GREEN SYNTHESIS OF 2-AMINO-3-CYANO-4H-CHROMENES IN WATER USING NANO SILICA-BONDED 5-N-PROPYL-OCTAHYDRO-PYRIMIDO[1,2-*A*]AZEPINIUM CHLORIDE AS AN EFFECTIVE AND REUSABLE NANO CATALYST

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ABSTRACT

Nano silica-bonded 5-n-propyl-octahydro-pyrimido[1,2-*a*]azepinium chloride (NSB-DBU) is reported as an highly efficient and recyclable nano catalyst for the preparation of 4*H*-chromene derivatives in aqueous media. This synthetic method offers a simple, mild and time-saving method under entirely green and environmentally friendly conditions.

Keywords: Nano silica-bonded 5-n-propyl-octahydro-pyrimido[1,2-*a*]azepinium chloride, 4*H*-chromene, green synthesis, aqueous media.

1. INTRODUCTION

In recent years, heterogeneous acid and base catalysts have been extensively studied and applied in organic synthesis.¹⁻³ They have many advantages compared to homogeneous catalysts, such as their easy recovery and reusability, non-toxicity, non-corrosive, low cost and environmentally benign.⁴ Among them, nano-sized catalysts have attracted more attention than their bulk materials because the size and surface area of nano materials allow the reactions to occur more efficiently than for bulk systems.^{5,6} It is known that surface modification of silica with homogenous catalysts is an excellent method for development of heterogeneous reusable catalysts for organic reactions.^{7,8}

The 4*H*-chromene derivatives are the privileged scaffold in the modern

medicinal chemistry due to their extensive range of interesting biological activities such as anticancer, antimicrobial, antifungal, antioxidant, antiallergenic, spasmolytic, and anti-anaphylactic.⁹⁻¹⁷ Furthermore, a number of these compounds are utilized as pigments¹⁸ and photoactive materials.¹⁹ Several methods have been already reported for the synthesis of these compounds (Table 1).²⁰⁻³² However, these methods are often associated with some drawbacks such as long reaction times, high temperatures, hazardous organic solvents, non-reusable catalysts and complicated work-up. Also, only a few reports existed on the synthesis of these compounds in aqueous media at low temperatures. Therefore, there is still the need to develop better alternatives that can proceed under green reaction conditions.

Table 1. Some examples of reported methods for the synthesis of 4*H*-chromene derivatives.

Entry	Catalyst	Solvent	Temp./°C	Time /min	Yield/%	Ref.
1	-	Trifluoroethanol	Reflux	300	80-96	20
2	(NH ₄) ₂ HPO ₄	H ₂ O	25	90-300	78-97	21
3	K ₃ PO ₄	H ₂ O:EtOH (4:1)	25	30-60	87-94	22
4	MgO	H ₂ O:EtOH (4:1)	Reflux	22-35	85-96	26
5	RE(PFO) ₃	EtOH	60	300-480	81-92	28
6	MSN ^a	EtOH	60	10-45	93-98	29
7	-	[BmIm]OH ^b	25	5-20	85-98	30
8	-	[omim]PF ₆ ^c	25	120-480	52-94	31
9	TBAF ^d	H ₂ O	Reflux	30	73-98	32

^a Mesoporous Silica Nanoparticles.

^b 1-Butyl-3-methylimidazolium hexafluorophosphate.

^c 1-Methyl-3-octylimidazolium hexafluorophosphate.

^d Tetrabutylammonium fluoride.

Recently, we prepared silica-bonded nano silica-bonded 5-n-propyl-octahydro-pyrimido[1,2-*a*]azepinium chloride (NSB-DBU) (Scheme 1) as a solid base nano catalyst for the synthesis of novel benzothiazole substituted 4-thiazolidinones.³³ In continuation of our previous work to develop new and eco-friendly synthetic methodologies in organic synthesis,^{33,36} we report herein the application of nano silica-bonded 5-n-propyl-octahydro-pyrimido[1,2-*a*]azepinium chloride (NSB-DBU) as a heterogeneous and easy recoverable catalyst in the green synthesis of 4*H*-chromene derivatives (Scheme 2).

Scheme 1. Preparation of NSB-DBU

Scheme 2. Synthesis of 4H-chromene derivatives.

2. RESULTS AND DISCUSSION

First, NSB-DBU was prepared from the reaction of nano silica-n-propyl chloride and DBU as shown in Scheme 1. The catalyst structure was characterized by X-ray diffraction (XRD), Fourier-transfer infrared (FT-IR) spectroscopy, field emission scanning electron microscopy (FE-SEM), thermogravimetric analysis (TGA) and elemental analysis (CHN). XRD diffractogram of NSB-DBU showed strong broad peak between 22° and 23° (2θ), which is characteristic of amorphous nano silica (Fig. 1). The FT-IR diagram of NSB-DBU (sp^3 C-H stretching at 2936 cm^{-1} , C=N stretching at 1647 cm^{-1} , CH_2 bending at 1449 cm^{-1} and Si-O stretching at 1099 cm^{-1} as a broad band) was in complete agreement with the proposed structure (Fig. 2). From the multiple SEM images, it can be determined that the average diameter of SiO_2 nanoparticles after immobilization of DBU is about 40 nm (Fig. 3).

Figure 1. XRD pattern of NSB-DBU

Figure 2. FT-IR spectra of (a) nano silica-n-propyl chloride and (b) NSB-DBU

Figure 3. FE-SEM of (a) Nano silica and (b) NSB-DBU

The amount of DBU grafted on nano silica was evaluated by the nitrogen content, 1.15 mmol/g, on the basis of elemental analysis (C: 16.92% H: 3.06% N: 3.22%). This amount was significantly higher than the loading level of DBU on silica gel as reported earlier (0.45 mmol/g).³⁸ Thermogravimetric (TG) analysis of NSB-DBU was also studied. The lost weight around 200°C can be related to the loss of the organic moiety (DBU) of NSB-DBU (Fig. 4). NSB-DBU showed almost 26% weight loss in this area (about 1.14 mmol of DBU per 1.0 g of the catalyst) which was in accordance with the results obtained from elemental analysis.

Figure 4. Thermal gravimetric analysis of nano silica and NSB-DBU

In order to evaluate the efficiency of NSB-DBU as catalyst, three-component synthesis of 2-amino-3-cyano-4*H*-chromenes was studied. For the optimization of the reaction conditions, the reaction of benzaldehyde, dimedone and malononitrile was chosen as a model reaction (Table 2). First, we studied the ability of different catalysts including nano SiO₂, nano MgO, nano TiO₂, nano ZnO and DBU in the synthesis of 2-amino-3-cyano-4*H*-chromene derivatives. As shown in Table 1, the reaction did not take place without any catalyst (Table 1, entry 1). It was observed that most interesting result was obtained with NSB-DBU as the catalyst. The best results were achieved by carrying out the reaction of benzaldehyde, dimedone and malononitrile (with

a 1:1:1 molar ratio) in the presence of 5 mol% of NSB-DBU in water at 50 °C. Subsequently, a series of differently substituted tetrahydrobenzo[*b*]pyran derivatives was prepared successfully under aqueous conditions (Table 3). The results clearly indicate that reactions can tolerate a wide range of differently substituted aldehydes. The reactions were complete within 20–40 min and excellent yields of products were obtained by this method. The aromatic aldehydes with electron withdrawing groups reacted faster with slightly improved yields than their electron donating counter parts (Table 3, entry 4–6). However, in case of aliphatic aldehydes, reactions were not complete under the above conditions and desired products were obtained in low yields.

Table 2. Optimization of reaction conditions^a

Entry	Catalyst (mol %)	Solvent	Temperature /°C	Time/min	Yields/% ^b
1	-	H ₂ O	50	180	Trace
2	SiO ₂ -NPs ^c (10)	H ₂ O	50	160	20
3	MgO- NPs (10)	H ₂ O	50	160	35
4	TiO ₂ - NPs (10)	H ₂ O	50	180	30
5	ZnO-NPs (10)	H ₂ O	50	180	30
6	DBU (10)	H ₂ O	50	75	45
7	NSB-DBU (20)	H ₂ O	50	30	93
8	NSB-DBU (10)	H ₂ O	50	15	93
9	NSB-DBU (5)	H ₂ O	50	20	93
10	NSB-DBU (5)	THF	50	120	48
11	NSB-DBU (5)	CHCl ₃	50	70	25
12	NSB-DBU (5)	CH ₂ Cl ₂	50	55	21
13	NSB-DBU (5)	EtOH	50	35	94
14	NSB-DBU (5)	CH ₃ CN	50	40	32
15	NSB-DBU (5)	H ₂ O	r.t.	30	78
16	NSB-DBU (5)	H ₂ O	reflux	15	93

^a Reaction and conditions: benzaldehyde (1 mmol), dimedone (1 mmol), malononitrile (1 mmol), different conditions, stirring.

^b Isolated yields.

^c NPs: Nano particles.

Table 3. Synthesis of 2-amino-4*H*-benzopyran derivatives in aqueous media^a

Entry	Aldehyde	Product	Time/min	Yield/% ^b	Melting point/°C	
					Found	Reported
1	PhCHO	4a	20	93	233-235	234–235 ³²
2	2-Cl-PhCHO	4b	25	91	212-213	214–215 ³⁹
3	4-Cl-PhCHO	4c	20	92	216-218	215-217 ⁴⁰
4	2-NO ₂ -PhCHO	4d	30	91	221-222	224–226 ⁴¹
5	3-NO ₂ -PhCHO	4e	20	95	211-212	212–214 ⁴¹
6	4-NO ₂ -PhCHO	4f	25	93	176-178	179–180 ⁴²
7	2-Br-PhCHO	4g	35	88	151-152	150–152 ⁴³
8	4-Br-PhCHO	4h	30	94	201-203	203–205 ⁴³
9	4-OMe-PhCHO	4i	30	90	199-200	201–202 ³²
10	4-Me-PhCHO	4j	40	86	229-231	223–225 ⁴²
11	4-CN-PhCHO	4k	30	89	208-210	208–210 ⁴²
12	4-Me ₂ N- PhCHO	4l	35	87	213-215	210–212 ⁴⁴
13	4-F-PhCHO	4m	35	88	206-209	210–211 ³⁸
14	4-OH-PhCHO	4n	30	90	204-205	206–208 ⁴³
15	CH ₃ (CH ₂) ₂ CHO	4o	480	12	-	-
16	CH ₃ CH ₂ CHO	4p	480	5	-	-

^a condition: Benzaldehyde derivative (1 mmol), malononitrile (1 mmol), dimedone (1 mmol), NSB-DBU (5 mol%, 0.05 g), H₂O (5 mL), 50 °C, stirring.

^b Isolated yield.

Figure 5. Reusability of the NSB-DBU in the synthesis of **4a**

A proposed mechanism for the synthesis of *4H*-chromenes is outlined in Scheme 3. Initially, NSB-DBU catalyzed the readily in situ formation of Knoevenagel product **5**. Afterward, enolate form of carbonyl compound **3** reacts with adduct **5** to produce intermediate **6**, which converts to product **4**, after proton transfer, cyclization and tautomerization.

Scheme 3. Proposed mechanism for the preparation of *4H*-chromenes.

3. EXPERIMENTAL

All chemicals and reagents were purchased from Fluka and Merck and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. NMR spectra were recorded with a Bruker DRX-400 AVANCE instrument (400.1 MHz for ^1H , 100.6 MHz for ^{13}C) with CDCl_3 or $\text{DMSO}-d_6$ as solvent. IR spectra were recorded on an FT-IR Bruker vector 22 spectrometer. Thermogravimetric analysis (TGA) was recorded on a Stanton Redcraft STA-780 (London, UK). The XRD was performed using PHILIPS Xpert pro diffractometer with $\text{Cu K}\alpha$ radiation (λ 1.54 Å). FE-SEM images were obtained on a Hitachi S-1460 field emission scanning electron microscope using an ACC voltage of 15 kV.

3.1. Preparation of nano silica-bonded 5-*n*-propyl-octahydro-pyrimido[1,2-*a*]azepinium chloride (NSB-DBU)

NSB-DBU was prepared according to our previously reported procedure.³³ First, nano silica-*n*-propyl chloride was prepared as reported earlier.³⁷ Then, a mixture of nano silica-*n*-propyl chloride (1.0 g) and 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.76 g, 5.0 mmol) in cyclohexane (30 mL) was added to a 50 mL round bottomed flask connected to a reflux condenser. The mixture was stirred under reflux conditions for 36 h. The resulting mixture was then filtered, extracted with toluene in a Soxhlet extractor for 24 h and dried at 60 °C in vacuo to give NSB-DBU as a white powder (1.3 g).

3.2. Synthesis of 2-amino-5-oxo-5,6,7,8-tetrahydro-4*H*-chromenes (**4a-n**)

A mixture of aldehyde derivatives (1 mmol), malononitrile (1 mmol), dimedone (1 mmol) and NSB-DBU (5 mol%, 0.05 g) in 5 mL H_2O was stirred at 50 °C until completion of reaction (TLC-control). Then, the solid was dispersed in hot ethanol, and the catalyst was removed by filtration. After cooling, the crude product was precipitated and then purified by recrystallization from ethanol. The recovered catalyst was dried and reused in further reactions.

3.3. Selected spectral data

2-Amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4a**)**. White powder; m.p.: 233-235 °C; yield (93%); IR (KBr) ν_{max} : 1681 (C=O), 2200 (CN), 2961 (H-Csp³), 3214 (N-H), 3323 (N-H) cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 0.96 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.10 and 2.26 (2d, $J=16.0$ Hz, 2H, CH_2), 2.50-2.52 (m, 2H, CH_2), 4.17 (s, 1H, CH), 7.01 (s, 2H, NH_2), 7.13-7.17 (m, 3H, 3 CH_{Ar}), 7.29 (t, $J=7.2$ Hz, 2H, 2 CH_{Ar}); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ : 27.3, 28.9, 32.3, 36.0, 39.6, 50.4, 58.7, 113.2, 120.2, 127.0, 127.6, 128.8, 145.2, 158.9, 163.0, 196.1.

2-Amino-4-(2-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (4b**)**. White powder; m.p.: 212-213 °C; yield (91%); IR (KBr) ν_{max} : 1673 (C=O), 2188 (CN), 3253 (N-H), 3372 (N-H) cm^{-1} ; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ : 0.92 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.09 and 2.22 (2d, $J=16.0$ Hz, 2H, CH_2), 2.52 (s, 2H, CH_2), 4.32 (s, 1H, CH), 7.03 (s, 2H, NH_2), 7.12 (t, $J=8.7$ Hz, 2H, 2 CH_{Ar}), 7.14-7.22 (m, 2H, 2 CH_{Ar}); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ : 27.4, 28.6, 32.3, 35.1, 50.2, 58.6, 113.5, 115.4, 115.8, 119.7, 129.5, 129.6, 140.6, 141.3, 158.8, 160.2, 162.4, 196.3.

4. CONCLUSIONS

In conclusion, highly efficient and environmentally green methodology for the synthesis of *4H*-chromene derivatives via the three-component reaction of aromatic aldehydes, malononitrile and dimedone has been developed in excellent yields (87-95%) within short reaction times (20-40 min). This protocol has several advantages including mild conditions, excellent yield, environmentally benign and an easy work-up procedure without the need for column chromatographic purification. The catalyst can be recovered and reused over several reaction cycles without considerable loss of reactivity.

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