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One-pot Synthesis of Amidoalkyl Naphthol Derivatives as Potential Nucleoside Antibiotics and HIV Protease Inhibitors using Nano-SnO_2 as an Efficient Catalyst

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Abstract

An efficient three-component one-pot synthesis of 1-amidoalkyl-2-naphthols from 2-naphthol, aldehydes, and acetamide using nano-SnO_2as catalyst is described. The reactions were carried out at 80 ^oC under water-solvent media. The structures of the compounds were characterized by IR, ^1H-NMR, ^{13}C-NMR, and Mass spectra and by elemental analysis. The advantages of the effective method were good yields, short reaction times, simple work-up, eco-friendly solvent, and inexpensive and reusable catalyst. The catalyst could be recycled and reused for five times without much loss in its activity.

Keywords: Amidoalkyl Naphthols, Multicomponent reactions (MCRs), One-pot synthesis, Nano-SnO_2, Eco-friendly solvent.

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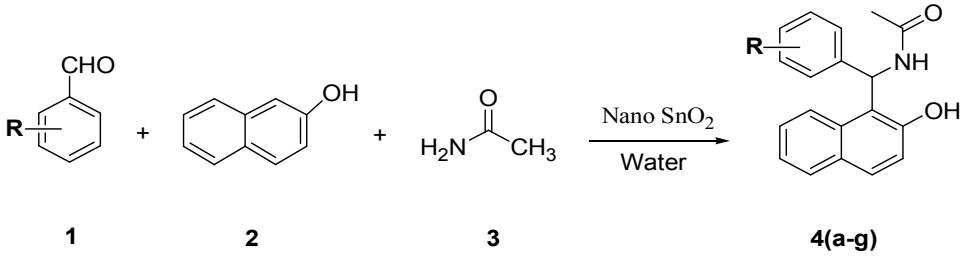
Introduction

In recent years, multicomponent reactions (MCRs) have gained much attention in organic synthesis as they furnish the desired products in a single operation without isolating the intermediates. Thus, reaction times are reduced and energy and raw materials saved. MCRs are an important tool for building of diverse and complex organic molecules through carbon-carbon and carbon-hetero atom bond formations taking place in tandem manner, particularly, three and four-component MCRs [1]. Compounds containing 1,3-amino-oxygenated functional groups are frequently found in biologically active natural products and potent drugs such as nucleoside antibiotics and HIV protease inhibitors. Furthermore, 1-amidoalkyl-2-naphthols can be converted to useful and important biological building blocks and to 1-aminomethyl-2-naphthols by an amide hydrolysis reaction, since these compounds exhibit antibacterial, hypotensive, and bradycardiac effects, etc [2-6].

1-Amidoalkyl-2-naphthols can be prepared by three-component condensation of 2-naphthol, aldehydes, and acetonitrile or different amides in the presence of Lewis or Brønsted acid catalysts [7]. Several protocol developed for this condensation reaction such as; *p*-TSA [8], ultrasound/sulfamic acid [9], Iodine [10] and montmorillonite K10 [11]. Although, these approaches are satisfactory for synthesis of 1-amidoalkyl 2-naphthols, prolonged reaction time, low product yields, toxic and corrosive reagents, and the use of additional microwave or ultrasonic irradiation, the harsh reaction conditions, and expensive reagents limit the use of these methods. Therefore, it was of interest to develop a more universal method for the synthesis of amidoalkyl naphthol derivatives. In this communication and in going on our works, a very simple and efficient method for the synthesis of 1-amidoalkyl-2-naphthol derivatives using nano-SnO_2 as a catalyst has been developed. Several derivatives of the title compounds with different substituents were synthesized, which shows the diversity of the method. The catalyst showed good efficiency for this transformation. Therefore, we believe this method could be an attractive alternative to existing methods for the synthesis of 1-amidoalkyl-2-naphthols (Scheme 1).



Scheme1. Synthesis of 1-amidoalkyl 2-naphthols.

Experimental

Material and equipments

Chemicals were supplied from Merck (Darmstadt, Germany) and Sigma-Aldrich chemical Co. (USA). Melting points were taken as uncorrected using a digital Electrothermal melting point apparatus **(***model 9100***,** *Electrothermal Engineering Ltd***.,** Essex,*UK*). ^{1}H-NMR spectra were obtained using a Bruker 300 MHz (model AMX, Karlsruhe, Germany) spectrometer (Internal standard: TMS) and values were expressed in ppm. The IR spectra were recorded using a Thermo Nicolet FT-IR (model *Nexus-870,* Nicolet Instrument Corp, Madison, Wisconsin, U.S.A.) spectrometer. Mass spectra were obtained using an Agilent Technologies 5973, Mass Selective Detector (MSD) spectrometer (Wilmington, USA). The purity of compounds was confirmed by TLC. Thin layer chromatography (TLC) on commercial aluminum-backed plates of silica gel, 60 F254 was used to monitor the progress of reactions. Elemental analyses were recorded using a Perkin-Elmer, CHN elemental analyzer model 2400 within ±0.4% of theoretical values for C, H and N. All products were characterized by spectra and physical data.

Preparation of catalyst

The $SnCl_2.2H_2O$ (2.26 g, 10 mmol, AR grade) and NaOH (0.08 g, 20 mmol, AR grade) were ground with a mortar and pestle for 15 min. Next, sodium chloride (NaCl) was added to the mixture at a molar ratio of 1:2 and further ground for another 30 min. The mixture was then oxidized and annealed for 2 h at 400°C. The final products were washed with water and dried for 2 h at 60 °C. This synthesis method produced a high yield (90% mass recovery) of SnO_2 nanoparticles [12].

General procedure for the synthesis of amidoalkyl naphthols

To a mixture of 2-naphthol (1 mmol), an aldehyde (1 mmol), and Aacetamide (1.5 mmol), and Water (5 ml), nano-SnO_2 (20 mg) was added. The reaction mixture was magnetically stirred and refluxed. The progress of the reaction was monitored by TLC using EtOAc**:**petroleum ether (1:2) as eluents. After completion of the reaction (monitored by TLC), the solvent evaporated. Acetone (10 ml) added to the mixture and stirred. After filtration, the solvent evaporated. The residue was re-crystallized from ethanol (15%) to give pure product. The products were characterized by comparing their mp, IR, ^{1}H-NMR, ^{13}-CNMR, and elemental analysis with those reported for authentic samples and with spectral data for some representative compounds.

Some representative compounds spectra data:

N-[(4-hydroxy-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide (**4d**)**:**
White-light yellow; FT-IR(KBr) cm^{-1}: 3409, 3288, 3190, 1630, 1233; ^1H NMR (400 MHz,$CDCl_3$) d (ppm): 1.96 (s, 3H), 6.16 (s, 1H), 6.64-7.86 (m, 10 HAr), 8.39 (s, OH), 8.41 (s, OH), 9.21 (s, NH). Anal. Calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.66; H, 5.90; N, 4.53. MS: m/z (regulatory intensity): 307 (100), 308 (21), 309 (3).

N-[(2-Hydroxy-naphthalen-1-yl)-(3-nitro-phenyl)-methyl]-acetamide **(4e):**
White needle; FT-IR(KBr) cm^{-1}: 3423, 3158, 1662, 1523, 1345; ^1H NMR (400 MHz,$CDCl_3$) d (ppm): 2.03 (s, 3H), 6.22 (s, 1H), 7.18-8.64 (m, 10 HAr), 8.66 (s, OH), 9.25 (s, NH). Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.55; H, 4.58; N, 8.56. Found: C, 67.66; H, 4.90; N, 8.53. MS: m/z (regulatory intensity): 336 (100), 337 (22), 338 (3).

N-[(2-Chloro-phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide **(4f):**
Faint white; FTIR(KBr) cm^{-1}: 3428, 3154, 1669, 1041; ^1H NMR (400 MHz,$CDCl_3$) d (ppm): 1.92 (s, 3H), 7.08-8.56 (m, 10 HAr), 8.58 (s, OH), 9.81 (s, NH). Anal. Calcd. for $C_{19}H_{16}ClNO_2$: C, 70.05; H, 4.95; N, 4.30. Found: C, 70.16; H, 4.90; N, 4.53. MS: m/z (regulatory intensity): 325 (100), 326 (21), 327 (2).

Results and discussion

To optimize the reaction conditions, the reaction of 2-naphthol, benzaldehyde, and acetamide was used as a model reaction. Armed with these experiences, herein, we wish to report an efficient and convenient rout for preparation of amidoalkyl naphthols using aldehydes, acetamide and 2-naphtol with catalytic amount of nano-SnO_2. The efficiency of this reaction evident from using the variety of withdrawing, and releasing electrons groups on aromatic moiety of aldehydes which are converted to the corresponding amidoalkyl naphthols in excellent yields and relatively short reaction time (Table 1).

Table 1. Synthesis of amidoalkyl naphthols.

Entry	R	Product	Time (min)	m.p. (°C)		Yield (%)[a]
				Observed	Reported	
1	Ph	**4a**	20	244-245	240-241 [13]	94
2	4-Me-Ph	**4b**	60	222-223	219-221 [13]	90
3	4-Cl-Ph	**4c**	15	233-235	235-238 [13]	96
4	4-OH-Ph	**4d**	40	223-224	221-223 [14]	92
5	3-NO_2-Ph	**4e**	15	240-241	241-243 [13]	95
6	2-Cl-Ph	**4f**	35	207-209	208-209 [13]	90
7	4-NO_2-Ph	**4g**	15	227-229	229-232 [13]	95

[a] Isolated yields.

We performed the effect of various solvents on the synthesis of **4a**. This reaction was carried out in various solvents and the best results in terms of yield and time obtained in water (Table 2).

Table 2. Synthesis of **4a** in the presence of different solvents using nano-SnO_2 as a catalyst.

Entry	Solvent	Yield (%)[a]
1	THF	68
2	C_2H_5OH	87
3	CH_3CN	90
4	EtOAc	88
5	water	94

[a]Yields were analyzed by GC

The reaction was studied with various amount of nano-SnO_2. In all cases, with 20 mg catalyst, the maximum yield of products was obtained and use of an increased amount of catalyst does not make much difference (Table 3).

Table 3. Synthesis of **4a**using various amount of nano-SnO_2.

Entry	Catalyst weight (mg)	Time (min)	Yield (%)[a]
1	No catalyst	24h	No reaction
2	10	20	91
3	20	20	94
4	30	20	94
5	50	20	94

[a]Yield of isolated products.

Reusability of nano-SnO_2

In Table 4, efficiency of nano-SnO_2 in synthesis of **4a**for the five runs is reported. As shown in Table 4, the first reaction using recovered nano-SnO_2 afforded similar yield to those obtained in the first run. In the second, third, fourth and fifth runs, the yield were gradually decreased.

Table 4. Reuse of the nano-SnO_2 for synthesis of **4a.**

Entry	Time (min)	Yield (%)[a]
First run	20	94
Second run	20	93
Third run	20	92
Fourth run	20	89
Fifth run	20	87

[a]Isolated yields

It is known that, the specific surface area and surface-to-volume ratio increase dramatically as the size of a material decreases. The high surface area brought about by nanoparticle size is beneficial to many SnO_2-based devices, as it facilitates reaction/interaction between the devices and the interacting media. The previous research works on SnO_2 were reported by Seiyama [15] in 1962 as semiconductor materials for gas sensor materials and alternative energy. Its outstanding electrical, optical an delectro-chemical properties of SnO_2 enable applications in solar cells, catalytic support materials, transparent electrodes, and solid state chemical sensors [16].They were successfully synthesized by different methods. Various methods, including molten-salt synthesis [17] sol-gel

[18], microwave technique [19,20],carbothermal reduction [21],chemical precipitation [22], laser-ablation synthesis [23], hydrothermal method [24,25], and sonochemical [26]have been developed to synthesize SnO_2 nanostructures. The investigation on nano-SnO_2 catalytic activity for the synthesis of many organic molecules is current work in our laboratory. Transmission electron microscope (TEM) images were obtained from a JEOL JEM-2010 Instrument (Houghton, MI, USA) (Figure 1). The morphology and structure of the nanostructures were characterized using a scanning electron microscope (SEM: JSM-6700F) operating at 10 kV and a transmission electron microscope (TEM: JEOL-2100) with an accelerating voltage of 300 kV (Figure 2).

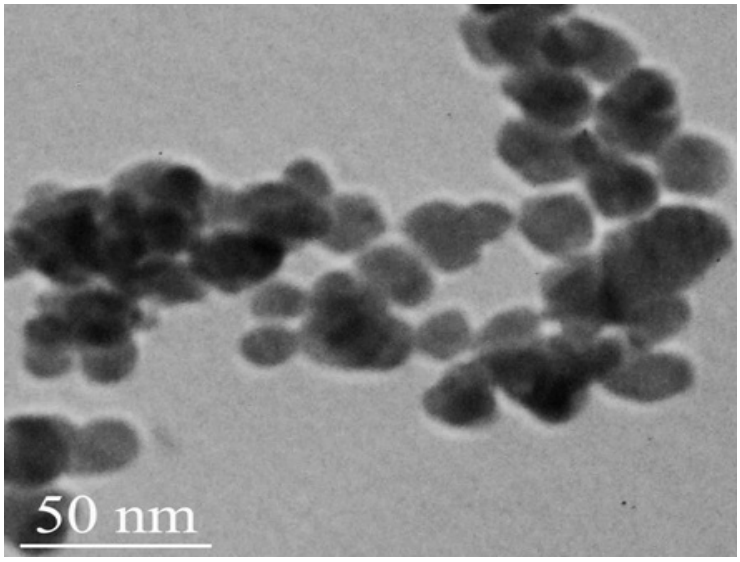


Figure 1. Transmission electron microscope (TEM) image of nano-SnO_2.

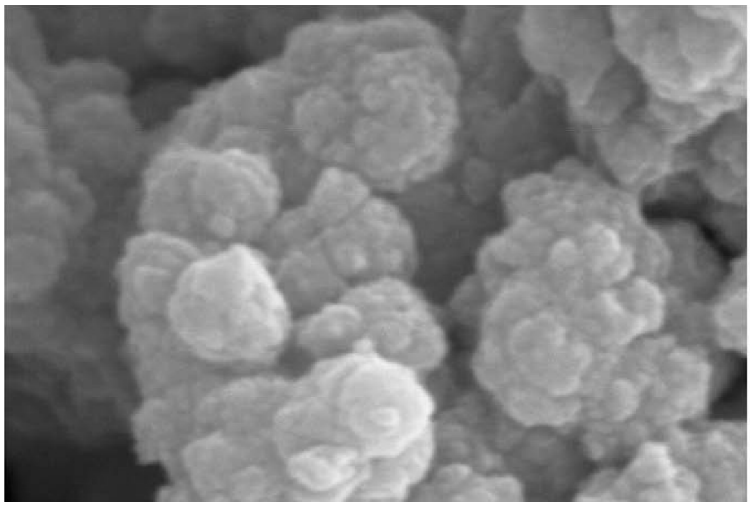
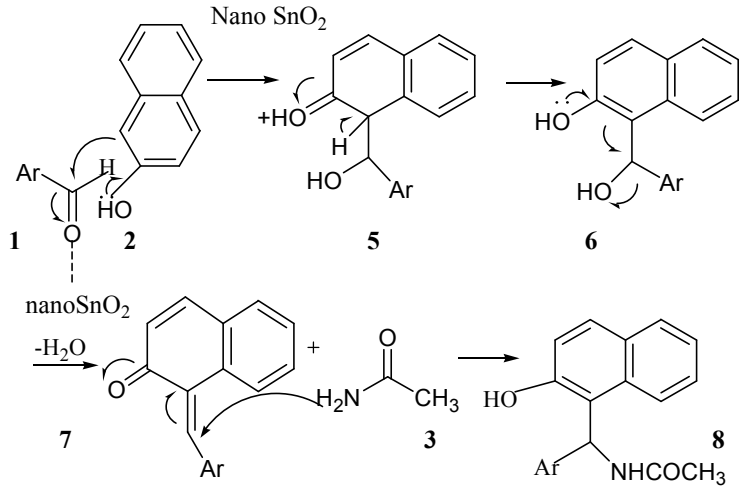


Figure 2. Scanning electron microscope (SEM) image of nano-SnO_2.

A probable mechanism for this reaction has been suggested in Scheme 2. In first step the naphthol condenses with aldehyde that activated with the catalyst to afford intermediate **5**. Then tautomerism

the intermediate **5** after remove water and the acetamide attack. Finally, the expected products **4** were obtained.



Scheme 2. Proposed mechanism for the synthesis of amidoalkyl naphthols.

Conclusion

In conclusion, we have developed a simple and efficient method for the synthesis of amidoalkyl naphthols via a one-pot three–component reaction of 2-naphthol, acetamide and aldehyde using nano-SnO_2 as heterogeneous and recyclable catalystsin good yields. The advantages of the present procedure are experimental simplicity, easy work-up procedure, use of an easy to handle, safe reagent and high yields of products.

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