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H_3PO_4/Al_2O_3 catalyzed IMCR : A Mild and efficient microwave-assisted Solvent-free Regioselective Synthesis of Imidazo[2,1-b]thiazole scaffold

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Abstract: A robust Solvent-free three-component protocol for the synthesis of imidazo-fused Imidazo[2,1-b]thiazole scaffold *via* microwave-assisted isocyanide based multicompound reaction catalyzed by Phosphoric acid supported on alumina (H_3PO_4/Al_2O_3) has been described. This is the first report of using H_3PO_4/Al_2O_3 catalyst for the Groebke- Blackburn- Bienayme reaction. The noteworthy characteristics of these catalytic procedures are shorter reaction times, high conversions, simple experimental, cleaner reaction, and easy work-up procedures. Phosphoric acid supported on alumina as catalyst can be reused several times without significant loss of its catalytic activity. This one step sequence provides diverse Imidazo[2,1-b]thiazole ring systems that have application in medicinal and material chemistry.

Keywords: Imidazo[2,1-b]thiazole derivatives, H_3PO_4/Al_2O_3 catalyst, Groebke- Blackburn- Bienayme reaction.

INTRODUCTION:

Thiazoles scaffold symbolize one of the most essential classes of biologically and pharmaceutical active compounds, and have been playing a pivotal role in modern medicinal chemistry. They also be present in various natural products and organic dyes.[1] Among these thiazoles derivatives, Imidazo[2,1-b] thiazole ring systems are one of the most attractive framework. Groebke- Blackburn-Bienayme (GBB) reaction is an important class of isocyanide based multicompound (MCR) name reaction employed widely for the synthesis of Imidazo[2,1-b]thiazole ring systems.[2] The Imidazo[2,1-b]thiazole ring systems that is the end product of Groebkee-Blackburne-Bienayme reaction is documented as a privileged structure. It represents a promising area for identification of lead structures towards the discovery of new synthetic drug molecules. Numerous bioactive molecules such as the 3-Methyl-5,6-diarylimidazo[2,1-b]thiazoles display anti-coccidia behaviour **(A)**.[3] Imidazo[2,1- b]

benzothiazoles demonstrate to be a good antibacterial and a excellent fluoro-probe in the positron emission tomography (PET) imaging analysis of Alzheimer's disease **(B)**.[4] 5,6-Diarylimidazo[2,1- b][1,3]thiazoles exhibit excellent antibacterial property **(C)** (Fig. 1).[5] In this framework, GBB reactions correspond to the one of the simplest route for the diversity-oriented synthesis of this pharmacophore.

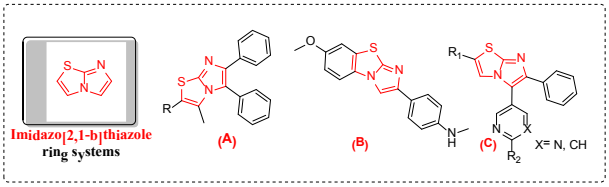


Figure 1. Some Biologically Active Imidazo[2,1- b]benzothiazoles and drug skeletal

Typically The GBB reaction is a , three-component, four-centre reaction, which necessarily involves a reaction among an aldehyde (1), thiazol-2-amine (2) and an isonitrile (3) in the existence of a suitable catalyst, which is generally a Bronsted acid or Lewis acid, to afford a highly substituted and fused **thiazoles** derivatives (4) (Fig. 2).

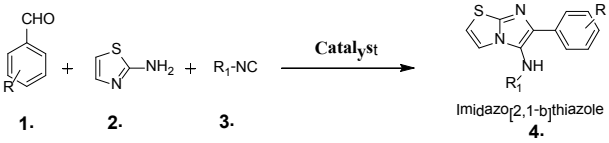


Figure 2. Groebke – Blackburn – Bienayme MCR

GBB reaction is the one pot multistep reaction, and it engage first condensation of amine substrates such as different type of 2-aminothiazoles and aldehydes to produce the imine in situ, which undergoes 5-endo cyclization to furnish the cyclized product with isocyanide respectively. This modification of the conventional reaction led to the synthesis of poly heterocyclic skeleton that mimics the natural products and drug. The GBB is elegantly catalyzed by presence of Bronsted acids such as AcOH,[6] $HClO_4$,[7] cellulose sulfuric acid,[8] p-toluene sulfonic acid[9]or Lewis acids such as $Sc(OTf)_3$,[10] $MgCl_2$,[11] $SnCl_2$,[12] $ZrCl_4$,[13] $ZnCl_2$,[14] $RuCl_3$,[15] and solvent free protocols like nanoparticle c-Fe2O3@–SiO2–OSO3H,[16] montmorillonite K10.[17]

However, numerous of these methodologies experience from drawbacks such as expensive reagents, long reaction time, harsh reaction conditions, presence of by-product, poor yield, tedious work-ups, inconvenient for industrial scale and complexity in isolation of products. Thus there is an ongoing quest for finding methodologies which are economically viable, simple to execute and produce desired compound with minimum side products.

During our continuous efforts on the development of novel green protocols, [18] have forced us to scrutinize an alternate proficient method for the synthesis of thiazole-fused polyheterocycles. Herein, we wish to report a green procedure for the synthesis of Imidazo[2,1-b]thiazole under microwave-assisted Solvent-free conditions by using Phosphoric acid supported on alumina (H_3PO_4/Al_2O_3) as catalyst under milder reaction conditions. The advance of cleaner methodology is a most important subject in green chemistry[19]. Among the numerous feature of green chemistry, the use of heterogeneous catalysts and substitution of volatile organic solvents with solvent-free reaction medium are of greatest concern [20]. Heterogeneous organic reactions and solvent-free reactions have a lot of advantages such as: low costs, reduced pollution, and effortlessness process, ease handling of catalyst, cleaner reactions, easier work up, decreasing corrosive problems, and reduced reaction times. Phosphoric acid supported Alumina was prepared by the mixing of alumina with phosphoric acid for the first time by Araujo et al.[21] So far to the best of our

knowledge, there are no reports on (H_3PO_4/Al_2O_3) catalyzed synthesis of thiazole -fused polyheterocycles derivatives *via* Groebke–Blackburn–Bienaymè reaction.

Materials and Methods

General experimental.

All reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with a 200, 300, 400 MHz spectrometers for ^{1}H NMR and 50, 75 MHz for ^{13}C NMR in deuterated solvents with TMS as internal reference (chemical shifts δ in ppm, coupling constant *J* in Hz.). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad singlet (br, s). Melting points were determined in open capillary tubes on an electrically heated block and are uncorrected. Mass spectra and HRMS were taken in the ESI positive ion mode. The reaction progress was routinely monitored by thin layer chromatography (TLC) on pre-coated silica gel plates. Column chromatography was performed over silica gel (230-400 flash). All compounds were characterized by TLC, ^{1}H NMR and ^{13}C NMR, MS and HRMS.

General procedure for the synthesis of Imidazo[2,1-b]thiazole polyheterocycles (4a-4l) derivatives and recyclability of the catalyst

To the solution of the aromatic hetero arylamine (1a, 1.06 mmol), benzaldehyde (2a, 1.06 mmol), and isocyanide (3a, 1.06 mmol) in 5 mol% **H_3PO_4/Al_2O_3 catalyzed** was introduced in 400 W microwave irradiation. The flask was attached to a 12 mm tip diameter probe and the reaction mixture was microwave irradiation at an ambient temperature for the specified period at 50% power of the processor and in a 4 s pulse mode till a solid product separates out. Completion of the reaction was monitored by TLC using n-hexane: ethyl acetate (7:3) as the eluent. All the reactions were regularly completed within 20-65 min. After completion of reaction, mixture was diluted with 10 ml of water and extracted with ethyl acetate (2× 10 ml). The organic layer containing desired product was evaporated under reduced pressure and the crude product was purified and recrystallised from ethanol. Aqueous layer was centrifuged to recover **H_3PO_4/Al_2O_3 catalyzed**. The recovered **H_3PO_4/Al_2O_3 catalyzed** was reused for the same experiment for over five cycles.

Characterization of compounds:

Compound 4a (N-(tert-butyl)-6-(3,4,5-trimethoxyphenyl)imidazo[2,1-b]thiazol-5-amine)

Semi-solid, Yield 91%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (d, *J* = 4.5 Hz, 1H), 7.29 (s, 2H), 6.75 (d, *J* = 4.5 Hz, 1H), 3.92 (s, 6H), 3.88 (s, 3H),1.13 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.9, 145.4, 139.6, 137.0, 130.5, 125.0, 117.8, 111.7, 104.4, 60.9, 56.1, 55.7, 30.4 ppm, HRMS (ESI) Calcd. for $C_{18}H_{24}N_3O_3S$ $[M+H]^+$ 362.1538 Found 362.15

Compound 4b (6-(2-bromophenyl)-N-(tert-butyl)imidazo[2,1-b]thiazol-5-amine)

Solid, Yield 79%, mp = 129-132 ^{0}C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (t, *J* = 8.1 Hz, 2H), 7.42- 7.34 (m, 2H), 7.21 (d, *J* = 6.6 Hz, 1H), 6.75 (s, 1H), 0.92 (s, 9H) pp; ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.1, 139.4, 136.6, 132.9, 132.6, 129.1, 127.4, 126.8, 122.5, 117.9, 111.6, 55.3, 29.9 ppm, HRMS (ESI) Calcd. for $C_{15}H_{17}BrN_3S$ $[M+H]^+$ 350.0326 Found 350.0342.

Compound 4c (6-(2-bromophenyl)-N-cyclohexylimidazo[2,1-b]thiazol-5-amine)

Semi-solid, Yield 82%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 6.3 Hz, 2H), 7.25-7.20 (m, 1H), 6.80 (d, *J* = 4.5 Hz, 1H), 2.70 (s, 1H), 1.68-1.51 (m, 5H), 1.12-0.99 (m, 5H) ppm;

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2, 139.5, 136.5, 132.9, 132.7, 132.6, 129.2, 127.3, 121.7, 117.1, 111.9, 57.1, 33.7, 25.4, 24.5 ppm, HRMS (ESI) Calcd. for $C_{17}H_{19}BrN_3S$ $[M+H]^+$ 376.0483 Found 376.0530.

Compound 4d (6-(2-bromophenyl)-N-butylimidazo[2,1-b]thiazol-5-amine)

Oily, Yield 88%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.8 Hz, 1H), 7.42-7.28 (m, 4H), 6.79 (d, *J* = 4.2 Hz, 1H), 2.88 (t, *J* = 6.6 Hz, 2H), 1.51-1.41(m, 2H), 1.25-1.17 (m, 2H), 0.80 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.1, 141.3, 139.5, 132.8, 132.7, 132.6, 129.2, 127.3, 123.1, 116.8, 112.1, 48.6, 32.2, 19.8, 13.7 ppm, HRMS (ESI) Calcd. for $C_{15}H_{17}BrN_3S$ $[M+H]^+$ 350.0327 Found 350.0339

Compound 4e (N-(tert-butyl)-6-(4-methoxyphenyl)imidazo[2,1-b]thiazol-5-amine)

Semi-solid, Yield 90%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, *J* = 4.2 Hz, 1H), 7.26 (s, 2H), 6.83 (d, *J* = 4.5 Hz, 1H), 3.91 (s, 3H),1.18 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8, 146.5, 138.6, 137.3, 132.5, 127.0, 117.2, 112.3, 108.3, 56.2, 53.7, 31.2 ppm, HRMS (ESI) Calcd. for $C_{16}H_{20}N_3OS$ $[M+H]^+$ 302.1327 Found 302.1321

Compound 4f (N-(tert-butyl)-6-(2-chlorophenyl)imidazo[2,1-b]thiazol-5-amine)

Solid, Yield 81%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (t, *J* = 8.4 Hz, 2H), 7.44- 7.36 (m, 2H), 7.24 (d, *J* = 6.6 Hz, 1H), 6.77 (s, 1H), 1.11 (s, 9H) pp; ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.3, 138.7, 135.1, 132.9, 132.4, 129.2, 128.2, 125.7, 123.5, 118.1, 111.7, 56.2, 29.6 ppm, HRMS (ESI) Calcd. for $C_{15}H_{17}ClN_3S$ $[M+H]^+$ 306.0832 Found 306.0830.

Compound 4g (N-(tert-butyl)-6-(4-chlorophenyl)imidazo[2,1-b]thiazol-5-amine)

Solid, Yield 84%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (t, *J* = 6.2 Hz, 2H), 7.40- 7.39 (m, 2H), 7.26 (d, *J* = 6.4 Hz, 1H), 6.69 (s, 1H), 1.11 (s, 9H) pp; ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.1, 141.4, 138.3, 134.4, 132.9, 128.1, 127.4, 125.3, 124.1, 120.3, 112.8, 56.7, 29.8 ppm, HRMS (ESI) Calcd. for $C_{15}H_{17}ClN_3S$ $[M+H]^+$ 306.0832 Found 306.0828.

Compound 4h (N-(tert-butyl)-6-phenylimidazo[2,1-b]thiazol-5-amine)

Solid, Yield 86%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64 (t, *J* = 7.2 Hz, 2H), 7.41- 7.38 (m, 2H), 7.22 (d, *J* = 6.6 Hz, 1H), 7.19 (s, 1H), 6.78 (s, 1H), 1.21 (s, 9H) pp; ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 142.8, 139.2, 134.0, 133.4, 129.8, 128.5, 126.3, 123.8, 120.3, 112.7, 60.2, 29.1 ppm, HRMS (ESI) Calcd. for $C_{15}H_{18}N_3S$ $[M+H]^+$ 272.1221 Found 272.1218.

Compound 4i (N-(tert-butyl)-6-(p-tolyl) imidazo[2,1-b]thiazol-5-amine)

Solid, Yield 82%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 2H), 7.59 (s, 2H), 7.24 (s, 1H), 6.80 (s, 1H), 1.19 (s, 9H) pp; ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 141.6, 139.8, 134.5, 133.0, 129.1, 128.2, 124.9, 122.2, 120.2, 111.8, 60.0, 57.3, 30.2 ppm, HRMS (ESI) Calcd. for $C_{16}H_{20}N_3S$ $[M+H]^+$ 286.1378 Found 286.1367.

Compound 4j (4-(5-(tert-butylamino) imidazo[2,1-b]thiazol-6-yl)benzonitrile)

Solid, Yield 68%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (dd, *J* = 8.4 Hz, 2H), 7.44 (s, 2H), 7.24 (d, *J* = 6.4 Hz, 1H), 6.78 (s, 1H), .98 (s, 9H) pp; ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 144.1, 139.8, 136.1, 132.4, 127.9, 127.2, 125.1, 123.4, 120.0, 114.5, 83.2 57.6, 29.8 ppm, HRMS (ESI) Calcd. for $C_{16}H_{17}N_4S$ $[M+H]^+$ 297.1174 Found 297.1170.

Compound 4k (N-(tert-butyl)-6-(4-fluorophenyl)imidazo[2,1-b]thiazol-5-amine)

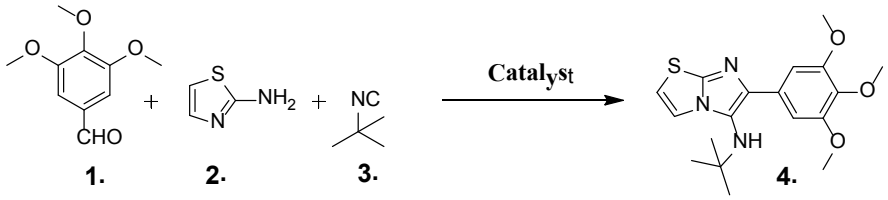
Solid, Yield 74 %, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64- 7.44 (m, 2H), 7.40- 7.39 (m, 2H), 7.31

(m, 1H), 6.72 (s, 1H), 0.89 (s, 9H) pp; ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4, 146.1, 142.1, 139.7, 136.5, 130.2, 128.4, 124.7, 121.6, 120.1, 111.6, 61.2, 29.9 ppm, HRMS (ESI) Calcd. for $C_{15}H_{17}FN_3S$ $[M+H]^+$ 290.1127 Found 290.1132.

RESULTS AND DISCUSSION:

The first step in the accomplishment of this goal was the convenient synthesis of Phosphoric acid supported Alumina. H_3PO_4/Al_2O_3 (50%w/w) was prepared according to the reported procedure (Zarei et al., 2009).[22] A set of experiments were carried out using 2-aminothiazole (1a, 1.06 mmol), 3,4,5-trimethoxybenzaldehyde (2a, 1.06 mmol), and t-butyl isocyanide (3a, 1.06 mmol) in solvent-free condition as a test reaction for optimum reaction conditions and the results are listed in Table 1. These were model substrate to optimize reaction conditions for the H_3PO_4/Al_2O_3 catalyzed Groebke–Blackburn–Bienaymè reaction, including temperature. No reaction occurred in the absence of catalyst at room temperature as well as microwave condition. Throughout the optimization of the reaction condition, the model reaction was also studied by varying microwave power (300, 400, and 500 W) and temperature. It was accomplished that 400 W power output at 60 ^{0}C was required to accomplish maximum conversion to product. However, when H_3PO_4/Al_2O_3 (10 mol %) was added at room temperature, the corresponding Imidazo[2,1-b]thiazole (4a) was obtained 50% yield in 88 min (Table 1, entry 2), but excellent result was achieved in microwave irradiation (Table 1, entry 3) . When loading of catalyst was decreased from 10 mol% to 5 mol%, lowering of the yield from 91% to 59% (Table 1, entry 6) was observed. Consequently, we chose 10 mol % H_3PO_4/Al_2O_3under solvent-free conditions at 60 ^{o}C with microwave as the optimized condition for additional study.

Table 1. Survey of the Reaction Condition for H_3PO_4/Al_2O_3 GBB catalyzed Reaction [a]

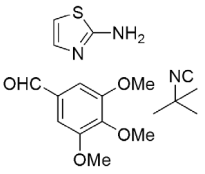
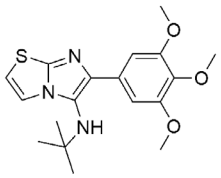
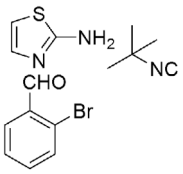
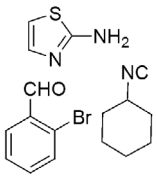
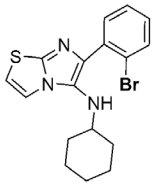
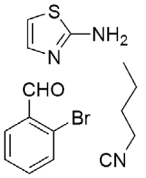
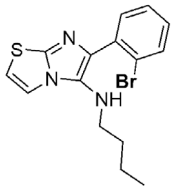
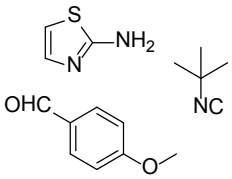
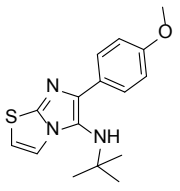


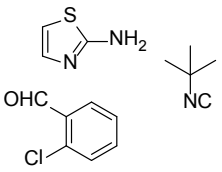
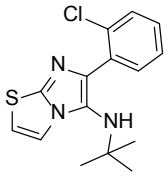
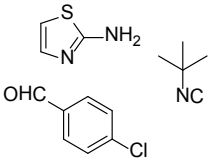
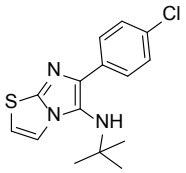
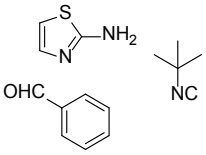
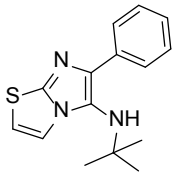
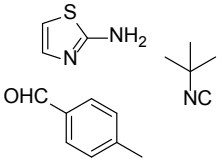
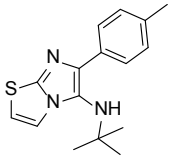
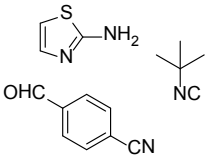
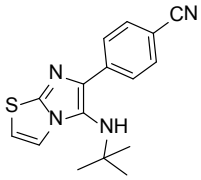
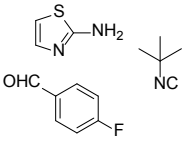
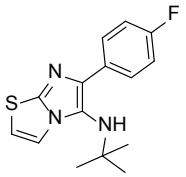
Entry	H_3PO_4/Al_2O_3 (50%w/w) **(mol %)**	**Temperature (^{O}C)**	**Time(min)**	**Yield % [b] (%)**
1.[c]	0	RT	90	0[c]
2.	10	RT	88	50
3.[d]	**5**	**MW heating conditions (400 W, 60 ^{O}C)**	**20**	**91**
4.	5	MW heating conditions (400 W, 60 ^{O}C)	45	89
5.	5	MW heating conditions (400 W, 100 ^{O}C)	50	67
6.	2	MW heating conditions (400 W, 60 ^{O}C)	64	59
7.	10	MW heating conditions (100 W, 60 ^{O}C)	35	90
8.	5	MW heating conditions (500 W, 60 ^{O}C)	38	81

[a]Reaction conditions: 1a (1.06 mmol), 2a (1.06 mmol), and 3a (1.06 mmol).
b Isolated yield after filtration through short pad of silica column.
c No catalyst used.
d Optimized condition.

Further, the optimized conditions equally applied for the synthesis of a wide variety of thiazole -fused polyheterocycles **4a-4t** (Table 2). All the products were purified by filtration through short pad of silica column. The products were confirmed by NMR spectroscopic techniques, FT-IR, and mass spectrometry.

Table 3. Synthesis of thiazole-fused polyheterocycles Product *via* H_3PO_4/Al_2O_3 catalyzed GBB Reaction [a]

Entry	Starting material	IMCR product [b] (4),	Time (min)	Yield% [c]
1.		 **4a**	**20**	**91**
2.		 **4b**	**40**	**79**
3.		 **4c**	**51**	**82**
4.		 **4d**	**48**	**88**
5.		 **4e**	**32**	**90**

6.		 **4f**	**35**	**81**
7.		 **4g**	**30**	**84**
8.		 **4h**	**44**	**86**
9.		 **4i**	**34**	**82**
10.		 **4j**	**65**	**68**
11.		 **4k**	**40**	**74**

[a]Reaction conditions: aminoazines 1 (1.06 mmol), aldehyde 2 (1.06 mmol), isocyanide 3 (1.06 mmol).
[b] Product was confirmed by 1H NMR, 13C NMR, and mass spectral analyses.
[c] Isolated yield after filtration through short pad of silica column.

Finally the stability and activity of the catalyst were tested in the recycle-use experiments. The **H_3PO_4/Al_2O_3 catalyzed** recycled for five times and it was found that during recycle experiments there was not much loss in yield of the product which shows the recyclability and reusability of catalyst without significant loss of its catalytic activity (Table 3).

Entry	Cycle	Yield%
1.	Ist	96
2.	IInd	90
3.	IIIrd	89
4.	IVth	86
5.	Vth	86

CONCLUSION:

In summary, we have reported a extremely efficient green approach for the synthesis of thiazole-fused polyheterocycles *via* microwave-assisted Groebke- Blackburn- Bienayme reaction catalyzed by **H_3PO_4/Al_2O_3 catalyzed**. This synthetic approach has various marvellous characteristics such as good yields, less reaction time, recyclability of catalyst and operational simplicity, ultimately foremost to a diverse array of medicinally-relevant Imidazo[2,1-b] thiazole ring systems.

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