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Mesoporous titanosilicate Ti-TUD-1 catalyzed Knoevenagel reaction: An efficient green synthesis of trisubstituted electrophilic olefins

Bikash Karmakar[a], Biswajit Chowdhury[b,*], Julie Banerji[a,*]

[a] Centre of Advances Studies on Natural Products including Organic Synthesis, Department of Chemistry, University of Calcutta, 92, A.P.C. Road, Kolkata 700 009, India
[b] Department of Applied Chemistry, Indian School of Mines University, Dhanbad 826 004, India

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ABSTRACT

A new, efficient and green methodology has been developed for the Knoevenagel condensation using catalytic amount of mesoporous titanosilicate catalyst Ti-TUD-1, under mild conditions at room temperature. The method generates trisubstituted electrophilic olefins in high yields within short reaction time. The mesoporous nature of the catalyst having high surface area helps in binding the substrate to the active site. The advantage of this catalyst is its reusability with almost consistent reactivity thereby making it viable for industrial applications.

1. Introduction

In recent times attention has been focused on the development of eco-friendly solid acid/base catalysts for organic synthesis. The advantage of these catalysts lies in their high atom efficiency, extreme selectivity and simple work-up procedure without generating any organic waste. Development of catalysts for C–C bond formation in organic synthesis following green approach always provides a challenge. One such example is the versatile Knoevenagel condensation reaction [1,2], a useful method for the synthesis of active dipolarophiles which finds application in 1,3-cycloaddition reactions [3]. The reaction also has wide application in the synthesis of drugs [4], polymer sciences [5], and natural products [6].

The classical Knoevenagel condensation involves the condensation of aldehydes/ketones with active methylene compounds in the presence of organic bases like pyridine, piperidine and ethylenediamine [7–9]. Normally malononitrile, cyanoesters, β-ketoesters, malonic acids, malonates are used as the active methylene components containing two electron withdrawing groups (EWG). However, the procedure results in a large amount of organic wastes due to polymerization and self condensation reactions. Hence, comes the necessity and importance of developing a clean and environment friendly catalytic methodology. Supported porous solid acids would be an effective solution of the problem. In continuation to our exploration of green synthetic methodology using porous solids [10,11], we would like to report here the efficiency of the mesoporous titanosilicate catalyst Ti-TUD-1 [12,13] towards the classical Knoevenagel condensation reaction. The catalyst has high surface area and Ti, being in a highly dispersed state on the silica surface, is catalytically highly active. We are the first to report the use of this catalyst in the Knoevenagel condensation reactions at room temperature with high selectivity and quantitative yields (Scheme 1).

2. Experimental

2.1. General

The NMR spectra (^{1}H and ^{13}C NMR) were recorded on a Bruker Avance 300 MHz and Bruker Avance 75.5 MHz spectrometer and TMS was used as the internal standard. Infrared spectra were recorded in KBr pellet in reflection mode with a Perkin–Elmer RX-1 FT-IR spectrophotometer. X-ray powder diffraction study was carried out on a Philips PW-1830 X-ray diffractometer at a voltage of 35 kV and a current of 25 mA using Cu $K\alpha$ radiation ($\lambda = 154$ nm) at the scanning rate of 1°/min in the 2θ range 0–5° and 10–70°. SEM was performed with a Hitachi-S 3400N microscope at an operating voltage of 15 kV. The sample was coated with gold for effective imaging before being charged. TEM images were obtained from a JEOL JEM-2100 Transmission Electron Microscope at an operating

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* Corresponding authors. Tel.: +91 326 223 5663; fax: +91 326 222 4072 (B. Chowdhury), tel.: +91 33 2350 8386; fax: +91 33 2351 9755 (J. Banerji).
E-mail addresses: biswajit_chem2003@yahoo.com (B. Chowdhury), juliebanerji47@gmail.com (J. Banerji).

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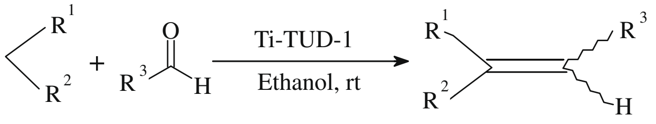


R^1,R^2 = CN; R^3 = Aryl, Cinnamyl, Furoyl

Scheme 1. Knoevenagel condensation reaction.

voltage of 100 kV. The sample was prepared by placing one drop of the dispersed solution of the catalyst in acetone as solvent on a carbon coated copper grid followed by drying over air. The emission fluorescence spectrum was recorded on a Perkin–Elmer spectrophotometer. Melting points (uncorrected) were determined on a Koffler Block apparatus. Synthetic grade chemicals from Acros and E-Merck were used for the preparation of the catalyst and from Spectrochem for carrying out the organic reactions. Analytical TLC was performed using E-Merck aluminium-backed silica gel plates coated with silica gel G. For column chromatography 60–120 mesh silica gel was used from Merck. All the solvents used in the reaction were distilled and dried over Na_2SO_4.

2.2. Catalyst preparation

The mesoporous titanosilicate Ti-TUD-1 was prepared following a simple and modified synthetic procedure. Modifications were done in terms of tuning of porosity development mechanism where a non-hydrothermal sol–gel technique was used and higher content of structure directing template. Tetraethyl orthosilicate (TEOS) and titanium (IV) butoxide were used as the precursor for silica and titanium, respectively. In the typical procedure titanium butoxide was added slowly to the TEOS solution. A mixture of triethanolamine (TEA) and water was added to a stirring solution and then triethyl ammonium hydroxide (TEAOH) (20% aqueous solution) was added dropwise to pH 10. The final molar ratio of the reagents was 1.0 SiO_2:m TiO_2 (m = 0.01, 0.03, 0.05):3.0 TEA:0.3 TEAOH:15 H_2O. The clear solution was aged for 24 h at room temperature. It was then dried at 115 °C for 16 h and finally calcined at 700 °C for 12 h at the rate of 2 °C/min under the flow of air. The nature of the as synthesized calcined product was glassy crystalline.

2.3. Typical reaction procedure

The aldehyde (0.2 g, 1.0 equiv.) and active methylene compound (0.14 g, 1.1 equiv.) were taken in a 50 mL round bottom flask. Five millilitres solvent was added and stirred at room temperature. Then the catalyst (0.02 g) was added and stirring was continued under normal atmosphere till the starting materials were no longer present (by TLC technique). The reaction mixture was separated from the catalyst by centrifugation. After drying under vacuum, the crude product was purified by column chromatography using 60–120 mesh silica gel and appropriate mixture of ethyl acetate/hexane as eluent. The purified products were characterized by IR spectroscopy, ^{1}H NMR and ^{13}C NMR spectrometry and elemental analysis.

3. Results and discussion

3.1. Characterization of the catalysts

Mesoporous Ti-TUD-1 (Ti/Si mole ratio = 0.01, 0.03, 0.05, referred to as catalysts Ti-1-TUD-1, Ti-3-TUD-1, Ti-5-TUD-1, respectively) catalysts were prepared by non-hydrothermal sol–gel

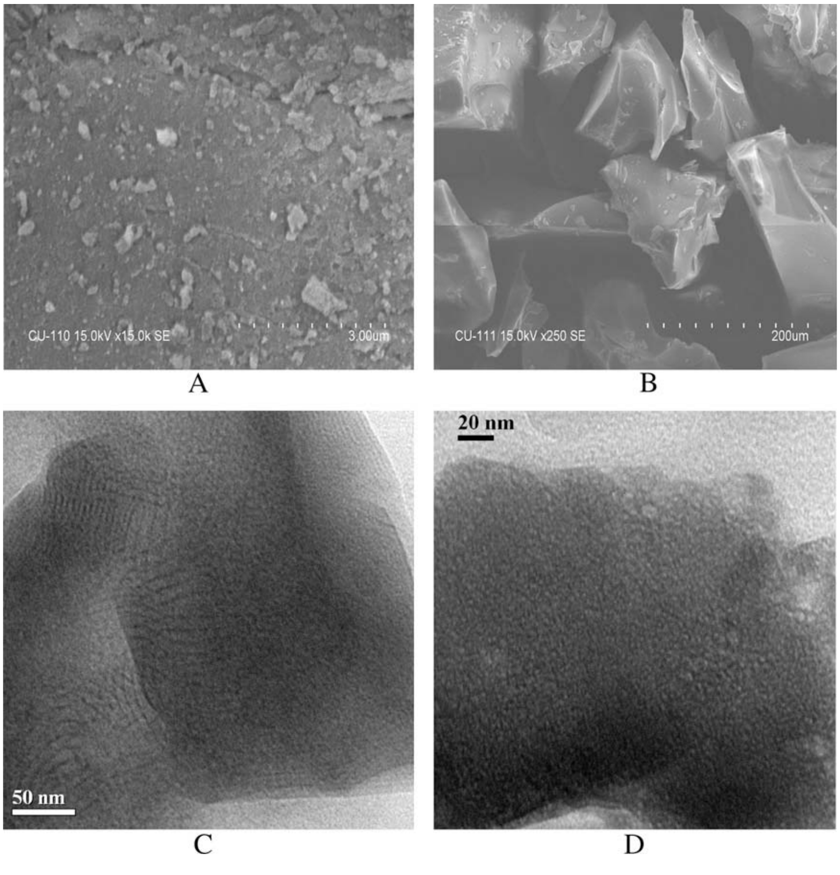


Fig. 1. SEM images of the surface morphology (A and B); TEM images of the lamellar channels (C) and porous surface (D) of the catalyst Ti-3-TUD-1.

method and modified from that followed by Maschmeyer et al. [12]. They were characterized by Scanning Electron Micrograph (SEM), Transmission Electron Microscopy (TEM), Powder X-ray diffraction (XRD), Fluorescence emission spectroscopy and surface area analysis by BET (Brunnauer–Emett–Teller) method. SEM images (Fig. 1A and B) depict the surface morphology of the material. Apparently the surface is spongy in nature. The particles are of uneven shape and size. TEM images (Fig. 1C and D) of the catalyst surface reflect a highly porous and wormhole-like arrangement. There are mixtures of small and large pores well distributed over the entire surface. Pore sizes found to range between 5 and 15 nm. The porous channels formed are also visible in the image. The pores are in the parallel arrangement with channels. However, the identification of Ti atoms could not be detected from TEM images. XRD spectral analysis was done with the catalyst Ti-3-TUD-1. Both the low angle and wide angle diffraction patterns were studied (Fig. 2). A sharp peak was observed in the 2θ range 0.5–1.0° which is a clear indication of the sample being mesoporous in nature [12]. A broad diffraction band at around $2\theta = 25°$ confirmed the amorphous silica matrix [14]. However, the XRD spectra did not show the characteristic diffraction lines for anatase or rutile titania phase [15] which indicates that there was no free titanium dioxide formed in the catalyst matrix. From the fluorescence emission spectra of Ti-5-TUD-1 catalyst (Fig. 3), the well defined characteristic bands of Ti were discernible. A sharp maxima at 425 nm appeared due to Ti^{4+} emission [16]. Due to high porosity, the surface area was also found to be high. BET surface area of the catalysts was found to range between 380 and 450 m^2/g. However, since the catalysts were prepared by a non-hydrothermal method, the development of pores might be less effective than hydrothermal method. Again due to loading the surface area was found to be somewhat lower than that prepared hydrothermally.

3.2. Study of catalytic activity

Knoevenagel condensation reactions were studied using aromatic aldehydes and active methylene compounds over Ti-TUD-1. In order to show the efficacy of this catalyst, comparative studies were made with several catalysts along with the Ti-TUD-1 with different Ti loadings. The results have been summarized in Table 1. Primarily benzaldehyde was treated with malononitrile in ethanol at room temperature. Mesoporous silica TUD-1 and bulk amorphous TiO_2 did not generate satisfactory yields. The Ti-3-TUD-1 catalysts with Ti/Si molar ratio 0.03 furnished the best yield. The optimization of the conditions was carried out using the best catalyst with different solvent variation. The observations have been

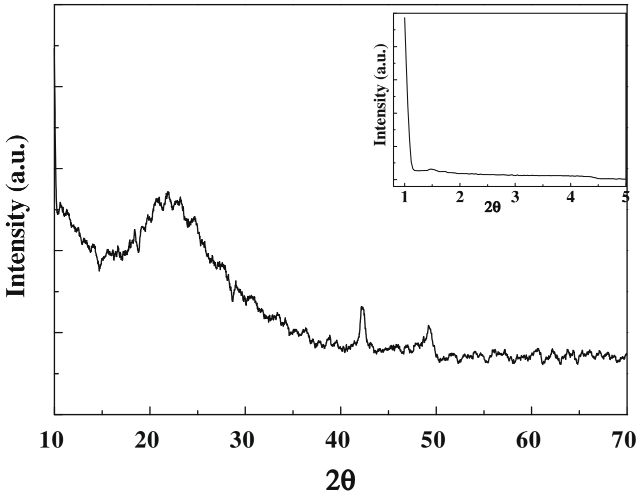


Fig. 2. Wide angle and low angle (inset) powder X-ray diffraction pattern of Ti-3-TUD-1 catalyst.

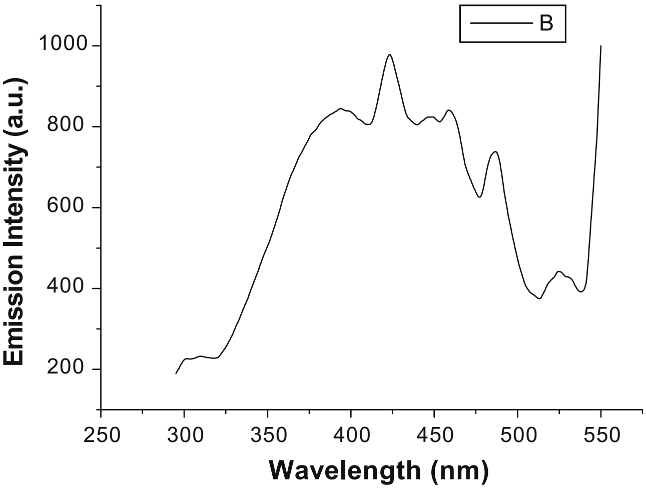


Fig. 3. Fluorescence emission spectrum of Ti-5-TUD-1 catalyst.

Table 1
Survey on the variation of catalysts.[a]

Entry	Catalyst	Time (h)	Yield[b] (%)
1	None	24	Trace
2	TUD-1	24	27
3	TiO_2	12	52
4	Ti-1-TUD-1	0.5	86
6	Ti-3-TUD-1	0.5	91
7	Ti-5-TUD-1	0.5	78

[a] *Reaction conditions:* benzaldehyde (1 mmol), malononitrile (1.1 mmol), catalyst (10 wt.%), ethanol (5 mL), rt.
[b] Isolated yield after purification.

Table 2
Solvent screening for the Knoevenagel condensation.[a]

Entry	Solvent	Time (h)	Yield[b] (%)
1	Toluene	24	31
2	DCM	12	47
3	Acetonitrile	2	73
4	Ethanol	0.5	91
5	THF	6	55
6	DMF	6	64

[a] *Reaction conditions:* benzaldehyde (1 mmol), malononitrile (1.1 mmol), Ti-TUD-1 catalyst (10 wt.%), ethanol (5 mL), rt.
[b] Isolated yield after purification.

Table 3
Variation of the active methylene components.[a]

Entry	Active methylene group	Time (h)	Yield[b] (%)
1	Malononitrile	0.5	91
2	Ethyl cyanoacetate	1.2	82
3	Acetylacetone	6	38
4	Ethyl acetoacetate	6	54
5	Diethyl malonate	6	Trace
6	Acetoacetanilide	6	Trace

[a] *Reaction conditions:* benzaldehyde (1 mmol), active methylene component (1.1 mmol), Ti-TUD-1 catalyst (10 wt.%), ethanol (5 mL), rt.
[b] Isolated yield after purification.

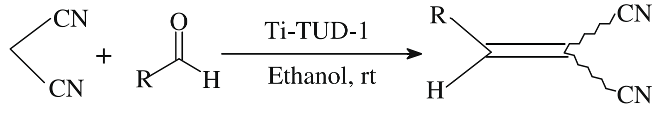
shown in Table 2. Ethanol yielded the best result in terms of time and yield. This was probably due to stabilization of the enolate of the active methylene compound and the polarized complex of aldehyde in ethanol due to solvation.

The reactivity of various active methylene compounds with benzaldehyde was also studied using catalyst Ti-3-TUD-1 in ethanol and the results are shown in Table 3. Malononitrile was found to be the most effective among the all active methylene compounds due to better electron withdrawing effect which was evident from the reaction time and yield. Reactions with several other active methylene compounds were attempted but the products were not obtained in good yields. Possibly, the lower activation of the methylene group and hence the formation of less stable enolate with Ti appeared to be the cause.

On standardizing the condition a series of reactions were carried out using various aromatic aldehydes and malononitrile and the results have been recorded in Table 4. The reactions went smoothly with aromatic aldehydes containing different functionalities producing remarkably good yields (entries 1–8). Strong electron withdrawing effect of nitro groups (entries 2–3) or the strong electron donating effect due to NMe_2 group (entry 7) showed the effect on yield and reaction time. The method was also found suitable for methoxyl substituted aromatic aldehydes (entries 8–12). Unsaturated aldehyde like *trans*-cinnamaldehyde (entry 13) or acid sensitive heterocycle like furfural (entry 14) furnished products in significantly good yield. In all the cases, the reaction product showed exclusive *E* selectivity as confirmed from NMR spectroscopy.

The high catalytic activity of Ti-TUD-1 is possibly due to the easy accessibility of the substrate molecules to the catalytic sites of the mesoporous system where Ti^{4+} is in tetrahedral coordination and symmetrically dispersed over the 3D surface. Ti-TUD-1 performs a dual role, polarizing the aldehydes to increase carbonyl activity and also binds with the active methylene carbon to form a stable enolate complex. The latter then attacks the polarized carbonyl group and subsequently water elimination takes place to furnish the product. The plausible reaction pathway is summarized in Scheme 2.

Table 4
Knoevenagel condensation between different aldehydes and malononitrile as active methylene compound.[a]



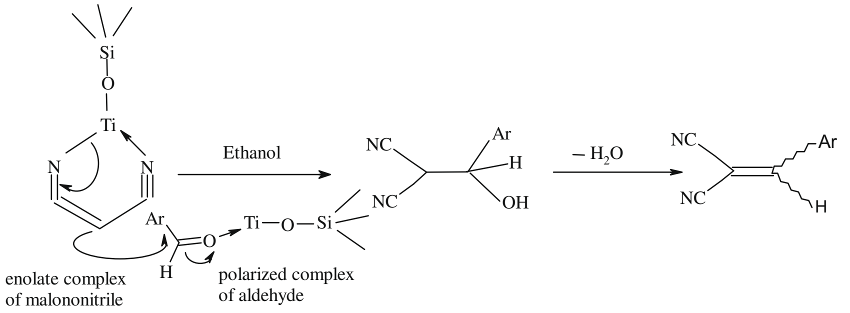
1 **2** **3**

Entry	R	Product **3**[b]	Time (min)	Yield (%)[c]
1	C_6H_5	**3a**	30	91
2	$4\text{-}NO_2\text{–}C_6H_4$	**3b**	20	95
3	$3\text{-}NO_2\text{–}C_6H_4$	**3c**	20	88
4	$4\text{-}CH_3\text{–}C_6H_4$	**3d**	60	82
5	$4\text{-}Cl\text{–}C_6H_4$	**3e**	40	84
6	$4\text{-}OH\text{–}C_6H_4$	**3f**	90	81
7	$4\text{-}NMe_2\text{–}C_6H_4$	**3g**	120	77
8	$4\text{-}OCH_3\text{–}C_6H_4$	**3h**	90	86
9	$3\text{-}OCH_3\text{–}C_6H_4$	**3i**	120	84
10	Vanillyl	**3j**	75	81
11	3,4-di OMe–C_6H_3	**3k**	90	80
12	3,4,5-tri OMe–C_6H_2	**3l**	45	84
13	C_6H_4 CH=CH	**3m**	75	79
14	Furfuryl	**3n**	30	94

[a] *Reaction conditions:* aldehyde (1 mmol), malononitrile (1.1 mmol), Ti-TUD-1 catalyst 10 wt.%, ethanol (5 mL), rt.

[b] Only *E* isomer was formed as confirmed from NMR spectroscopy.

[c] Isolated yield after purification.



Scheme 2. Probable mechanism of the Knoevenagel condensation.

3.2.1. Representative characterization data

3.2.1.1. 2-[(3,4-Dimethoxyphenyl) methylidene] propanedinitrile

3k. Bright yellow crystalline solid, mp 142 °C; IR (KBr): 3437.2, 2222.9, 1573.1, 1501.5, 1333.9, 1129.9 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.54–7.60 (m, 2H), 7.17 (s, 1H), 3.83 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.75, 154.58, 148.89, 127.38, 124.25, 114.9, 114.15, 112.12, 112.08, 76.8, 56.17, 55.6;

Table 5
Recycling of the catalyst.[a]

Cycles	Benzaldehyde (g)	Catalyst (mg)	Yield (%)[b]
Fresh	0.5	50	91
1	0.4	40	88
2	0.35	35	88
3	0.2	20	85
4	0.1	10	82

[a] *Reaction conditions:* benzaldehyde (1 mmol), malononitrile (1.1 mmol), Ti-TUD-1 catalyst 10 wt.%, Ethanol (5 mL), rt.
[b] Isolated yield after purification.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 14.94. Found: C, 67.31; H, 4.75; N, 14.88.

3.2.1.2. 2-[(3,4,5-Trimethoxyphenyl) methylidene] propanedinitrile ***3l***. Pale yellow crystalline solid, mp 140 °C; IR (KBr): 3436.0, 2216.6, 1570.6, 1507.0, 1269.5, 1141.9 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.33 (s, 2H), 3.78 (s, 3H), 3.77 (s, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.46, 152.96, 126.45, 114.46, 113.71, 108.64, 79.6, 60.94, 56.17, 48.66; Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.96; H, 4.91; N, 11.49.

3.3. Reusability of the catalyst

From the context of green approach, reusability study of the catalyst was performed through condensation of benzaldehyde and malononitrile. Under the stabilized condition the reaction was carried out in presence of Ti-3-TUD-1 catalyst. After completion of the reaction, the reaction mixture was centrifuged at 3000 rpm for 10 min and the supernatant layer was decanted. The deposited catalyst was collected after washing several times with ethanol to remove all the organic substance. It was then dried well at 60 °C for 4 h and was reused five consecutive times with the fresh batch of reactants following same process. All the batches proceeded smoothly with almost reproducible results each time (Table 5) which proved the reusability of the catalyst. Atomic absorption spectroscopy was performed with the reaction filtrate to test whether Ti leached out from the catalyst surface. However, the assay did not show any trace of Ti atom in the solution which proved the efficacy of the catalyst in industry.

4. Conclusion

We have developed a new inexpensive, reusable and environmentally benign catalytic process using mesoporous solid acid catalyst Ti-TUD-1 for the C=C bond formation in Knoevenagel condensation reaction under mild conditions with high selectivity and excellent yield. No side reactions like self condensation, dimerization and rearrangements were observed. The catalyst can be easily recovered from the reaction mixture by centrifugation and there no trace of leaching of Ti could be detected in the filtrate. Ti-TUD-1 therefore provides an efficient and excellent alternative to the classical catalysts used in the versatile Knoevenagel condensation reaction.

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