



Original Research Article

TiCl₃-silica: A recyclable solid support for efficient synthesis of substituted imidazoles

Raju Subba^a, Hridaydip Ranjan Dasgupta^a, Bittu Saha^a, Gyan Chandra Pariyar^a, Abiral Tamang^b, Pranab Ghosh^{a,*}

^a Department of Chemistry, University of North Bengal, District-Darjeeling-734013, India

^b Department of Physics, Jadavpur University, Kolkata 700032, India

ARTICLE INFORMATION

Received: 30 August 2020

Received in revised: 2 October 2020

Accepted: 9 October 2020

Available online: 18 November 2020

DOI: [10.48309/JMNC.2021.1.3](https://doi.org/10.48309/JMNC.2021.1.3)

KEYWORDS

2, 4, 5-trisubstituted imidazoles

Solvent free

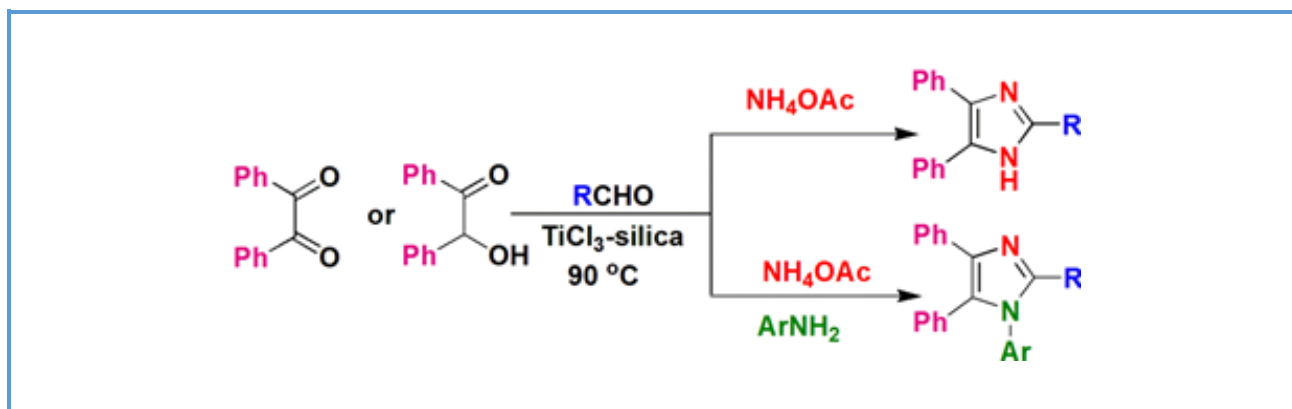
Recyclable

One-pot

ABSTRACT

In this research study, a library of highly substituted imidazoles were efficiently synthesized from benzil/benzoin, aldehydes and ammonium acetate *via* multicomponent solvent free one pot protocol on TiCl₃-silica solid catalyst. The general applicability of the solid support was assessed by the synthesis of wide varieties of imidazole derivatives. TiCl₃-silica solid catalyst was recycled, reused and found no loss of catalytic activity up to fifth consecutive reaction runs.

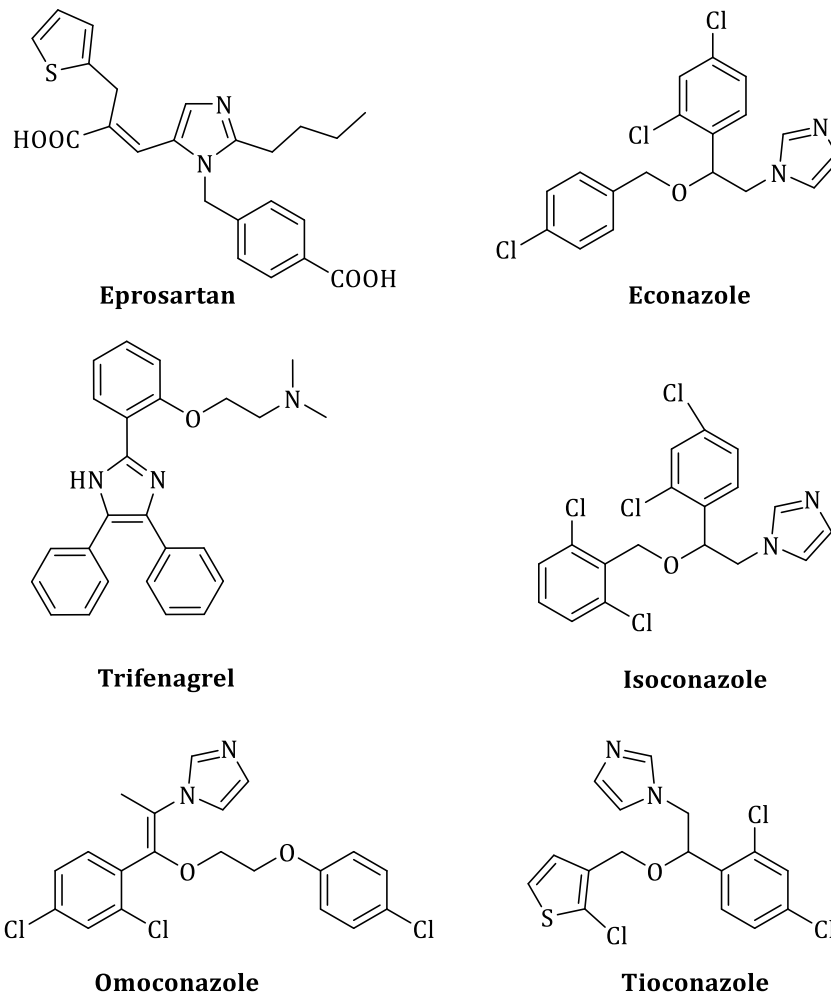
Graphical Abstract



Introduction

Imidazoles and their derivatives have long been recognized as important *N*-containing heteroaromatic compounds. Imidazoles are ample testimony to the worldwide distribution of these skeletons in many bioactive compounds including natural products [1]. Suitable derivatives of imidazole act as important precursor for the natural product synthesis [2]. Among them, multi substituted imidazole provides significant core structure used in medicinal chemistry due to their wide spectrum of biological activities (Scheme 1), such as glucagon receptor-antagonism [3], anti-allergic [4], anti-inflammatory [5], analgesic [6], cytotoxicity against several cancer cell lines [7].

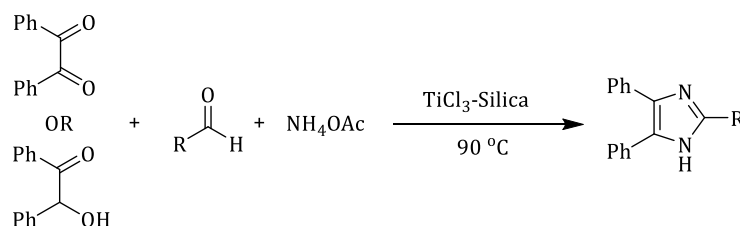
Trifenagrel [8] is a potent 2, 4, 5-triaryl imidazole that reduces platelet aggregation in several animal species and humans. In recent years, substituted imidazoles are substantially used as ionic liquid [9] and ligand to transition metals [10]. Despite of having numerous applications, more interestingly, imidazoles and self-assembled polymeric imidazole complexes show the excellent catalytic activities for the various organic transformation [11]. The derivatives of this heterocycle has been in other area of research such as biological imaging [12], fluorescence labelling agents [13] and chromophores for non-linear optics [14].



Scheme 1. Biologically potent imidazole derivatives

In view of the diverse biological, pharmacological and material properties associated with these derivatives, the development of more convenient synthetic protocol is highly encouraging for the present demand. In the last decades, the numbers of protocol have been developed for the synthesis of multisubstituted imidazoles by using diverse catalytic system, including silica gel or Zeolite HY [15], Cu(NO₃)₂-zeolite [16], HClO₄-SiO₂ [17], silica gel/NaHSO₄ [18], MoO₃-silica [19], TiCl₄-silica [20], silica-sulphuric acid [21], L-proline [22], K₅CoW₁₂O₄₀.3H₂O [23], heteropolyacids [24], molecular iodine [25], BF₃-SiO₂ [26], FeCl₃.6H₂O [27], InCl₃.3H₂O [28], ZrCl₄ [29], ionic liquids [30], NiCl₂.6H₂O/Al₂O₃ [31], CAN [32], PEG [33], DABCO [34], Fe₃O₄ nanoparticles [35], propylpiperazine-*N*-sulfamic acid [36], glycerol-based carbon catalyst [37], sulphated tin oxide [38], microwave irradiation [39], and refluxing in acetic acid [40]. The recent literature revealed that, the precursor other than 1, 2 diketone, alpha hydroxy ketone or aldehydes have been also utilized for the direct synthesis of substituted imidazole under different catalytic system [41].

However, the principal drawbacks of various reported protocols are non-recyclable solid support or catalyst, use of expensive reagents, metal contamination, highly moisture sensitive metal salts, large amount of catalyst loading, tedious workup procedure, which in turn results in the generation of large amount of toxic metal salts and solvents into the environment.

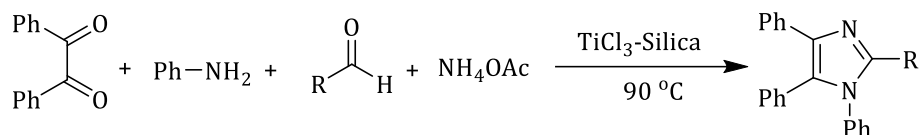


Scheme 2. Synthesis of 2, 4, 5-trisubstituted imidazole under solvent-free condition

A present research area is led by the development of environmental friendly protocol for the organic synthesis and transformations. In this context, researchers are devoting to developed protocol for solid phase-solvent free synthesis or the reaction in water. The major advantage of solid phase and aqueous media synthesis is no requirement of hazardous solvent which definitely reduce chemical pollution into the environment and in the same way, the cost of the work.

With this background, the development of new recyclable solid support to overcome these shortcomings and fulfil the criteria of mild, efficient and green protocol for the synthesis of these derivatives is an important task for the present demand of green and sustainable development. We report herein, one-pot synthesis of 2, 4, 5-trisubstituted imidazoles by multi-component reaction involving benzil/benzoin, aldehydes and NH₄OAc using a recyclable TiCl₃-silica solid support under solvent free condition (Scheme 2). The same solid support was found equally efficient for the synthesis of 1, 2, 4, 5-tetrasubstituted imidazole (Scheme 3).

The demand of titanium based solid support or catalyst in the area of organic synthesis and transformation is continuously increasing. In order to find a possible applications and exploring the use of titanium based solid support into wide prospective, we have carried out one-pot synthesis of substituted imidazole on TiCl₃-silica solid support without using any solvent.



Scheme 3. Synthesis of 1, 2, 4, 5-tetrasubstituted imidazole under solvent-free condition

Experimental

Materials and methods

The chemicals used in this work were purchased from the Sigma-Aldrich and the Loba Chemie. IR spectra were recorded on KBr disc in the range 4000-400 on Shimadzu FT-IR 8300 spectrometer. ^1H NMR and ^{13}C NMR were recorded on 300 MHz Bruker Avance FT-NMR Spectrometer using TMS as internal standard. SEM images were taken in inspect F50 SEM, SE detector R580, emission current during analysis was 163.2 micro ampere. Energy-dispersive X-ray spectroscopy (EDX) was recorded using a nano bruker, Xflash detector 410-M, bruker. Mass spectra were recorded on a JEOL-AccuTOF JMS-T100LC Mass Spectrometer.

Preparation of titanium-silica solid support: To a solution of TiCl_3 (0.25 mmol) in methanol (10 mL) at 70-80 °C, silica gel (1 g, 254 HF) was added. The mixture was allowed to stirrer at 70-80 °C for 5 h. The solvent was evaporated rotary evaporator and solid mass was kept in hot oven at 200 °C for 8 h and allowed to cool at room temperature and used for the desired transformation.

Reaction Procedure

Synthesis of 2,4,5- trisubstituted imidazole: benzil/benzoin (0.5 mmol), aldehyde (0.5 mmol) and ammonium acetate (2 mmol) were mixed intimately with titanium-silica (1.0 g). The mixture mixed intimately in motor and pestle. The resulting mixture was poured in round bottom flask (50 mL) and allowed to stir

on magnetic stirrer at 90 °C for appropriate time (Table 5). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3×15 mL) washed several times with water. The combined organic mixture was dried over anhydrous Na_2SO_4 , concentrated, and purified by column chromatography on silica gel 60-120 mesh using petroleum ether/ethyl acetate as eluent to afford pure compound.

Synthesis of 1, 2, 4, 5-tetrasubstituted imidazole: benzil (0.5 mmol), aldehyde (0.5 mmol), amine (0.5 mmol) and ammonium acetate (1 mmol) were mixed intimately with titanium-silica (1.0 g). The mixture was mixed intimately in motor and pestle. The resulting mixture was poured in round bottom flask (50 mL) and allowed to stir on magnetic stirrer at 90 °C for appropriate time (Table 6). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3×15 mL) washed several times with water. The combined organic mixture was dried over anhydrous Na_2SO_4 , concentrated, and purified by column chromatography on silica gel 60-120 mesh using petroleum ether/ethyl acetate as eluent to afford pure compound.

Catalyst recycling: After the completion of the reaction, the catalyst was washed with methanol (2×25 mL) followed by washing with water (2×25 mL) and the solid mass was kept in hot oven at 200 °C for 8 h. The resulting recycled solid support was used for the reactions.

Results and Discussion

In our initial studies towards the development of milder reaction conditions for the synthesis of these derivatives, TiCl_3 (0.25 mmol) and silica gel (silica gel HF 254) (1000 mg) were added successively in methanol (10 mL). The mixture was allowed to stir on magnetic stirrer at 70-80 °C for 5 h and then allowed to cool at room temperature, evaporated the solvent on rotary evaporator. The dried titanium based solid support was further activated by keeping in hot oven at 200 °C for 8 h and allowed to cool at room temperature and used for the desired transformation.

The model reaction comprising benzil (0.5 mmol), ortho hydroxy benzaldehyde (0.5 mmol) and ammonium acetate (2 mmol) on pure silica (1000 mg) at room temperature gives no yield in 15 h, only starting material was recovered. Further gradual increase in reaction temperature up to 100 °C furnishes no significant yield (Table 1).

Only trace amount of the desired product was formed when the same reaction was carried out on TiCl_3 -silica solid support at room temperature (Table 2). The gradual increase in temperature up to 90 °C found that the TiCl_3 -silica is catalyzing the reaction efficiently. The transformation is excellent at 90 °C (Table 2). It is clear from the (Table 1) and (Table 2) that the catalytic activity of the solid support is due to titanium incorporation. We attempted reusing the solid support to assess its efficiency for the second reaction run and found no significant loss of its activity. For the reusability of solid support, the product was extract from reaction mixture in ethyl acetate, washed the solid support by methanol (10×2 mL), several times by water and reactivated under vacuum at 200 °C for 8 h. The catalytic activity of used solid support were checked for five consecutive run

and found almost equally active for all consecutive runs (Table 3). The invariable catalytic activity after recycling indicates that no significant loss of titanium from solid support.

Table 1. Model reaction on pure silica^a

Entry	Temp (°C)	Time (h)	Yield (%) ^b
1	r.t	15	NR ^c
2	40	15	NR
3	60	10	NR
4	80	10	Trace
5	90	8	10-12
6	100	8	36

^aReaction of benzil (0.5 mmol), ortho hydroxy benzaldehyde (0.5 mmol) and ammonium acetate (2 mmol) in pure activated silica (1000 mg)

^bIsolated yield

^cNo reaction

Table 2. Optimization of temperature in presence of TiCl_3 -silica catalyst^a

Entry	Temperature (°C)	Time (h)	Yield (%)
1	r.t	4	Trace
2	40	4	18
3	60	4	38
4	70	4	57
5	80	4	76
6	90	4	92

^aReaction of benzil (0.5 mmol), orthohydroxy benzaldehyde (0.5 mmol) and ammonium acetate (2 mmol) on TiCl_3 -silica solid support under solvent-free condition

Table 3. Screening of catalyst recycling^a

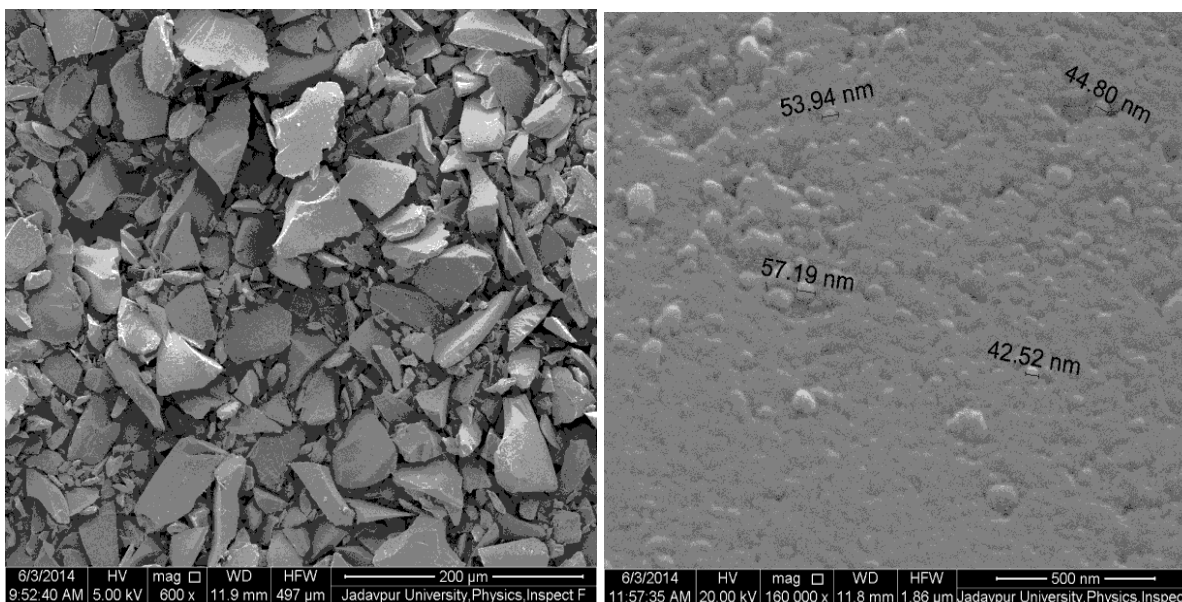
Entry	Time (h)	No. of runs	Yield (%) ^b
1	4	1	92
2	4	2	92
3	4	3	90
4	4	4	88
5	4	5	87

^aReaction of benzil (0.5 mmol), orthohydroxy benzaldehyde (0.5 mmol) and ammonium acetate (2 mmol) on TiCl_3 -silica solid support at 90 °C under solvent-free condition

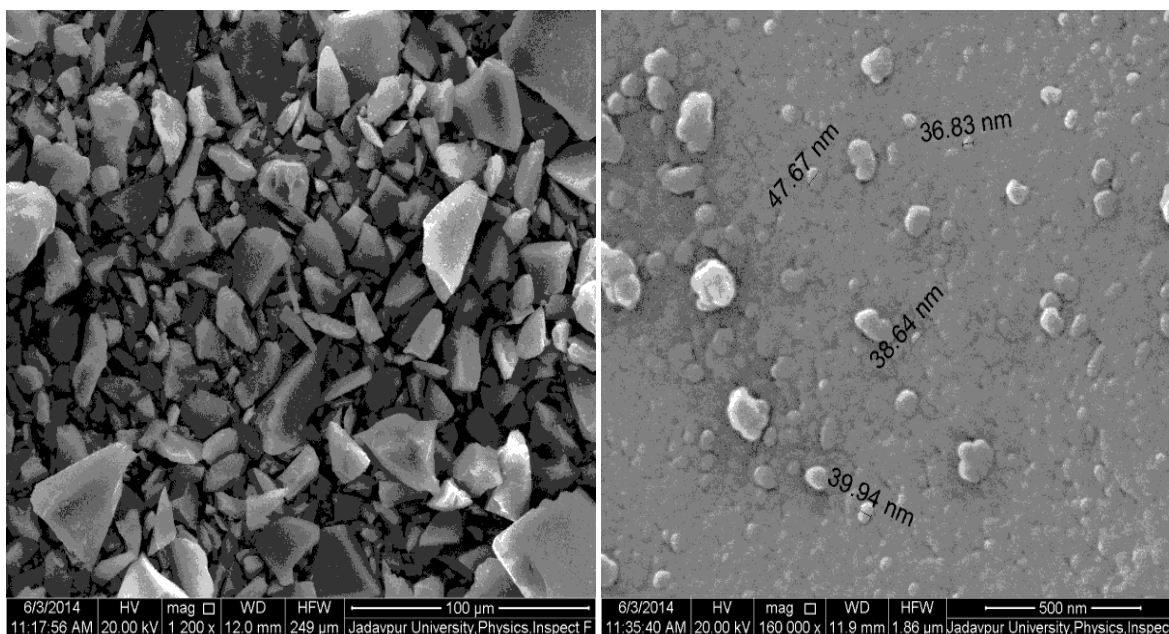
^bIsolated yield

As seen in Figure 1, the pure silica is converted into TiCl₃-silica. The SEM images of pure silica (Figure 1a), freshly prepared TiCl₃-silica (Figure 1b) and reused TiCl₃-silica (Figure 1c and 1d) were compared for the conformation. The dissimilarities in surface

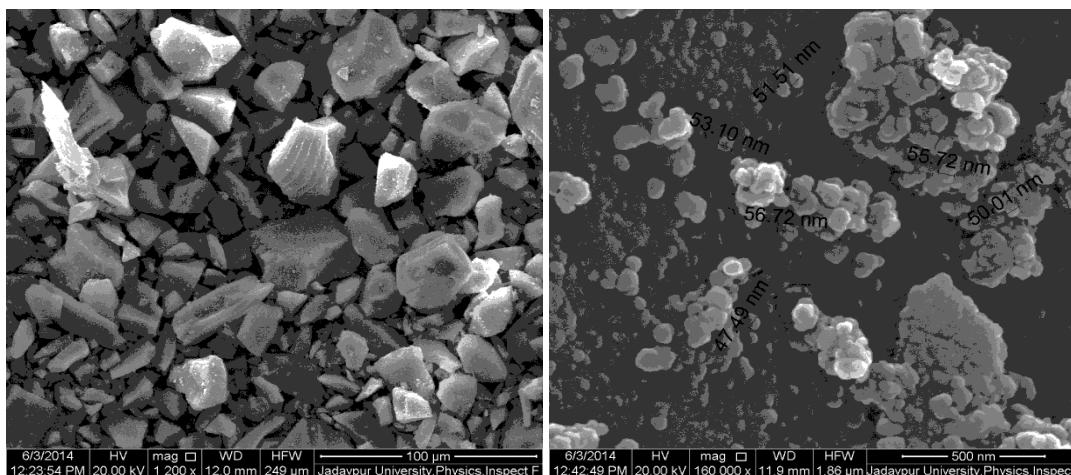
morphology of pure silica and TiCl₃-silica clearly indicate the incorporation of titanium in silica. The similar surface morphology of TiCl₃-silica on recycling up to five consecutive runs also signify no loss of titanium from TiCl₃-silica solid support.



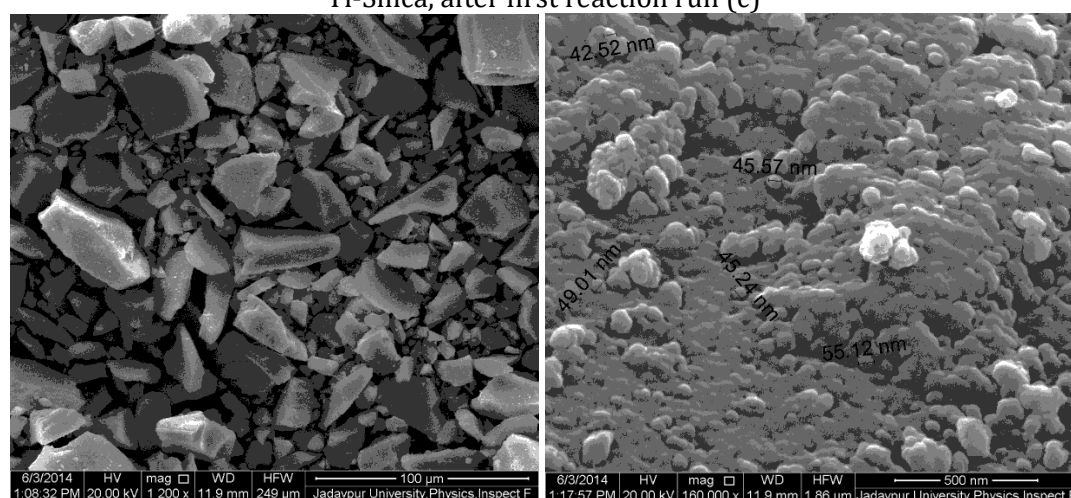
Silica (a)



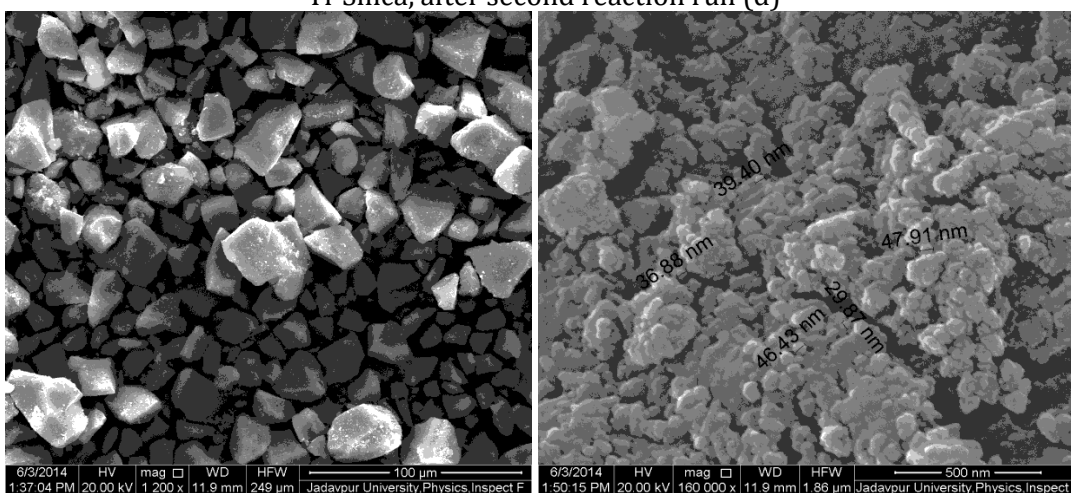
Freshly prepared Ti-Silica solid support (b)



Ti-Silica, after first reaction run (c)



Ti-Silica, after second reaction run (d)



Ti-Silica, after fifth reaction run (e)

Figure 1. SEM images of a) pure silica, b) freshly prepared Ti-Silica solid support, c) recycled Ti-Silica solid support after first reaction run, d) recycled Ti-Silica solid support after second reaction run, e) recycled Ti-Silica solid support after fifth reaction run

The further characterization by EDX point scan and elements mapping analysis clearly confirmed the incorporation of titanium into silica. The comparative EDX studies also revealed small leaching of titanium during recycling (Table 4). The EDX mapping and EDX comparative data of the pure silica (a) freshly prepared TiCl₃-silica (b) and recycled TiCl₃-silica provides an excellent evidence for the presence of titanium after recycled (Figure 2).

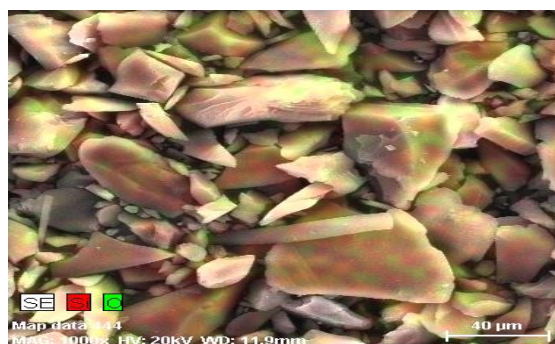
The small loss of titanium during recycle indicates the existence of strong interaction between titanium and silica.

Atom composition according to EDX measurements pure silica (a), freshly prepared Ti-Silica solid support (b), recycled Ti-Silica solid support after first reaction run (c), recycled Ti-Silica solid support after second reaction run (d), recycled Ti-Silica solid support after fifth reaction run (e).

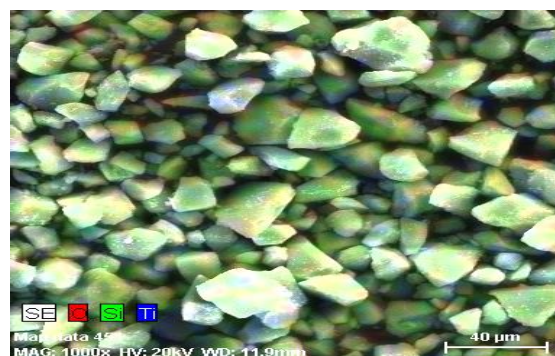
Table 4. Comparative profile of the atom compositions according to EDX measurements

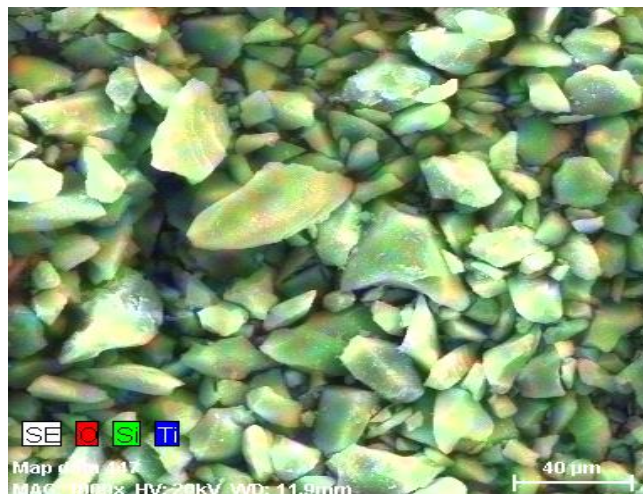
Support	Elements	Weight (%)	Atomic (%)	Total
Silica	O	53.26	66.67	100.00
	Si	46.74	33.33	
Fresh Si-Ti support	O	52.37	66.67	100.00
	Si	43.61	31.62	
	Ti	4.02	1.71	
Recycled Si-Ti support (second run)	O	52.43	66.67	100.00
	Si	43.81	31.73	
	Ti	3.77	1.60	
Recycled Si-Ti support (After fifth run)	O	52.70	66.67	100.00
	Si	44.78	32.27	
	Ti	2.52	1.06	

Elements mapping of pure silica (A-1)

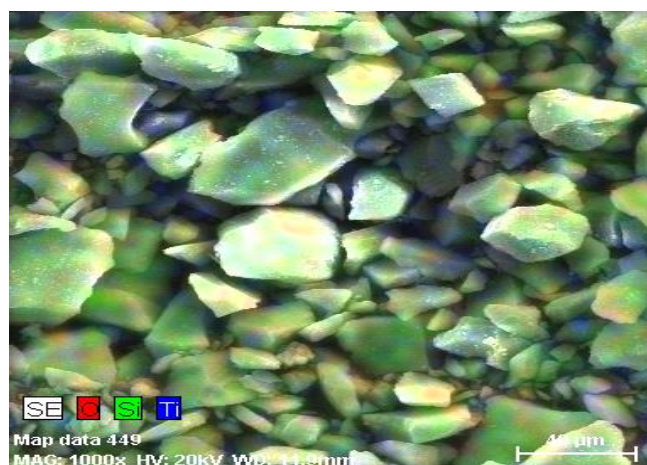


Freshly prepared Ti-Silica solid support (B-1)





Ti-Silica after second reaction run (C-1)



Ti-Silica after second reaction run (D-1)



Ti-Silica after fifth reaction run (E-1)

Figure 2. Elements mapping of pure silica (A-1), freshly prepared Ti-Silica solid support (B-1), recycled Ti-Silica solid support after first reaction run (C-1), recycled Ti-Silica solid support after second reaction run (D-1), recycled Ti-Silica solid support after fifth reaction run (E-1)

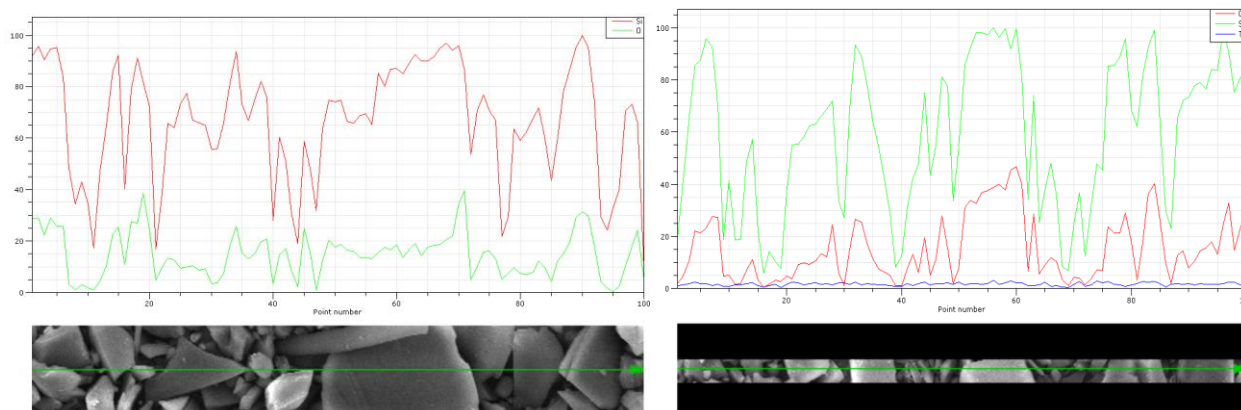
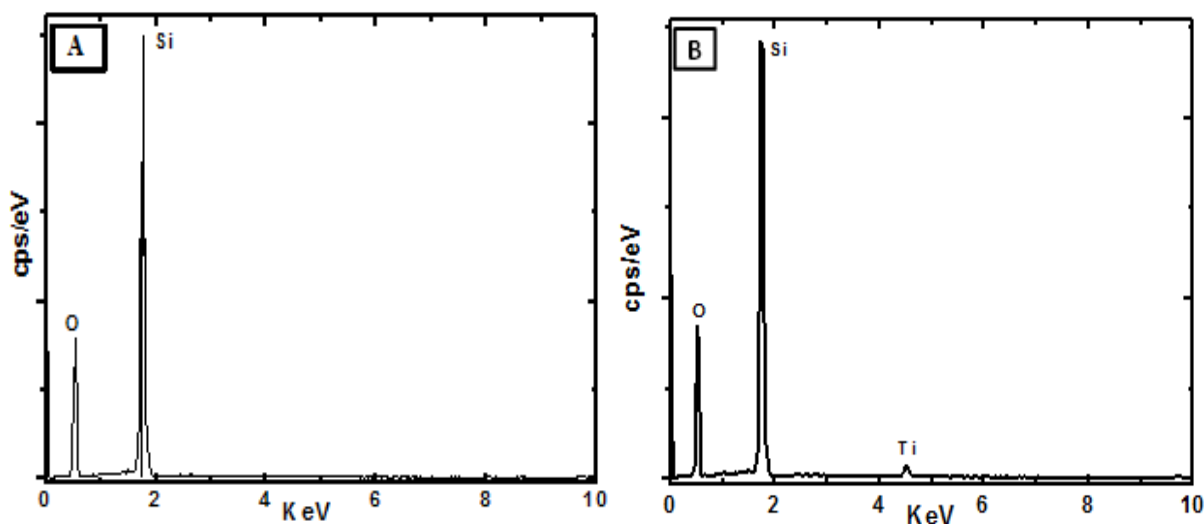


Figure 3. Line scanning of the sample indicates the uniform distribution of titanium in silica. Line scanning of silica indicating distribution of oxygen and silicon, (red line indicates silicon and green line indicates oxygen) (L-1). Line scanning of the Ti-Silica solid support after fifth reaction run, (green line indicates oxygen silicon, red line indicates oxygen and blue line indicates titanium) (L-2). Line scanning of silica indicating distribution of oxygen and silicon (L-1), Ti-Silica solid support after fifth reaction run (L-2)

The general applicability of the solid support was examined by the synthesis of wide varieties of imidazole derivatives. The synthesis were carried out by taking benzil/benzoin (0.5 mmol), aldehyde (0.5 mmol) and NH₄OAc (2 mmol) on freshly prepared TiCl₃-silica (1000 mg) at 90 °C under solvent free condition. The

results are summarized in Table 5. No loss of catalytic activity was found up to 30 days from the day of preparation of solid support. The solid support is also used to synthesized the 1, 2, 4, 5-tetrasubstituted imidazole (Scheme 3) and found equally efficient for their synthesis (Table 6).



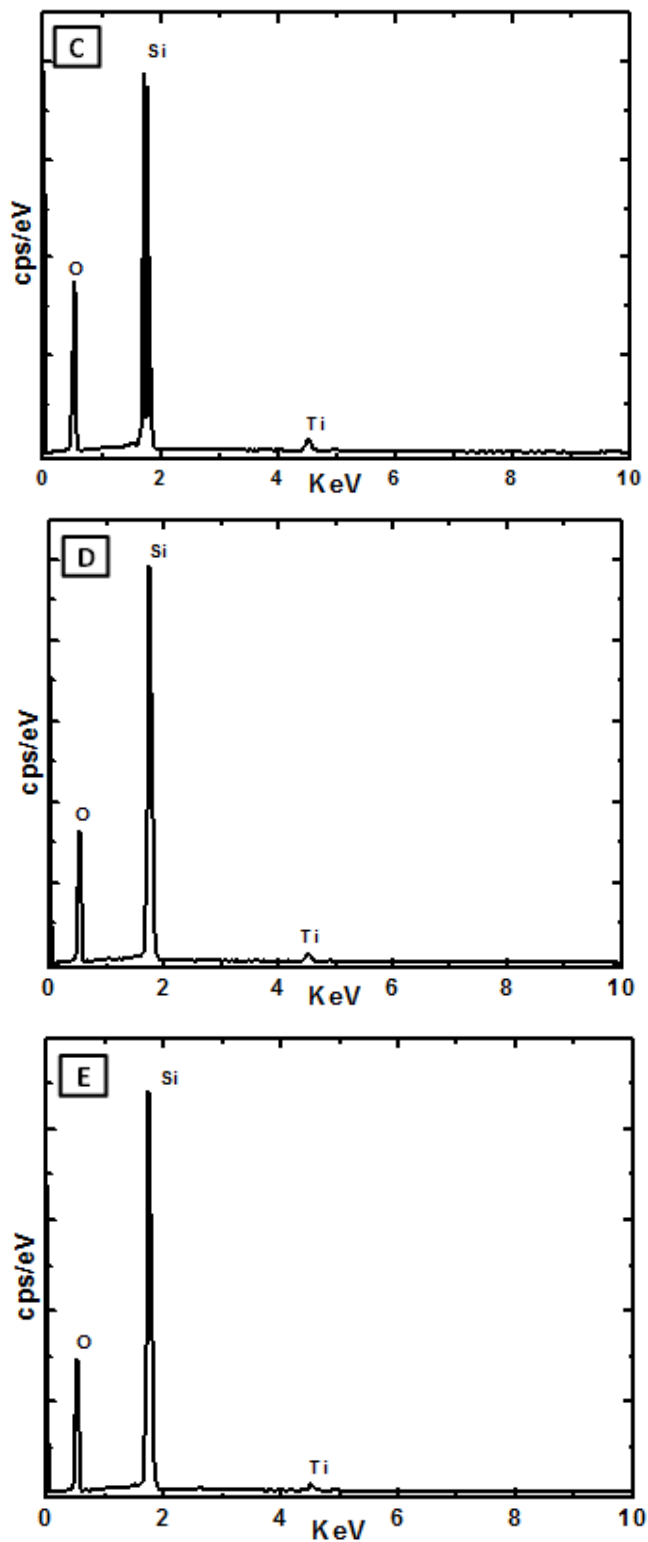
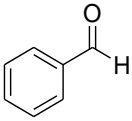
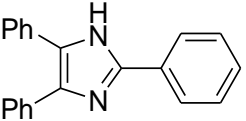
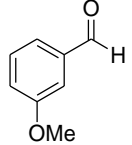
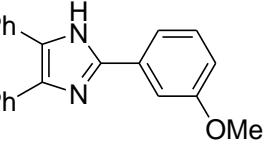
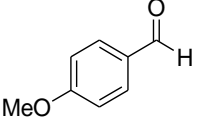
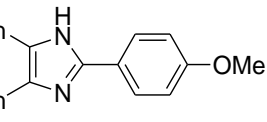
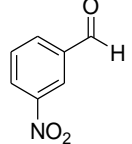
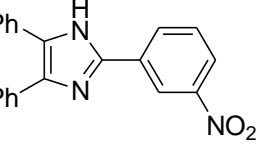
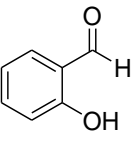
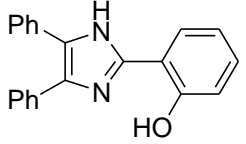
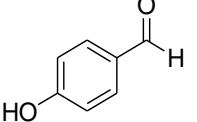
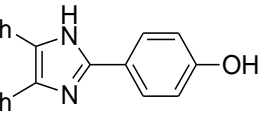
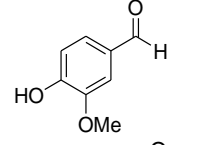
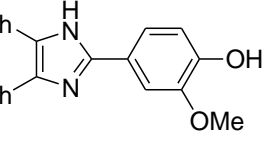
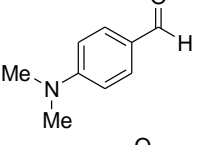
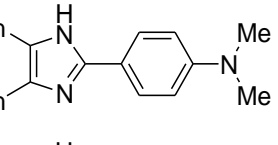
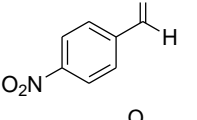
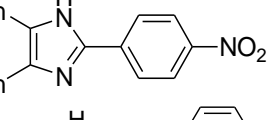
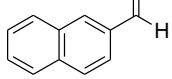
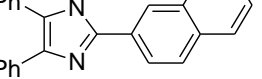
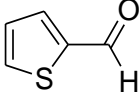
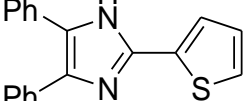


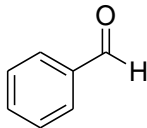
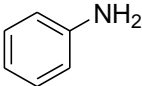
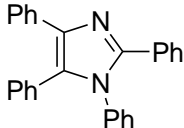
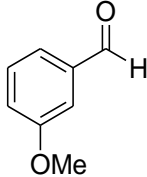
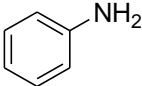
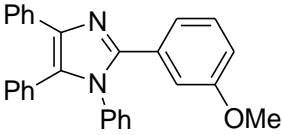
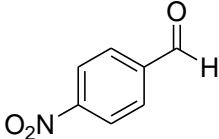
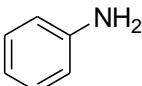
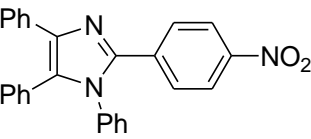
Figure 4. EDX measurement data of pure a) silica, b) freshly prepared Ti-Silica solid support, c) recycled Ti-Silica solid support after first reaction run, d) recycled Ti-Silica solid support after second reaction run, e) recycled Ti-Silica solid support after fifth reaction run

Table 5. Synthesis of 2,4,5-trisubstituted imidazole

Entry	Aldehyde	Amine	Time (h)		Product	Yields (%) ^b	
			Benzil	Bezoïn		Benzil	Bezoïn
a		NH ₄ OAc	4	6		94	91
b		NH ₄ OAc	5	6		91	90
c		NH ₄ OAc	5	6		90	88
d		NH ₄ OAc	4	5		93	91
e		NH ₄ OAc	4	5		92	88
f		NH ₄ OAc	5	6		87	86
g		NH ₄ OAc	6	8		84	82
h		NH ₄ OAc	6	8		89	86
i		NH ₄ OAc	4	5		90	88
j		NH ₄ OAc	4	5		89	84
k		NH ₄ OAc	4	5		74	68

^bIsolated yield

Table 6. Synthesis of 1,2,4,5-tetrasubstituted imidazole

Entry	Aldehyde	Amine	Amine	Product	Yield (%) ^b
a		NH ₄ OAc			88
b		NH ₄ OAc			86
c		NH ₄ OAc			90

^bIsolated yield

Conclusions

Our investigation established an efficient, solvent free and a green protocol for highly substituted imidazoles. The protocol was found to be broadly applicable to wide varieties of aldehydes having different functional groups, without any significant variation in yield. The stability and recyclability of the solid support made the present investigation greatly advantageous.

Acknowledgements

One of the authors (R.S) is grateful to CSIR New Delhi for financial support.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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How to cite this manuscript: Raju Subba, Hridoydip Ranjan Dasgupta, Bittu Saha, Gyan Chandra Pariyar, Abiral Tamang, Pranab Ghosha*. *TiCl₃-silica: A recyclable solid support for efficient synthesis of substituted imidazoles. Journal of Medicinal and Nanomaterials Chemistry*, 3(1) 2021, 31-45. DOI: [10.48309/JMNC.2021.1.3](https://doi.org/10.48309/JMNC.2021.1.3)