (DMSO- d_6) δ (ppm): 14.6, 24.5, 25.6, 30.1, 33.4, 35.4, 59.1, 73.5, 120.3, 122.8, 123.1, 125.2, 125.9, 126.8, 127.3, 136.2, 145.7, 146.3, 158.5, 165.2. Anal. calcd. For $C_{24}H_{25}N_3S$: C 74.38, H 6.50, N 10.84 %; found: C, H, N.

5-(Cyclohexylimino)-5*H*-spiro[imidazo[2,1-*b*][1,3,4]thiadiazole-6,3'-indolin]-2'-one. (5a) M.p. 205-207°C. IR (KBr) (ν_{\max} cm^{-1}): 3364 (NH), 2934 (CH), 1670 (CO), 1655 (ArH), 1550 (ArH), 1225 (C-N). ^1H NMR (DMSO- d_6) δ (ppm): 1.44-1.90 (m, 10H, CH_2), 4.12-4.25 (m, 1H, $\text{CHN}=\text{C}$), 7.10-8.05 (m, 5H, ArH), 10.78 (s, 1H, NH). ^{13}C NMR (DMSO- d_6) δ (ppm): 24.7, 25.6, 33.5, 58.3, 84.1, 116.3, 125.7, 127.1, 127.9, 129.3, 142.3, 148.7, 158.5, 164.8, 169.6. Anal. calcd. For $C_{17}H_{17}N_5OS$: C 60.16, H 5.05, N 20.63 %; found: C 60.08, H 4.98, N 20.55.

5-(Tert-butylimino)-5*H*-spiro[imidazo[2,1-*b*][1,3,4]thiadiazole-6,3'-indolin]-2'-one. (5e) M.p. 185-187°C. IR (KBr) (ν_{\max} cm^{-1}): 3361 (NH), 2932 (CH), 1670 (CO), 1651 (ArH), 1550 (ArH), 1224 (C-N). ^1H NMR (DMSO- d_6) δ (ppm): 1.03 (s, 9H, CH_3), 7.15-8.04 (m, 5H, ArH), 10.76 (s, 1H, NH). ^{13}C NMR (DMSO- d_6) δ (ppm): 30.6,

62.4, 84.4, 116.3, 125.6, 127.2, 127.9, 129.4, 142.3, 148.7, 158.4, 164.9, 169.6. Anal. calcd. For $C_{15}H_{15}N_5OS$: C 57.49, H 4.82, N 22.35 %; found: C 57.42, H 4.76, N 22.26.

3-(Cyclohexylimino)-3*H*-spiro[benzo[*d*]imidazo[2,1-*b*]thiadiazole-2,1'-cyclopentane]-(5i). M.p. 170-172°C. IR (KBr) (ν_{\max} cm^{-1}): 2850-2935, 1660, 1550. ^1H NMR (DMSO- d_6) δ (ppm): 1.44-1.90 (m, 18H, CH_2), 4.10-4.20 (m, 1H, $\text{CHN}=\text{C}$), 8.02 (s, 1H, ArH). ^{13}C NMR (DMSO- d_6) δ (ppm): 24.7, 25.5, 27.3, 33.5, 36.3, 58.9, 67.7, 148.7, 158.6, 164.8. Anal. calcd. For $C_{14}H_{20}N_4S$: C 60.84, H 7.29, N 20.27 %; found: C 60.72, H 7.21, N 20.17.

3-(Cyclohexylimino)-3*H*-spiro[benzo[*d*]imidazo[2,1-*b*]thiadiazole-2,1'-cyclohexane]-(5k). M.p. 174-176°C. IR (KBr) (ν_{\max} cm^{-1}): 2840-2922, 1660, 1550. ^1H NMR (DMSO- d_6) δ (ppm): 1.44-1.92 (m, 20 H, CH_2), 4.09-4.22 (m, 1H, $\text{CHN}=\text{C}$), 8.04 (s, 1H, ArH). ^{13}C NMR (DMSO- d_6) δ (ppm): 24.1, 24.7, 25.4, 25.8, 31.3, 33.6, 58.7, 63.8, 148.6, 158.5, 165.3. Anal. calcd. For $C_{15}H_{22}N_4S$: C 62.03, H 7.64, N 19.29 %; found: C 61.91, H 7.53, N 19.23.

3-(Cyclohexylimino)-3*H*-spiro[benzo[*d*]imidazo[2,1-*b*]thiadiazole-2,1'-tetrahydronaphthalene]-(5m). M.p. 183-185°C. IR (KBr) (ν_{\max} cm^{-1}): 2854-2920, 1656, 1550. ^1H NMR (DMSO- d_6) δ (ppm): 1.45-2.89 (m, 16 H, CH_2), 4.15-4.22 (m, 1H, $\text{CHN}=\text{C}$), 6.80- 8.03 (m, 5H, ArH). ^{13}C NMR (DMSO- d_6) δ (ppm): 14.6, 24.6, 25.7, 30.4, 33.3, 35.1, 59.0, 73.8, 125.2, 127.3, 136.4, 145.3, 148.5, 158.7, 165.3. Anal. calcd. For $C_{19}H_{22}N_4S$: C 67.42, H 6.55, N 16.55 %; found: C 67.34, H 6.48, N 16.48.

Conclusion

In conclusion, we have presented an efficient and environmentally benign isocyanide-based domino protocol for the synthesis of structurally diverse spiroheterocycles spiroannulated with imidazothiazole and imidazothiadiazole involving three-component reaction of 2-aminobenzothiazole/2-amino-1,3,4-thiadiazole, cyclohexyl/tert.- butyl isocyanides and isatines/cyclic carbonyl compounds catalyzed by recyclable and reusable nanocrystalline TiO_2 . The present synthetic protocol is probably the first report on isocyanide-based nanocatalyzed multicomponent synthesis of spiroheterocycles and offers several advantages such as operational simplicity with easy workup, shorter reaction times, excellent yields with superior atom economy and environmentally benign reaction conditions with the use of recyclable, reusable, non-toxic catalyst and aqueous ethanol as green solvent. Moreover, easy separation of the catalyst by simple filtration after completion of the reaction, and reusability of the catalyst for even 8 repeated reaction cycles (after simple calcinations treatment) make this protocol interesting for large scale synthesis.

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