J IRAN CHEM SOC
DOI 10.1007/s13738-015-0607-y

ORIGINAL PAPER

Nano silica-bonded aminoethylpiperazine: a highly efficient and reusable heterogeneous catalyst for the synthesis of 4*H*-chromene and 12*H*-chromeno[2,3-*d*]pyrimidine derivatives

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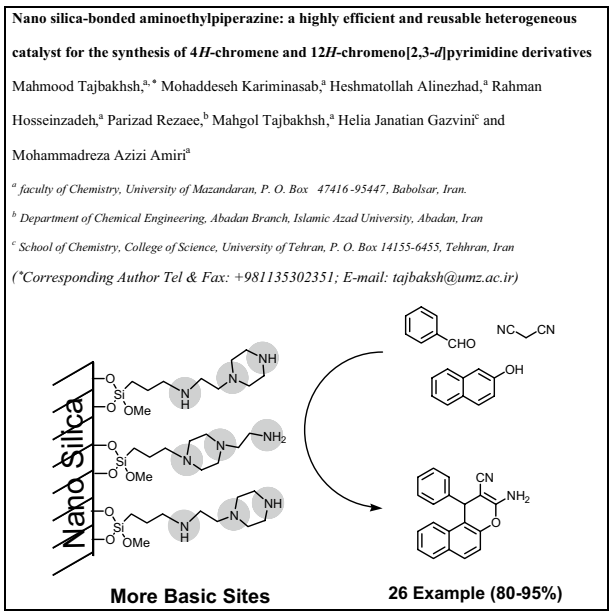
Received: 6 September 2014 / Accepted: 6 February 2015

Abstract The reaction of nano silica with 3-chloropropyltrimethoxysilane followed by treatment with aminoethylpiperazine afforded nano silica-bonded aminoethylpiperazine (SB-APP). The structure of the synthesized SB-APP was characterized by FT-IR, TGA, BET, SEM and elemental analysis and identified as an efficient basic catalyst for the preparation of 2-amino-4*H*-chromenes and 12*H*-chromeno[2,3-*d*]pyrimidine derivatives. One-pot three-component reaction of phenols, aromatic aldehydes and malononitrile in the presence of the catalytic amounts of SB-APP afforded high yield of the corresponding 2-amino-4*H*-chromenes under mild reaction conditions. 12*H*-Chromeno[2,3-*d*]pyrimidines were successfully synthesized with reasonable yield by reacting the 2-amino-4*H*-chromenes with acetic anhydride in the same pot without purification of the corresponding chromene intermediates. All products were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and MS data. The catalyst was simply recovered from the reaction mixture and reused several times without significant loss of catalytic activity.

Graphical abstract



Keywords Nano silica · Aminoethylpiperazine · Basic catalyst · Chromene

Introduction

Heterogeneous catalysts play an important role in the current industrial scenario because of their significant advantages in terms of easier product recovery, minimizing disposal problems, regeneration of active sites and environmental perspectives [1]. However, due to the ever growing demand of the day-to-day products, hazardous homogeneous reagents (H_2SO_4, HF, NaOH, KOH, CH_3COOH and

Electronic supplementary material The online version of this article (doi:10.1007/s13738-015-0607-y) contains supplementary material, which is available to authorized users.

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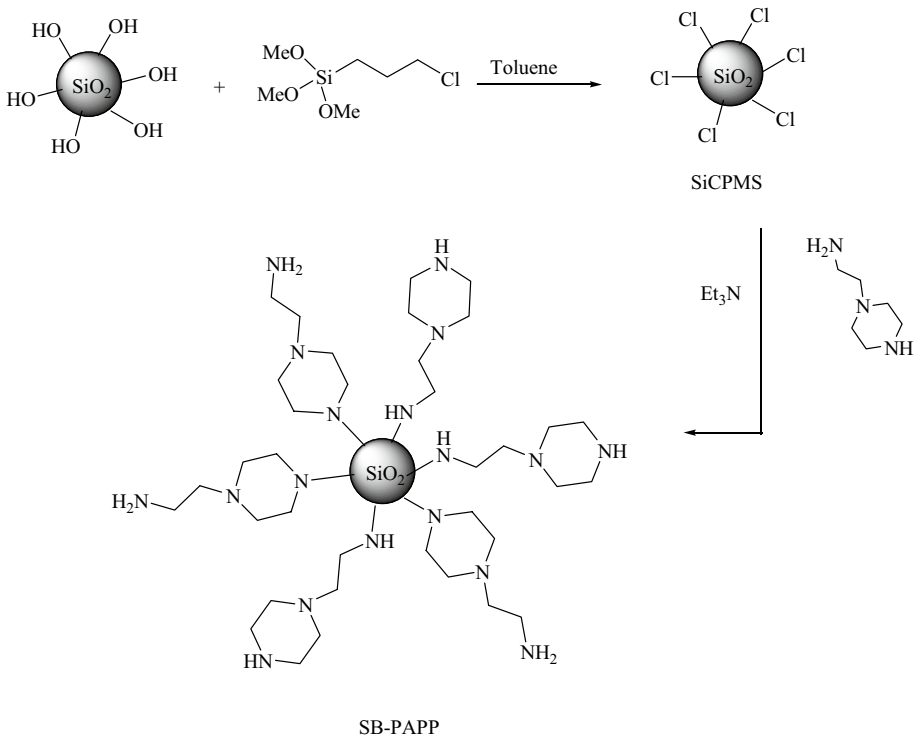
Published online: 24 February 2015

Scheme 1 Preparation of SB-APP



transition metal containing catalysts) are still in use as catalysts for many organic transformations. The heterogeneous catalysts are known to suppress side reactions and proceed selectively with higher rates and product yield [2]. This means cost and energy savings for the downstream separation and purification of the product. It also avoids the complex neutralization and separation steps needed to recover the homogeneous catalyst from the reaction mixture. The recovered solid catalysts can be readily regenerated for further use. The covalently bonded groups are resistant to removal from the surface of the supporting materials by solvent molecules [3].

It is well known that one-pot multi-component condensations represent a possible instrument to perform a near ideal synthesis because of their ability for the possibility of building up complex molecules with maximum simplicity and brevity [4]. Reactions under solvent-free conditions [5] are also attractive for researchers, both from academia and industry, due to the fact that without solvent, reactions usually need shorter reaction time, simpler reactors and simple and efficient workup procedures.

Beside these remarkable properties which led to a number of industrial usages of heterogeneous catalysts based on silica, utilizing these structures in organic synthesis has been well studied. A large surface area, high thermal and chemical stability and numerous active sites especially in functionalized nano size silica make it excellent candidate to catalyze organic reactions. To explore its sufficiency, we intended to survey functionalized nano silica as a catalyst in the synthesis of the well-known 2-amino-4*H*-chromene family. 2-Amino-4*H*-chromenes are interesting derivatives of chromenes which are used as cosmetics and pigments [6], anticoagulant, spasmolytic, antianaphylactic, diuretic [7], antibacterial [8] and anticancer agents [9]. On the other hand, pyrimidine scaffold is the base of many bioactive molecules such as antitubercular [10], antibacterial [11] and antitumor compounds [12]. Moreover, nitrogen-containing heterocycles are also of broad pharmaceutical interest and significance, which justifies our continuing efforts in exploring synthetic strategies which lead to structures formed from a combination of both types of heterocycles [13].

A literature survey revealed several modified procedures using different catalysts for the synthesis of 2-amino-4*H*-chromenes including cetyltrimethylammonium chloride (CTAC) [14], cetyltrimethylammonium bromide (CTAB) coupled with ultrasound [15], c-alumina [16], K_2CO_3 [8], nano size MgO [17], heteropolyacid [18], hexadecyltrimethylammonium bromide (HTMAB) [19], triethylbenzylammonium chloride (TEBA) [20], $TiCl_4$ [21], N,N-dimethylaminoethylbenzyldimethylammonium chloride [22], sodium carbonate [23], NaOAc/KF [24], Amberlyst A21 [25], NaI [26], acetic acid functionalized ionic liquid [27] and DABCO/agar–agar [28]. Recently, electrochemically induced multi-component condensation for the synthesis of chromenes by electrolysis in an undivided cell in the presence of NaBr as an electrolyte was reported [29, 30]. However, most of these methods suffer from some drawbacks such as low yields, long reaction times, harsh

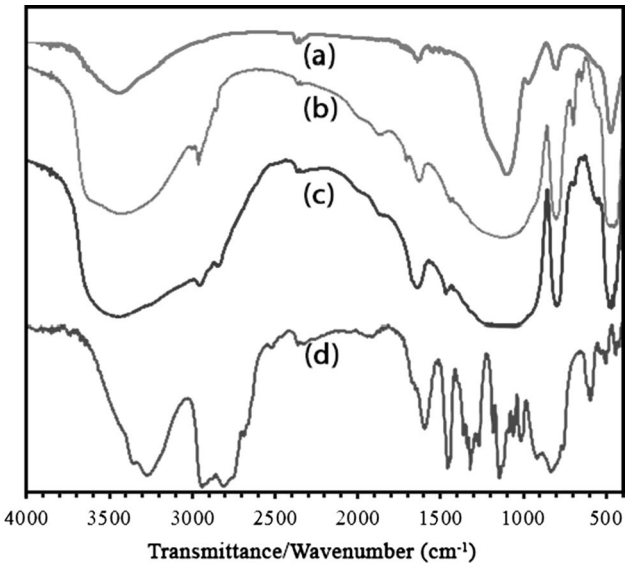


Fig. 1 FTIR spectra of **a** nano SiO_2, **b** SiCPMS, **c** SB-APP and **d** pure APP

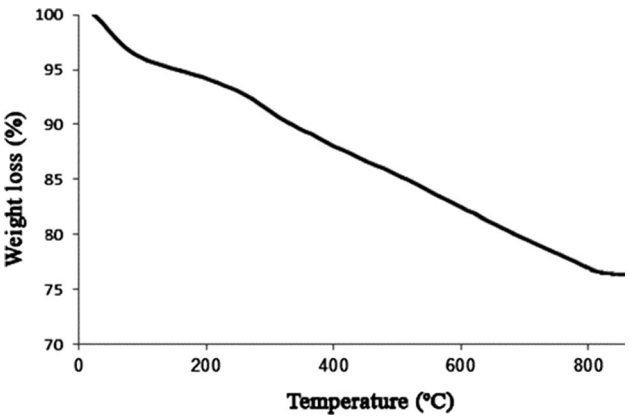


Fig. 2 The thermogeravimetric analysis of SB-APP

reaction conditions, tedious workup procedures and application of expensive catalysts. Moreover, in many of the reported methods, catalysts are not recyclable.

Therefore, use of supported and reusable catalysts in organic transformations has economic and environmental benefits. Some attempts have been made to immobilize silica framework catalysts for the synthesis of 4*H*-chromenes [31–37], which leads us to present a green procedure for the synthesis of 4*H*-chromene derivatives by immobilized heterogeneous catalysts.

Due to the advantages of one-pot multi-component reactions and heterogeneous catalysts, herein we report the preparation of nano silica-bonded *n*-propyl-aminoethylpiperazine as a novel heterogeneous and recyclable catalyst and its successful application in the synthesis of 4*H*-chromene derivatives under solvent-free conditions. Also, chromeno pyrimidines were further synthesized by reacting the 2-amino-4*H*-chromenes with acetic anhydride in the same pot without purification of the corresponding chromene intermediates.

Experimental section

General procedure

Nano silica with average grain size (10 nm) and specific surface area (>600 m^2/g) was purchased from US Research Nanomaterial and other materials were purchased from Fluka, Merck and Aldrich chemical companies. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 AVANCE (400 and 100 MHz for ^1H and ^{13}C respectively) in DMSO-d_6 as solvent. Chemical shifts were on the δ scale, relative to internal Me_4Si. Melting points were determined on a Thermo Scientific IA9200 and uncorrected. Mass spectra were obtained on an Agilent Technologies instrument and FT-IR spectra were determined on a Bruker instrument. Thermogravimetric analysis (TGA) was recorded on a Stanton Redcraft STA-780 (London, UK). All the products were characterized by comparison of their FT-IR, ^1H NMR, and ^{13}C NMR spectra, and their melting points with the reported data.

Preparation of nano silica-bonded n-propyl chloride (SiCPMS)

The modified catalyst was prepared as previously described [38]. Initially, the surface of nano silica was activated by refluxing of nano silica (5.0 g) in HCl (6 M, 50 mL) for 24 h. Then, activated nano silica was filtered and repeatedly washed with double distilled water until the pH of the solution was adjusted to 6. Finally, the treated nano silica was dried in an oven at 110 °C for 12 h. Afterward, 2 g of activated nano silica was suspended in 20 mL of dry toluene containing 2 mL of 3-chloropropyltrimethoxysilane (CPMS) as silylating reagent and refluxed for 12 h to produce the chloro functionalized nano silica (SiCPMS). At the end of this period, the SiCPMS was filtered off, washed with toluene (70 mL), ethanol (40 mL) and diethyl ether (40 mL), respectively, to eliminate the unreacted reagent and then dried at 70 °C for 6 h.

Preparation of nano silica-bonded aminoethylpiperazine (SB-APP)

SiCPMS (1.5 g), aminoethylpiperazine (1.5 mL), triethylamine (1 mL) and dry toluene (20 mL) were added into a 50 mL round bottom flask, under continuous stirring and

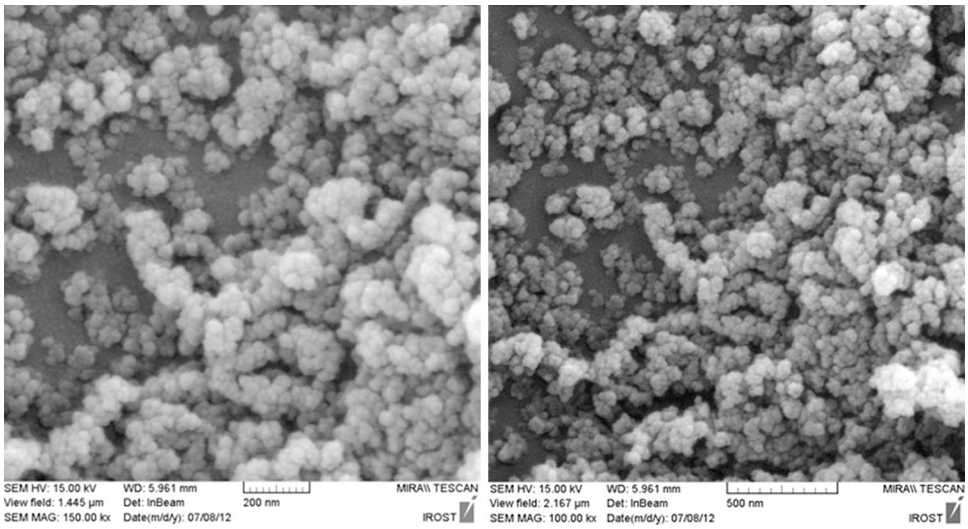


Fig. 3 The SEM images of SB-APP

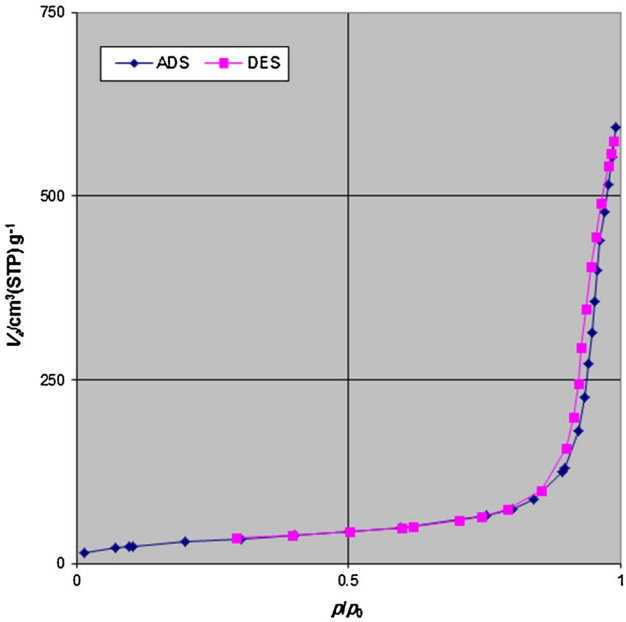


Fig. 4 The N_2 adsorption–desorption isotherm of SB-APP

Table 1 Effect of solvent and evaluation of catalytic activity of SB-APP on the rate of the reaction and yield of the product

Entry	Solvent	Catalyst (g)	*T* (°C)	Time (min)	Yield (%)[a]
1	Toluene	0.10	110	24 h	40
2	Xylene	0.10	140	24 h	10
3	Water	0.10	100	24 h	–
4	Ethanol	0.10	87	24 h	–
5	DMF	0.10	120	24 h	–
6	Acetonitrile	0.10	80	24 h	–
7	Solvent free	0.10	80	30	95
8	Solvent free	0.05	80	45	85
9	Solvent free	0.08	80	30	95
10	Solvent free	0.15	80	40	95
11	Solvent free	–	80	60	–

Reaction conditions: β-naphthol (0.5 mmol), 4-chlorobenzaldehyde (0.5 mmol), malononitrile (0.5 mmol) and solvent volume (3 mL) at reflux temperature

[a] Isolated yields

argon atmosphere at 70 °C for 48 h. Afterward, the reaction mixture was cooled to room temperature, transferred to a vacuum glass filter and washed with toluene and ethanol. Then, the solid product was transferred to a Soxhlet extractor with ethanol as extraction solvent to eliminate the excess amount of reagents and the resulting SB-APP was separated and dried in vacuum at 80 °C for 12 h.

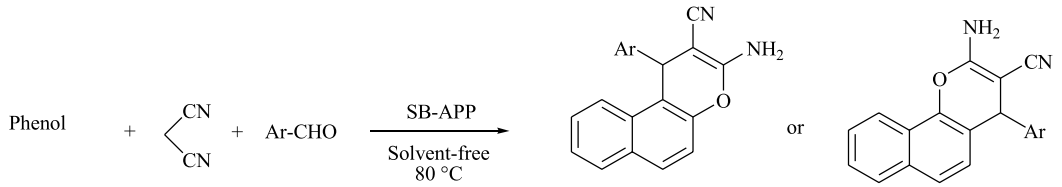
General procedure for the preparation of 2-amino-4*H*-chromene derivatives

To a mixture of phenol derivatives (0.5 mmol), aromatic aldehydes (0.5 mmol) and malononitrile (0.5 mmol), SB-APP (0.08 g) was added and the mixture was heated at 80 °C under solvent-free conditions. After completion of the reaction (monitored by TLC), ethanol was added and the reaction mixture was filtered. The remaining solid was washed with warm ethanol to separate the catalyst. The solvent was evaporated and the crude product purified by recrystallization from ethanol–water. The recycled catalyst was washed with acetone, dried and reused.

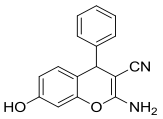
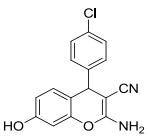
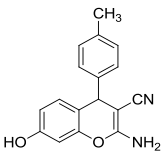
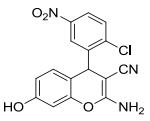
General procedure for the preparation of 12*H*-chromeno[2,3-d]pyrimidines

To a mixture of β-naphthol (0.5 mmol), aromatic aldehydes (0.5 mmol) and malononitrile (0.5 mmol), SB-APP

Table 2 Preparation of various 2-amino-4*H*-chromenes in the presence of SB-APP



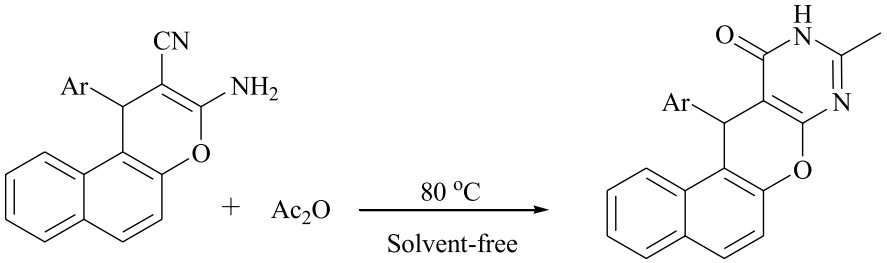
1a-n 2a-h

Entry	Ar-CHO	Phenol	Product	Time (min)	Yield (%)[b]	M.P (Lit. M.P) (°C)
1	Ph-	β-naphthol	**1a**	40	94	279-282(282-284)[38]
2	4-Cl-Ph-	β-naphthol	**1b**	30	95	208-210(210-211)[39]
3	4-Br-Ph-	β-naphthol	**1c**	45	93	211-212(221-222)[39]
4	4-OH-Ph-	β-naphthol	**1d**	80	90	284-286(289-291)[27]
5	4-NO_2-Ph-	β-naphthol	**1e**	60	80	183-185(184-185)[38]
6	4-CN-Ph-	β-naphthol	**1f**	30	90	257-259(258-261)[23]
7	3-Cl-Ph-	β-naphthol	**1g**	50	92	232-235(240-241)[39]
8	3-Br-Ph-	β-naphthol	**1h**	30	92	220-223
9	3-OMe-Ph-	β-naphthol	**1i**	40	89	250-252(256-258)[40]
10	4-CH_3-Ph-	β-naphthol	**1j**	50	86	242-244(253-254)[39]
11	2-Br-Ph-	β-naphthol	**1k**	60	82	197-199(181-183)[33]
12	2-Cl-5-NO_2-Ph-	β-naphthol	**1l**	80	80	252-254
13	2-naphthyl	β-naphthol	**1m**	90	81	210-214
14	4-pyridyl	β-naphthol	**1n**	60	90	227-229(229-231)[40]
15	Ph-	α-naphthol	**2a**	30	92	200-202(209)[18]
16	4-Cl-Ph-	α-naphthol	**2b**	10	93	228-230(232)[23]
17	4-CN-Ph-	α-naphthol	**2c**	10	90	261-264(275-277)[23]
18	3-Br-Ph-	α-naphthol	**2d**	10	93	215-217
19	3-OMe-Ph-	α-naphthol	**2e**	30	91	225-227(231-233)[40]
20	2-Cl-5-NO_2-Ph-	α-naphthol	**2f**	40	82	209-211
21	1-naphthyl	α-naphthol	**2g**	30	80	216-219
22	4-pyridyl	α-naphthol	**2h**	20	84	199-202(199.5-200)[14]
23	Ph-	resorcinol		30	92	232-234(235-236)[29]
24	4-Cl-Ph-	resorcinol		25	87	166-167(163-164)[29]
25	4-CH_3-Ph-	resorcinol		45	90	181-183(182-184)[29]
26	2-Cl-5-NO_2-Ph-	resorcinol		30	94	246-248

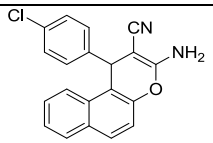
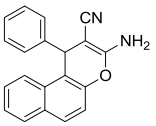
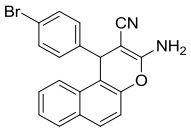
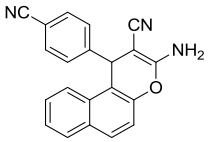
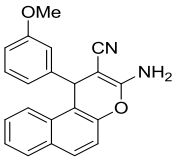
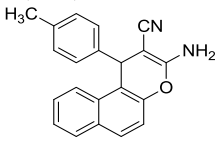
Reaction conditions: phenols (0.5 mmol), aromatic aldehydes (0.5 mmol), malononitrile (0.5 mmol) and SB-APP (0.08 gr) under solvent-free conditions at 80 °C

[a] Isolated yields

Table 3 One-pot synthesis of 12*H*-chromeno[2,3-*d*] pyrimidines



3a-f

Entry	2-Amino-4*H*-benzo[*f*]-chromene	Product	Yield (%)[a]	M.P (°C)
1		**3a**	80	>300
2		**3b**	88	>300
3		**3c**	65	>300
4		**3d**	60	>300
5		**3e**	86	>300
6		**3f**	75	>300

[a] Isolated yields

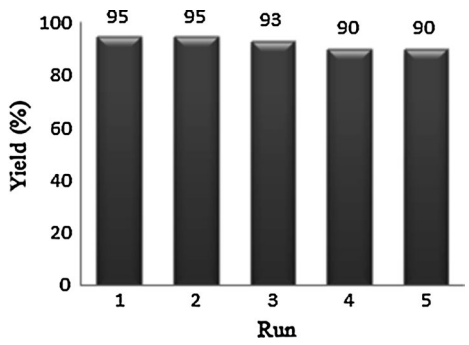


Fig. 5 Catalyst recyclability

(0.08 g) was added and the mixture was heated at 80 °C under solvent-free conditions. After completion of the reaction (monitored by TLC), acetic anhydride (1 ml) was added and the reaction mixture heated at 80 °C for 24 h. After cooling, the reaction mixture was diluted with dichloromethane and then filtered to separate the catalyst. The filtrate was washed with brine and dried over magnesium sulfate. The solvent was evaporated and the solid product crystallized from ethyl acetate.

Spectral data for selected products:

2-Amino-4-(4-chlorophenyl)-4*H*-benzo[*f*]chromene-3-carbonitrile (Table 2, entry 2) ^{1}H NMR (400 MHz,

Table 4 Comparison of SB-APP with some other reported catalysts

Entry	Solvent and catalyst	*T* (°C)	Time (h)	Yield (%)	Ref.
1	Solvent free, tetrabutylammonium chloride (TBAC) (10 mol %)	100	0.6	80	[40]
2	DCM, thiourea-tertiary amines (20 mol %)	r.t.	48	72	[41]
3	Solvent free, Na_2CO_3 (10 mol %)	125	0.6	100	[23]
4	3-Butyl-1-methylimidazolium hexafluorophosphate [bmim[a]][PF_6] (1.5 ml)	80	2	86	[42]
5	H_2O, 1-butyl-3-methylimidazolium hydroxide [bmim[a]][OH] (50 mol %)	100	1	90	[43]
6	M.W., aq.K_2CO_3 (10 ml)	105	3.2 min	90	[8]
7	Acetic acid functionalized ionic liquid {[cmmim]Br[b]}(10 mol %), H_2O/EtOH	110	0.5	91	[27]
8	Solvent free, [Cu(bpdo)[c]$_2$.2H_2O]$^{2+}$/SBA -15	150	0.25	90	[31]
9	EtOH, Amberlyst A21 (30 mg)	r.t.	6	72	[25]
10	Solvent free, SB-APP (0.08 gr)	80	0.6	94	This work

Reaction conditions: β-naphthol, benzaldehyde and malononitrile

[a] [bmim]: 1-butyl-3-methyl imidazolium

[b] [cmmim]Br: 1-carboxymethyl-3-methylimidazolium bromide

[c] (bpdo) = 2,20-bipyridine,1,10-dioxide

DMSO-d_6): $\delta = 5.36$ (s, 1H, CH), 7.05 (s, 2H, NH_2), 7.19–7.22 (d, 2H, $J = 8.4$ Hz), 7.31–7.35 (m, 3H), 7.4–7.47 (m, 2H), 7.8–7.82 (d, 1H, $J = 7.2$ Hz), 7.91–7.96 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 37.74, 57.79, 115.62, 117.27, 120.82, 124.02, 125.48, 127.65, 128.99, 129.17, 129.32, 130.17, 130.49, 131.28, 131.61, 145.17, 147.24, 160.16. IR (KBr) υ: 3,424, 3,324, 2,196, 1,654, 1,592, 1,234 cm^{-1}.

12-(4-Chlorophenyl)-9-methyl-10,12-dihydro-11*H*-benzo [5, 6] chromeno[2,3-*d*] pyrimidine-11-one (Table 3, entry 1) ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.28$ (s, 3H, CH_3), 5.75 (s, 1H, CH), 7.25-7.27 (d, 2H, $J = 8.4$ Hz), 7.32–7.34 (d, 2H, $J = 8.8$ Hz), 7.42–7.46 (td, 1H, $J = 8$ Hz, $J = 2.4$ Hz), 7.47–7.51 (m, 2H), 7.93–7.98 (m, 3H), 12.56 (s, 1H, NH).^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.44, 35.28, 100.63, 116.36, 117.89, 123.81, 125.52, 127.8, 128.67, 129.08, 130.17, 130.42, 130.81, 131.49, 131.52, 143.67, 148.21, 159.14, 161.02, 162.72. IR (KBr) υ: 3,425, 3,005, 2,867, 2,781, 1,646, 1,599, 1,231 cm^{-1}. *m/z* 347 (M^+, 15 %), 263.1 (M-C_6H_4Cl, 100 %), 75 (6 %).

Complete experimental and spectral data are available online in the Supplementary Material.

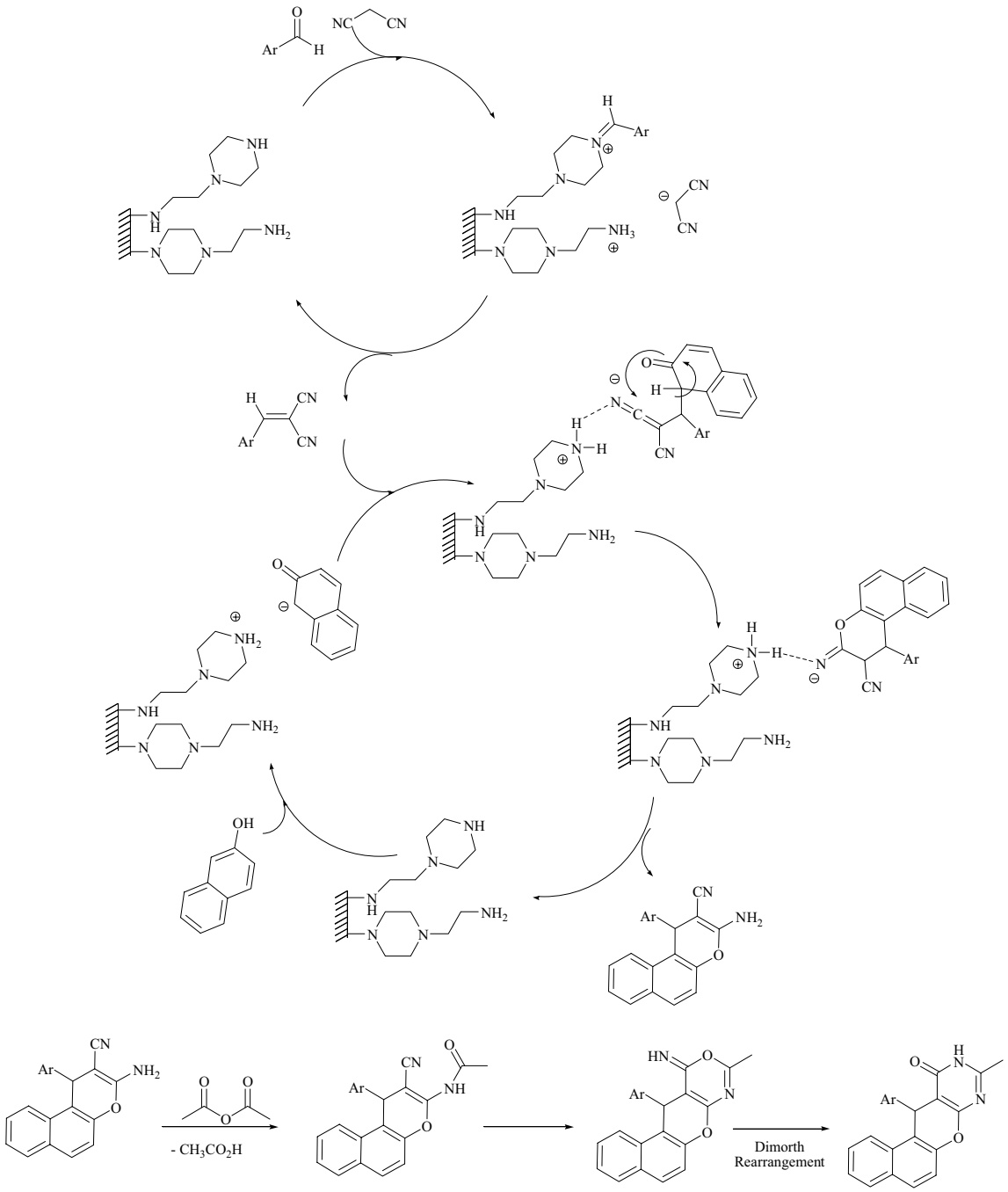
Results and discussion

The synthesis of SB-APP is shown in Scheme 1. The surface of nano silica was activated by HCl (6 M) at reflux temperature. Afterward, activated nano silica was suspended in dry toluene containing CPMS as silylating reagent and the mixture was refluxed to produce SiCPMS. Then, aminoethylpiperazine was reacted with SiCPMS to yield SB-APP.

The immobilization of aminoethylpiperazine onto the nano silica have led to formation of a high loading of multiple types of amine sites on the silica surface. For each molecule of aminoethylpiperazine, three amine groups would be immobilized and the loading amounts increased. Therefore, a lower weight percent would be required for catalytic reaction.

The FT-IR spectra of the nano silica (a), SiCPMS (b), SB-APP (c) and aminoethylpiperazine (APP) (d) are presented in Fig. 1. The pure nano SiO_2 shows characteristic absorbance peaks at 1,098 cm^{-1} for stretching vibration of Si–O–Si and at 3,447 cm^{-1} for stretching vibration of the OH group (Fig. 1a). In the spectrum of nano silica-bonded n-propyl chloride, peaks at 1,460 and 1,210 cm^{-1} were observed which indicate the presence of CH bending and Si–C stretching vibrations, respectively. The FT-IR spectrum shows an overlap of the CH bending and Si–C stretching bands with the Si–O–Si stretching bands in the functionalized nano silica (Fig. 1b). Figure 1c shows the FT-IR spectrum of SB-APP with characteristic peaks of Si–O–Si and OH groups at 1,098 and 3,447 cm^{-1}, respectively. As seen in Fig. 1c, the absorption peak of NH of aminoethylpiperazine at 3,273 cm^{-1} and C–N at 1,330 cm^{-1} (Fig. 1d) overlapped with peaks of OH and Si–O–Si. However, CH stretching at 2,938 and 2,808 cm^{-1} and CH bending at 1,456 cm^{-1} were observed. These results prove that the APP was successfully grafted onto the nano silica-bonded n-propyl chloride to give SB-APP.

The thermal stability of SB-APP was investigated by TG analysis, and the result is shown in Fig. 2. The weight loss around 100 °C is related to the water molecules and other volatile organic compounds which have been adsorbed on the surface of the catalyst. Following the thermogram, the weight decrease observed in the diagram starting at around



Scheme 2 Plausible mechanism for synthesis of chromene derivatives

250 °C can be related to the loss of the covalently bounded organic group. Weight loss of 15 % occurred in the range of 250–800 °C, corresponding to the decomposition of the organic groups, which yielded the final siloxane groups. From this weight loss, the loading amount of APP was calculated to be 0.88 mmol/g.

The elemental analysis data along with the summary of the measured and calculated values for C, H and N, gave the following results: C, H and N, 9.82, 2.56 and 3.28 %, respectively. From the CHN analysis, the loading amount of APP was calculated to be 0.78 mmol/g, which is in good agreement with TG analysis.

The scanning electron microscopy (SEM) images are shown in Fig. 3. The SEM images show that the sample is granular and porous. The size of granular particles are between 25 and 33 nm.

Figure 4 shows the nitrogen adsorption isotherm obtained for SB-APP, the hysteresis loop observed in the

range of $0.57 < P/P_0 < 1.0$, is associated with capillary condensation according to IUPAC classification. The isotherm exhibited by SB-APP is of type IV and exhibited an H3 hysteresis loop [39]. The specific surface area and the total pore volume were calculated by the BET method, 106.07 m^2/g and 0.89 cm^3/g, respectively. The pore size was found to be 18.94 nm with the BJH method.

The catalytic activity of the synthesized SB-APP was investigated in the three-component condensation reaction of 4-chlorobenzaldehyde, malononitrile and β-naphthol as a model reaction for the preparation of 2-amino-4*H*-chromene. To evaluate the effect of solvent, various solvents such as toluene, acetonitrile, xylene, DMF, ethanol and water were used for the synthesis of 2-amino-4*H*-chromene in the presence of SB-APP (Table 1). Use of toluene and xylene as the reaction solvent afforded a low yield of the product after 24 h. In the presence of water, ethanol, DMF and acetonitrile, no product was obtained. The reaction under solvent-free conditions not only went to completion efficiently, but also furnished the product in excellent yield.

When the reaction was carried out in the absence of any catalyst, no product was detected. In the presence of SB-APP the reaction was possible and, to determine the appropriate amount of the catalyst, we investigated the model reaction at different amounts of SB-APP, 0.05, 0.08, 0.1 and 0.15 g (Table 1, entries 7–10). This indicates that 0.08 g of SB-APP is sufficient to carry out the reaction smoothly (Table 1, entry 9).

The synthesis of 2-amino-4*H*-chromenes was achieved by the three-component condensation of various aromatic aldehydes, malononitrile and phenols in the presence of SB-APP under solvent-free conditions. In all the cases, excellent yield of the products was observed (Table 2).

As further investigation in the synthesis of new heterocyclic compounds, we synthesized various 12*H*-chromeno[2,3-*d*]pyrimidines by the reaction of unisolated 2-amino-4*H*-benzo[*f*]-chromene with acetic anhydride in the same pot (Table 3).

The recyclability of the catalyst was examined using the model reaction under the optimized condition. Upon completion, the reaction mixture was filtered and the remaining solid was washed with hot ethanol and acetone, dried and reused in the next run. The recycled catalyst could be reused four times in the presence of SB-APP without any additional treatment. As seen in Fig. 5, no significant loss of catalytic activity was observed on comparing with the fresh catalyst (run 1).

A comparison between efficiency of various reported catalysts for the synthesis of 2-amino-4*H*-chromene derivatives is listed in Table 4. It demonstrates that the present protocol is indeed superior to several others.

The reaction is expected to proceed via the Knoevenagel condensation of an aromatic aldehyde and malononitrile, followed by the cyclo-condensation reaction with β-naphthol to form the desired 2-amino-4*H*-chromene. Although the detailed mechanism of the synthesis of chromeno pyrimidine was not very clear, a possible mechanism has been proposed in Scheme 2.

Conclusions

We have developed a novel and highly efficient protocol for the multi-component synthesis of 2-amino-4*H*-chromenes by the reaction of malononitrile with various aryl aldehydes and phenols in the presence of SB-APP. The synthesis of various 12*H*-chromeno[2,3-*d*]pyrimidines in the same pot without isolating the chromene intermediate was also performed. The method offers several significant advantages such as high conversion, easy handling, clean reaction profile and short reaction times which makes it a useful and an attractive protocol compared to the existing ones.

Acknowledgments We are thankful to the Research Council of University of Mazandaran for the partial support of this work.

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