Journal of Pharmaceutical and Scientific Innovation
www.jpsionline.com
Research Article

ONE POT PREPARATIONS 1-AMIDOALKYL-2-NAPHTHOLS DERIVATIVE CATALYZED BY NANO-$TiCl_4.SiO_2$ WITH ANTIMICROBIAL STUDIES OF SOME PRODUCTS

Leila Zamani[1], Kamiar Zomorodian*[2], Bi Bi Fatemeh Mirjalili[1], Soghra Khabnadideh[3]
[1]Department of Chemistry, Yazd University, Yazd , Iran
[2]Center of Basic Researches in Infectious Diseases and Department of Medical Mycology and Parasitology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
*Corresponding Author Email: zomorodian@sums.ac.ir , kzomorodian@gmail.com
DOI: 10.7897/2277-4572.033141
Published by Moksha Publishing House. Website www.mokshaph.com

Received on: 25/05/14 Revised on: 12/06/14 Accepted on: 20/06/14

ABSTRACT
Nano-$TiCl_4{\cdot}SiO_2$ has been introduced to be an extremely efficient catalyst for the preparation of 1-amidoalkyl-2-naphthols from various aldehydes and amides under mild conditions. We synthesized this solid Lewis acid catalyst by the reaction of nano-SiO_2 and $TiCl_4$. The processor was simple and environmentally benign with high to excellent yields. Our method has the advantages of high yields, simple methodology, and easy work-up. We studied the different properties of the catalyst by FT-IR (ATR), X-ray diffraction (XRD), scanning electron microscope (SEM), transmission electron microscopy (TEM) and thermal gravimetric analysis (TGA). It was stable at high temperature and also it was reusable for at least three times. The antimicrobial and antifungal activities of some of the synthetic compounds were determined by broth microdilution methods as recommended by Clinical Laboratory Standard Institute. Further studies still needed to investigate the other biological activities of the compounds.
Keywords: Nano-$TiCl_4.SiO_2$, Heterogeneous catalyst, Aminoalkyl naphthols, antifungal, antibacterial.

INTRODUCTION

Aminoalkyl naphthols are precursors for the synthesis of 1-aminomethyl-2-naphthol derivatives, which can be easily converted into biologically active 1-aminoalkyl-2-naphthols derivatives by amide hydrolysis. Aminoalkyl naphthols have been frequently applied as hypotensive and bradycardiac agents.[1-3] Amidoalkyl naphthols can be also converted to 1,3 Oxazine derivatives.[4] Compounds containing 1,3-amino-oxygenated functional groups arerequently found in biologically active natural products and strong drugs such as antitumor,[5] analgesic,[6] anticonvulsant,[7] antianginal,[8] antihypertensive,[9] antipsychotic,[10] antirheumatic properties,[11] antimalarial,[12] nucleoside antibiotics and HIV protease inhibitors.[13-15]

The preparation of aminoalkyl naphthols can be carried out by one pot reaction condensation of aldehydes and 2-naphtole and amide or urea in the presence of Lewis or Bronsted acid or heterogonous catalysts like $H_3PW_{12}O_{40}$,[16] $H_4SiW_{12}O_{40}$,[17] $KHSO_4$,[18] P_2O_5,[19] $HClO_4.SiO_2$,[20] and thiamine hydrochloride,[21] have been utilized for the synthesis of 1-amidoalkyl-2-naphthols. However, some of the catalysts used suffer drawbacks such as long reaction time, toxicity, cost and unavailability of the catalyst. To avoid these limitations, our studies towards the development of more efficient methods accompanied with higher yields for the synthesis of 1-amidoalkyl-2-naphthols in the presence of nano-$TiCl_4{\cdot}SiO_2$. In addition, the antimicrobial and antifungal activities of some of the synthetic compounds were evaluated by broth microdilution methods.

MATERIALS AND METHODS

General

The chemicals were purchesed from Merck Company and used without any additional purification. The products were characterized by FT-IR (ATR), ^{1}H-NMR, and a comparison of their physical properties with those reported in the literature. FT-IR (ATR) spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-400 Avance) NMR was used to record the ^{1}H NMR spectra. The X-ray diffraction (XRD) patterns of materials were recorded by employing a Philips Xpert MPD diffractometer equipped with a Cu Kα anode (λ=1.54 A°) in the 2θ range from 10 to 80°. The SEM of nano particles determined with VEGA/TESCAN scanning electron microscope and TEM photograph was prepared by Leo 912AB OMEGA microscope. The thermal gravimetric analysis (TGA) was done with "NETZSCH TG 209 F1 Iris" instrument, Spectrophotometer (Company BAUSCH & LOMB, US), Vortex mixer (Company Lab net).

Preparation of nano-$TiCl_4.SiO_2$

0.5 g (0.29 ml) of $TiCl_4$ was added drop wise to a mixture of 0.5 g of nano silica gel and 5 ml of chloroform. The mixture was stirred at room temperature for one hour and the resulted suspension was filtered. The obtained solid was washed with chloroform and dried at room temperature.

General experimental procedure for the synthesis of 1-amidoalkyl-2-naphthols

A mixture of an aldehyde (1 mmol), 2-naphthol (1 mmol, 0.144 g), amide (1.2 mmol), and 50% $TiCl_4.SiO_2$ (0.05 g) was heated under solvent free condition with good stirring. The progress of the reaction was followed by TLC. After completion of the reaction, the mixture was cooled to room temperature. Chloroform was added to the mixture and filtrated to removal of the catalyst. By cooling the filtrate, the 1-amidoalkyl-2-naphthol was appeared as pure solid that re-crystallized in hot ethanol.

N-[(2-hydroxynaphthalen-1-yl)-phenyl-methyl]acetamide (N1)
Benaldehyde (1 mmol), 2-naphthol (1 mmol, 0.144 g), acetamide (1.2 mmol), and 50% $TiCl_4.SiO_2$ (0.05 g) according to the general procedure to give the desired product N1 as a white solid, FT- IR: vmax (ATR, neat, cm-1): 3398 (NH stretch), 3350-3000 (OH, CH stretch), 1636 (C=O stretch), 1582, 1436 (C=C stretch), 1513 (NH bend), 740, 695 (CH bend); 1H NMR (400 MHz, DMSO-d6, ppm): δ = 1.96 (s, 3H), 7.18 (m, 8H), 7.33 (br s, 1H), 7.79 (m, 3H), 8.45 (br s, 1H), 9.99 (br s, 1H).

N-[(2-hydroxynaphthalen-1-yl)-p-chlorophenyl-methyl]acetamide (N2)
4-Chlorobenaldehyde (1 mmol), 2-naphthol (1 mmol, 0.144 g), acetamide (1.2 mmol), and 50% $TiCl_4.SiO_2$ (0.05 g) according to the general procedure to give the desired product N2 as a white solid, FT- IR: vmax (ATR, neat, cm-1): 3391 (NH stretch), 3200-2500 (OH, CH stretch), 1620 (C=O stretch), 1600, 1438 (C=C stretch), 1513 (NH bend), 818, 747 (CH bend); 1H NMR (400 MHz, DMSO-d6, ppm): δ = 1.96 (s, 3H), 7.07 (d, J= 7.2 Hz, 1H), 7.12-7.35 (m, 7H), 7,77 (m, 3H), 8.45 (d, J= 7.6 Hz, 1H), 10.02 (s, 1H).

N-[(2-hydroxynaphthalen-1-yl)-p-bromophenyl-methyl]acetamide (N3)
4-Bromobenaldehyde (1 mmol), 2-naphthol (1 mmol, 0.144 g), acetamide (1.2 mmol), and 50% $TiCl_4.SiO_2$ (0.05 g) according to the general procedure to give the desired product N3 as a white solid, FT- IR: vmax (ATR, neat, cm-1): 3391 (NH stretch), 3300-2500 (OH, CH stretch), 1624 (C=O stretch), 1579, 1438 (C=C stretch), 1514 (NH bend), 846, 746 (CH bend); 1H NMR (400 MHz, DMSO-d6, ppm): δ = 1.98 (s, 3H), 7.08 (br s, 3H), 7.23 (m, 2H), 7.37 (br s, 1H), 7.43 (br s, 2H), 7.76 (s, 1H), 7.78 (br s, 2H), 8.49 (br s, 1H), 10.05 (s, 1H).

N-[(2-hydroxynaphthalen-1-yl)-p-methylphenyl-methyl]acetamide (N4)
4-Methylbenaldehyde (1 mmol), 2-naphthol (1 mmol, 0.144 g), acetamide (1.2 mmol), and 50% $TiCl_4.SiO_2$ (0.05 g) according to the general procedure to give the desired product N4 as a white solid, FT- IR: vmax (ATR, neat, cm-1): 3396 (NH stretch), 3200-2590 (OH, CH stretch), 1624 (C=O stretch), 1581, 1437 (C=C stretch), 1514 (NH bend), 812, 743 (CH bend); 1H NMR (400 MHz, DMSO-d6, ppm): δ = 1.95 (s, 3H), 2.21 (s, 3H), 7.05 (m, 4H), 7.2 (m, 2H), 7.35 (br s, 1H), 7.74 (d, J= 8 Hz, 2H), 7.79 (d, J= 7.2 Hz, 2H), 8.4 (br s, 1H), 9.95 (br s, 1H).

N-[(2-hydroxynaphthalen-1-yl)-p-nitrophenyl-methyl]acetamide (N5)
4-Nitrobenaldehyde (1 mmol), 2-naphthol (1 mmol, 0.144 g), acetamide (1.2 mmol), and 50% $TiCl_4.SiO_2$ (0.05 g) according to the general procedure to give the desired product N5 as a white solid, FT- IR: vmax (ATR, neat, cm-1): 3390 (NH stretch), 3300-2800 (OH, CH stretch), 1639 (C=O stretch), 1620, 1438 (C=C stretch), 1520, 1349 (N=O stretch) 824, 751 (CH bend); 1H NMR (400 MHz, DMSO-d6, ppm): δ = 2.02 (s, 3H), 7.13 (d, J= 9 Hz, 1H), 7.17 (d, J= 9 Hz, 1H), 7.22 (t, J= 7.6 Hz, 1H), 7.34 (d, J= 8.6 Hz, 2H), 7.38 (br s, 1H), 7.64 (d, J= 8.8 Hz, 1H), 7.7 (d, J= 8 Hz, 1H), 7.91 (br s, 1H), 7.97 (d, J= 8.6 Hz, 2H), 8.03 (d, J= 8 Hz, 1H), 9.72 (s, 1H); 13C NMR (100 MHz, DMSO-d6, ppm): δ = 22.98, 48.34, 118.32, 118.86, 123.05, 123.38, 123.70, 127.18, 127.59, 128.90, 129.14, 130.35, 132.65, 146.35, 151.69, 153.80, 170.23.

N-[(2-hydroxynaphthalen-1-yl)-3-prydil-methyl]acetamide (N6)
4-Pyridinecarboxaldehyde (1 mmol), 2-naphthol (1 mmol, 0.144 g), acetamide (1.2 mmol), and 50% $TiCl_4.SiO_2$ (0.05 g) according to the general procedure to give the desired product N6 as a white solid, FT- IR: vmax (ATR, neat, cm-1): 3300-3000 (NH, OH, CH stretch), 1642 (C=O stretch), 1577, 1425 (C=C stretch), 1514 (NH bend), 743 (CH bend); 1H NMR (400 MHz, DMSO-d6, ppm): δ = 1.98 (s, 3H), 7.14 (d, J= 7.6 Hz, 1H), 7.21 (d, J= 8.8 Hz, 1H), 7.26 (br s, 2H), 7.39 (br s, 1H), 7.51 (d, J= 6.8 Hz, 1H), 7.81 (m, 3H),8.36 (br s, 2H), 8.55 (d, J= 7.2 Hz, 1H), 10.11 (s, 1H).

N-[(2-hydroxynaphthalen-1-yl)-phenyl-methyl]benzamide (N7)
Benzaldehyde (1 mmol), 2-naphthol (1 mmol, 0.144 g), benzamide (1.2 mmol), and 50% $TiCl_4.SiO_2$ (0.05 g) according to the general procedure to give the desired product N7 as a white solid, FT- IR: vmax (ATR, neat, cm-1): 3420 (NH stretch), 3400-2900 (OH, CH stretch), 1627 (C=O stretch), 1572, 1435 (C=C stretch), 1532 (NH bend), 750, 696 (CH bend); 1H NMR (400 MHz, DMSO-d6, ppm): δ = 7.25 (m, 8H), 7.47 (t, J= 6.4 Hz, 3H), 7.53 (d, J= 6.8 Hz, 1H), 7.82 (m, 4H), 8.07 (d, J= 8 Hz, 1H), 9.03 (d, J= 8 Hz, 1H), 10.34 (br s, 1H).

N-[(2-hydroxynaphthalen-1-yl)-p-methylphenyl-methyl]benzamide (N8)
4-Methylbenzdehyde (1 mmol), 2-naphthol (1 mmol, 0.144 g), benzamide (1.2 mmol), and 50% $TiCl_4.SiO_2$ (0.05 g) according to the general procedure to give the desired product N8 as a white solid, FT- IR: vmax (ATR, neat, cm-1): 3414 (NH stretch), 3400-3000 (OH, CH stretch), 1626 (C=O stretch), 1575, 1437 (C=C stretch), 1513 (NH bend), 816, 750 (CH bend); 1H NMR (400 MHz, DMSO-d6, ppm): δ = 2.22 (s, 3H), 7.06 (d, J= 8 Hz, 2H), 7.15 (d, J= 8 Hz, 2H), 7.22 (d, J = 9 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 7.29 (t, J = 8.8 Hz, 1H), 7.47 (m, 3H), 7.54 (t, J= 7.2 Hz, 1H), 7.78 (d, J= 8.8 Hz, 1H), 7.83 (m, 3H), 8.05 (d, J= 8 Hz, 1H), 8.99 (d, J= 8, 1H), 10.3 (s, 1H).

N-[(2-hydroxynaphthalen-1-yl)-p-nitrolphenyl-methyl]benzamide (N9)
4-Nitrobenzaldehyde (1 mmol), 2-naphthol (1 mmol, 0.144 g), benzamide (1.2 mmol), and 50% $TiCl_4.SiO_2$ (0.05 g) according to the general procedure to give the desired product N9 as a white solid, FT- IR: vmax (ATR, neat, cm-1): 3412 (NH stretch), 3400-3200 (OH, CH stretch), 1638 (C=O stretch), 1605, 1439 (C=C stretch), 1514 (NH bend), 1577,1343 (N=O stretch) 851, 748 (CH bend), 1H NMR (400 MHz, DMSO-d6, ppm): δ = 7.31 (d, J= 8.8 Hz, 1H), 7.39 (t, J= 7.4 Hz, 1H), 7.49 (t, J= 7.4 Hz, 2H), 7.59 (m, 5H), 7.89 (t, J= 8 Hz, 2H), 7.96 (d, J= 8 Hz, 2H), 8.16 (d, J= 8 Hz, 2H), 8.24 (d, J= 8 Hz, 1H), 8.82 (br s, 1H), 9.52 (s, 1H); 13C NMR (100 MHz, DMSO-d6, ppm): δ = 49.51, 117.86, 119.03, 123.11, 123.25, 123.86, 127.46, 127.91, 128.03, 128.90, 129.19, 130.45, 132.05, 132.75, 134.44, 146.61, 150.76, 153.94, 166.77.

N-[(2-hydroxynaphthalen-1-yl)-2,6-dichlorophenyl-methyl]benzamide (N10)

2,6-Dichlorobenaldehyde (1 mmol), 2-naphthol (1 mmol, 0.144 g), benzamide (1.2 mmol), and 50% $TiCl_4.SiO_2$ (0.05 g) according to the general procedure to give the desired product N10 as a white solid, FT- IR: vmax (ATR, neat, cm-1): 3419 (NH stretch), 3300-3000 (OH, CH stretch), 1628 (C=O stretch), 1578, 1435 (C=C stretch), 1515 (NH bend), 743 (CH bend); 1H NMR (400 MHz, DMSO-d6, ppm): δ = 7.02 (d, J= 7.6 Hz, 1H), 7.25 (m, 2H), 7.35 (d, J= 6.8 Hz, 2H), 7.45 (m, 5H), 7.73 (d, J= 7.6 Hz, 1H), 7.8 (d, J= 8 Hz, 1H),7.84 (br s, 1H), 7.94 (br s, 2H), 9.19 (br s, 1H), 9.68 (br s, 1H).

Biological study

Microorganisms

The antifungal activities of some of the synthetic compounds against 12 American Type Culture Collection (ATCC) strains of fungi, including C. albicans (ATCC 10261), C. tropicalis (ATCC 750), C. krusei (ATCC 6258), C. glabrata (ATCC 90030), C. dubliniensis (CBS 8501), C. parapsilosis (ATCC 4344), C. neoformance, A. flavus (ATCC64025), E. floccosum, M. gypseum, T. mentagrophytes, and A. fumigatus (ATCC 14110) were determined.

The antibacterial activities of the above compounds against standard species of S. aureus (ATCC 25923), En. Faecalis (ATCC 11700) and P. aeruginosa (ATCC 27853) were also determined in this study. The susceptibility of all clinical isolates of fungi against select compounds was examined by microdilution and disk diffusion methods.[22]

Determination of minimum inhibitory concentration (MIC)

MICs were determined using broth microdilution method recommended by the CLSI with some modifications.[23-25] Briefly, for determination of antifungal activities against fungi, serial dilutions of the synthetic compounds (0.25 to 256.0 µg/ml) were prepared in 96-well microtitre plates using RPMI-1640 media (Sigma, St. Louis, USA) buffered with MOPS (Sigma, St. Louis, USA). In order to determine the antibacterial activities, serial dilutions of the synthetic compounds (0.25 to 256.0 µg/ml) were prepared in Muller-Hinton Broth media (Merck, Darmstadt, Germany). Test fungi or bacteria strains were suspended in the media and the cell densities were adjusted to 0.5 McFarland standards at 530 nm wavelength using a spectrophotometeric method (this yields stock suspension of 1-5 × 10^6 cells/ml for yeast and 1-1.5 × 10^8 cells/ml for bacteria). One hundred microliter of the working inoculums was added to the micotiter plates which were incubated in a humid atmosphere at 30°C for 24 - 48 h (fungi) or at 37°C for 24 h (bacteria). Two hundred microliter of the uninoculated medium was included as a sterility control (blank). In addition, growth controls (medium with inoculums but without drugs) were also included. The growth in each well was compared with that of the growth control well. MICs were visually determined and defined as the lowest concentration of the synthetic compounds or drugs produced no visible growth. Each experiment was performed in triplicate. Media from wells with fungi showing no visible growth were further cultured on Sabouraud Dextrose Agar (Merck, Darmstadt, Germany) and from wells with bacteria showing no visible growth on Muller-Hinton agar (Merck, Darmstadt, Germany) specified as minimum fungicidal concentration (MFC) and minimum bactericidal concentration (MBC) respectively. MFCs and MBCs were determined as the lowest concentration yielding no more than 4 colonies, which corresponds to a mortality of 99.9% of the microorganisms in the initial inoculums.

RESULTS AND DISCUSSION

Identification of Nano-$TiCl_4.SiO_2$

$TiCl_4.SiO_2$,[26-27] is an efficient and reusable acidic catalyst. This catalyst is synthesized via reaction of nano-silica gel with $TiCl_4$ in chloroform at room temperature. For the identification of the structure of nano-$TiCl_4.SiO_2$, we studied IR spectra of nano-SiO_2, nano-$TiCl_4.SiO_2$ and $TiCl_4$ (Figure 1). In spectra of chloroform washed nano-SiO_2 and nano-$TiCl_4.SiO_2$, OH stretching bands are very flat. The process of washing with chloroform removed the moisture from nano-silicagel or nano-$TiCl_4.SiO_2$ and therefore the number of O-H bonds in comparison with Si-O-Si bonds in silicagel is decreased. In FT-IR spectra of nano-$TiCl_4.SiO_2$ and nano-SiO_2, the absorption bands for Si-OH and Si-O-Si appear in ~700 cm^{-1} and ~1100 cm^{-1}, respectively. The absorption band of Ti-Cl appear in 1600 cm^{-1} in $TiCl_4$ spectrum. In FT-IR spectrum of nano-$TiCl_4.SiO_2$, the O-Ti-Cl, Si-OH and Si-O-Si absorption bands are observed in 900, 700 and 1100 cm^{-1} respectively. In this study on nano-$TiCl_4.SiO_2$ structure led to more exactly configuration containing SiO_2-$TiCl_3$ (19%) and SiO_2-$TiCl_2$-SiO_2 (81%) as Figure 2.

The X-ray diffraction (XRD) patterns of nano-SiO_2 and nano-$TiCl_4.SiO_2$ are shown in Figure 3. According to Scherrer equation, the broadening of peaks implies the decrease in crystalline size of nano-$TiCl_4.SiO_2$. The XRD pattern of nano-SiO_2 has a strong peak in 2θ value of 21.8024° with FWHM equal to 0.1771. According to XRD pattern of nano-$TiCl_4.SiO_2$, the values of 2θ and FWHM are shown in Table 1.

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) image of nano-$TiCl_4.SiO_2$ were shown in Figure 4. The particle size in TEM pattern is calculated between 14-20 nm by GetData Graph program.

Thermal gravimetric analysis (TGA) pattern of nano-$TiCl_4.SiO_2$ was detected from 23.43 to 513.43°C (Figure 5). The catalyst is stable bellow 173.43°C and only 2.98% of its weight was reduced in 173.43°C. By heating of catalyst between 173 to 513.43°C, the reducing amount of its weight is 2.15%. Only 5.13% of the catalyst weight was reduced between 23.43 to 513.43°C. This initial reducing mass (2.98%) of catalyst is related to removal of catalyst moisture.

Nano-$TiCl_4.SiO_2$ was catalyzed synthesis of 1-amidoalkyl-2-naphthols

The reaction of 2-naphthol (1 mmol), 4-nitrobenzaldehyde (1 mmol) and acetamide (1.2 mmol) was performed under various conditions and different quantities of 50%$TiCl_4.SiO_2$ (Table 1). According to the obtained data, the best conditions are the reaction at 90 °C in solvent free condition using 0.05 g of 50% $TiCl_4.SiO_2$ or 0.02 g of 50% nano-$TiCl_4.SiO_2$ (Table 2, Entries 7, 12). It was found that the activity of 50% nano-$TiCl_4.SiO_2$ is 2.5 times of 50% $TiCl_4.SiO_2$. To examine the reusability of nano-$TiCl_4.SiO_2$ in a solvent-free condition, after each run, the product was dissolved to $CHCl_3$ and filtered.

Reusability of catalyst

Once the scope of the reaction condition was established, the reusability of catalyst was examined. After performing the

reaction, the catalyst was separated, washed with acetone, dried and re-used up to 3 times in reaction without losing its activity (Figure 6).

The catalyst was reusable although a gradual decline was observed in its activity. The applicability of the present method to preparation of large amount of product was examined. We have condensed 5 mmol of 2-naphthol, 5 mmol of benzaldehyde and 7 mmol of acetamide in the presence of 0.1 g of 50% nano-$TiCl_4 \cdot SiO_2$ under solvent free condition at 90 °C which gave N-[(2-hydroxynaphthalen-1-yl)- phenyl-methyl]acetamide in 95% yield. According to the obtained best condition, we have applied 2-naphthol and various aldehydes, and amide for the synthesis of 1-amidoalkyl-2-naphthols derivatives (Scheme 1 and Table 3). With aldehydes containing electron withdrawing group such as 4-nitrobenzaldehyde, the yield of product is higher in shorter time (Table 3, Entries 6-9). On the contrary, the aldehydes with electron releasing groups act with lower yields in longer times (Table 3, Entry 5).

Aliphatic aldehydes were also examined, but the yields of them were low as compared to those of products from aromatic aldehydes. The reactions of urea or thiourea with acetamide and 2-naphthol were examined, but no corresponding products were produced. Also, aniline was utilized and N-[(2-hydroxynaphthalen-1-yl)-p-nitrophenyl-methyl]aniline as a green solid with high yield (98%) was produced (Scheme 2). Meanwhile, this product was formed by reaction of 2-naphthol with imine (1) (Scheme 3).

The reaction among 4-nitrobenzaldehye, phenol and benzamide produce N-[(2-hydroxyphenol-1-yl)-p-nitrolphenyl-methyl]benzamide with medium yield (80 %) (Scheme 4). Previously, two type of mechanism were suggested for 1-amidoalkyl-2-naphthols formation. In the first one, the ortho-quinone methides (O-QMs)[16,17,21] and in the second one an N-acylimine[21] was introduced as intermediate. For investigation about mechanism of 1-amidoalkyl-2-naphthols formation, when we have reacted 1 mmol of 4-nitrobenzaldehyde with 1 mmol of 2- naphthol, only 14-(4-nitrophenyl)-14H-dibenzo[a,j]xanthene was formed without o-QMs intermediate. When we have reacted 1 mmol of acetamide with 1 mmol of 4-nitrobenzaldehye in the presence of $TiCl_4.SiO_2$, the product N,N'-(4-nitrophenylmethylene) diacetamide (2) was formed, isolated and identified. By reaction of (2) with 2- naphthol in the presence of $TiCl_4.SiO_2$, the final product N-[(4-nitro phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]-acetamide was formed (Scheme 5).

According to our data, we have established another mechanism for the formation of 1-amidoalkyl-2-naphthols in Scheme 6.

None of the selected compounds exhibited antifungal activity against the examined fungi at the tested concentrations. Moreover, the examined compounds failed to inhibit the growth of the Gram-positive and gram-negative bacteria at the concentration up to and including 256µg/mL. Further studies still needed to investigate other biological activities of these compounds.

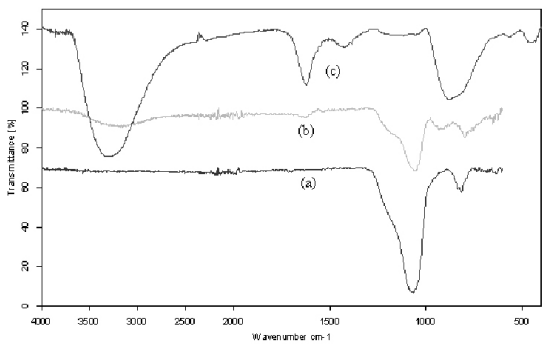


Figure 1: FT-IR spectrum of: (a) SiO_2, (b) nano-$TiCl_4.SiO_2$, and (c) $TiCl_4$.

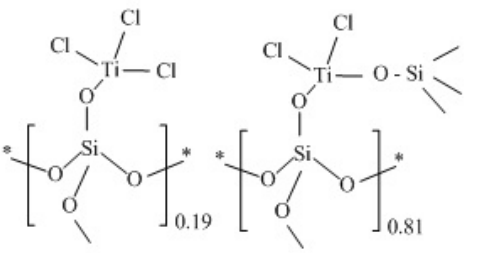


Figure 2: Suggested structure for nano-$TiCl_4.SiO_2$.

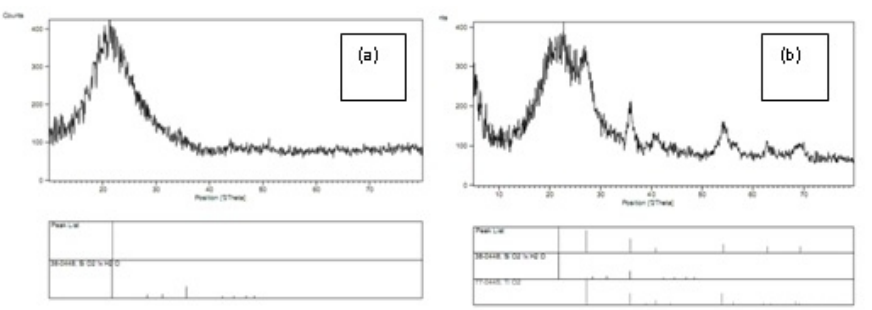


Figure 3: X-ray diffraction (XRD) pattern of a) nano-SiO_2 and b) nano-$TiCl_4.SiO_2$

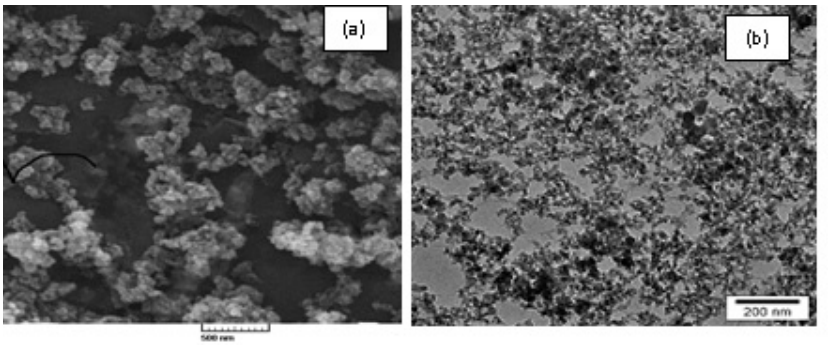


Figure 4: a) SEM and b) TEM image of nano-$TiCl_4.SiO_2$

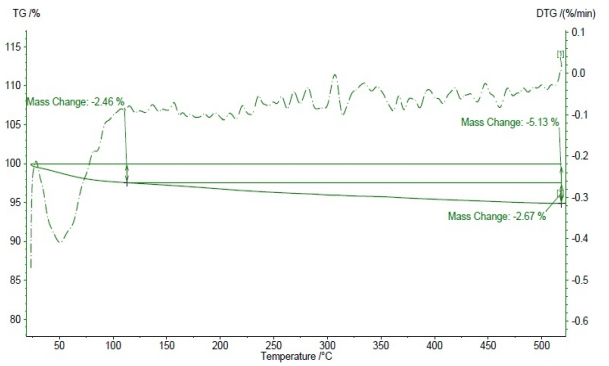


Figure 5: TGA pattern of nano-$TiCl_4.SiO_2$

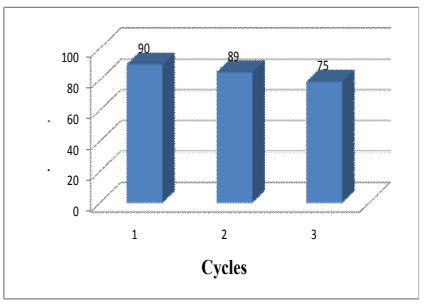
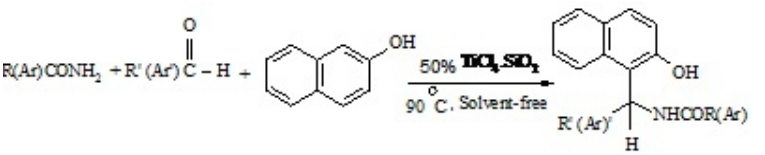
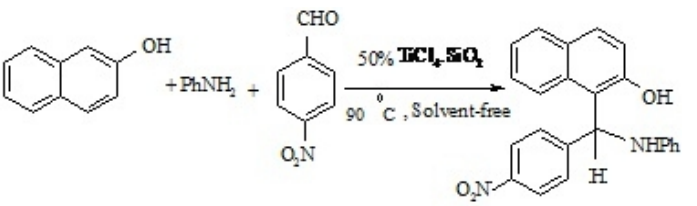


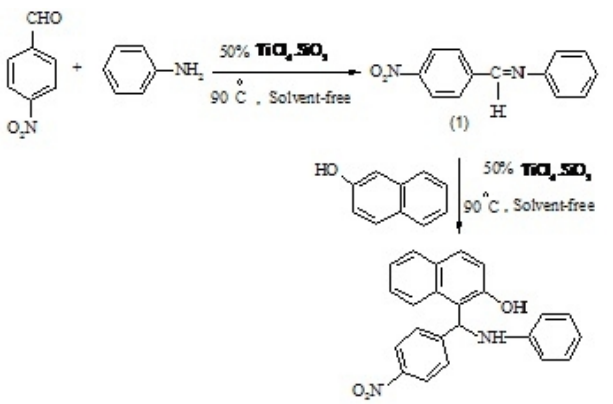
Figure 6: Reusability of nano-$TiCl_4.SiO_2$ catalyst.



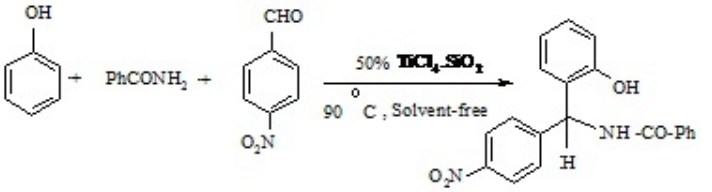
Scheme 1: Synthesis of 1-amidoalkyl-2-naphthols derivatives in the presence of 50% nano-$TiCl_4.SiO_2$



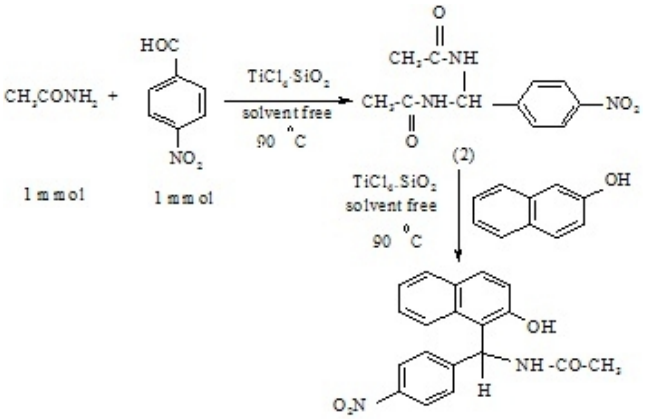
Scheme 2: Synthesis of N-[(2-hydroxynaphthalen-1-yl)-p-nitrophenyl-methyl]aniline in the presence of 50% $TiCl_4.SiO_2$



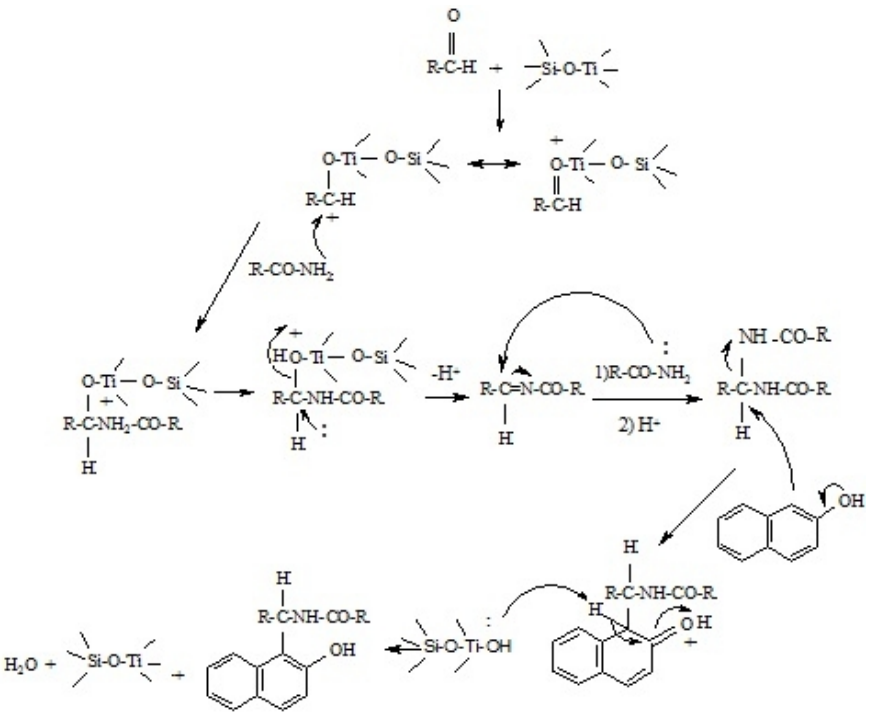
Scheme 3: Stepwise synthesis of N-[(2-hydroxynaphthalen-1-yl)-4-nitrophenyl-methyl]aniline in the presence of 50% $TiCl_4.SiO_2$



Scheme 4: Synthesis of N-[(2-hydroxyphenol-1-yl)-4-nitrolphenyl-methyl]benzamide in the presence of 50% $TiCl_4.SiO_2$



Scheme 5: Synthesis of 1-amidoalkyl-2-naphthol

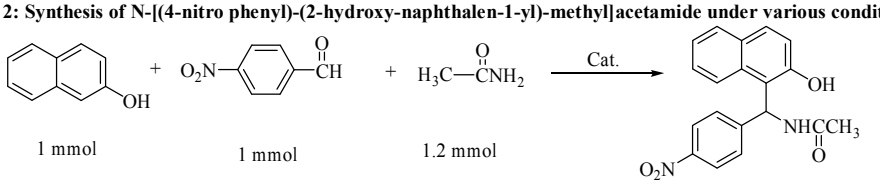


Scheme 6: A suggested mechanism for the formation of 1-amidoalkyl-2-naphthols

Table 1: Nano-$TiCl_4.SiO_2$ reflexes in XRD diffractogram

Entry	Pos [°2Th.]	FWHM [°2Th.]	Particle size (A°)
1	21.7587	0.3542	22
2	27.1424	1.6531	5
3	35.8287	0.4723	17
4	40.8394	1.1808	7
5	54.1881	1.1808	7.5
6	62.8214	0.7085	13
7	69.3466	2.3040	4

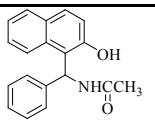
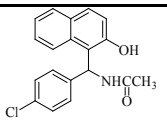
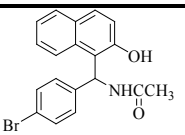
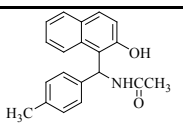
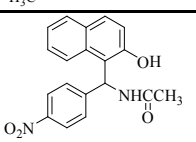
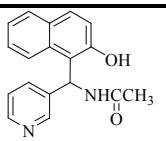
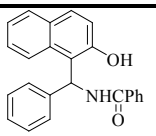
Table 2: Synthesis of N-[(4-nitro phenyl)-(2-hydroxy-naphthalen-1-yl)-methyl]acetamide under various conditions

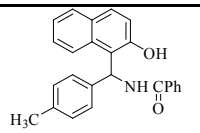
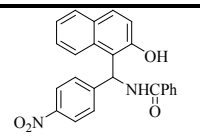
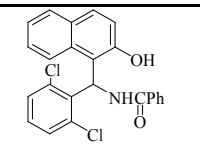


Entry	Catalyst (g)	Solvent/T °C	Time (h)/yield (%)[a]	Ref.
1	50% $TiCl_4.SiO_2$ (0.1)	Solvent-free/90	1/100	-
2	50% $TiCl_4.SiO_2$ (0.1)	Solvent-free/70	1/80	-
3	50% $TiCl_4.SiO_2$ (0.1)	Ethanol/60	12/0	-
4	50% $TiCl_4.SiO_2$ (0.1)	EtOAc/80.	15/90	-
5	50% $TiCl_4.SiO_2$ (0.1)	CH_2Cl_2/R.T	4/60	-
6	50% $TiCl_4.SiO_2$ (0.02)	Solvent-free/90	2/100	-
7	50% $TiCl_4.SiO_2$ (0.05)	Solvent-free/90	1/100	-
8	40% $TiCl_4.SiO_2$ (0.05)	Solvent-free/90	1/90	-
9	30% $TiCl_4.SiO_2$ (0.05)	Solvent-free/90	1/80	-
10	60% $TiCl_4.SiO_2$ (0.05)	Solvent-free/90	1/100	-
11	Nano-50% $TiCl_4.SiO_2$ (0.05)	Solvent-free/90	1/100	-
12	Nano-50% $TiCl_4.SiO_2$ (0.02)	Solvent-free/90	1/100	-
13	Nano-50% $TiCl_4.SiO_2$ (0.02)	MM/Solvent free	1.5/40	-[b]
14	Nano-50% $TiCl_4.SiO_2$ (0.02)	Sonication/EtOAc	0.3/-	-[c]
15	Nano-50% $TiCl_4.SiO_2$ (0.02)	MW/Solvent free	0.1/90	-[d]
16	50% Nano-$TiCl_4.SiO_2$ (0.02), 2nd run	Solvent-free/90	1/89	-
17	50% Nano-$TiCl_4.SiO_2$ (0.02), 3rd run	Solvent-free/90	1/75	-
18	$HClO_4/SiO_2$	S. F. /110	0.5/95	20
19	$HClO_4/SiO_2$	MW	0.2/91	20
20	P_2O_5	S. F./60	0.1/96	19
21	$KHSO_4$	S. F./100	0.5/96	18
22	$H_3PW_{12}O_{40}$	Et_4NCl/100	1.4/ 95	16
23	$H_4SiW_{12}O_{40}$	S.F./110	0.25/82	17

[a] Isolated yield. [b] Using mixer mill (MM 400) in 25 Hz frequency. [c] Using BANDELIN Sonopulse HD 3200 Ultrasonic apparatus with power equal to 20 Khz. [d] Using microwave oven Kenwood, 1300W

Table 3: Synthesis of 1-amidoalkyl-2-naphthols in the presence of 50% $TiCl_4.SiO_2$

Entry	R´ (Ar´)	R (Ar)	Product	Time (min)	Yield[a]	M.P. °C Found	M.P. °C reported[Ref.]
N1	C_6H_5	CH_3		30	94	219–220	218-220[28]
N2	4-ClC_6H_4	CH_3		60	92	230-231	-
N3	4-BrC_6H_4	CH_3		80	94	227-229	229–231[28]
N4	4-MeC_6H_4	CH_3		450	90	212-213	214-216[28]
N5	4-$O_2NC_6H_4$	CH_3		30	96	220-221	222-223[28]
N6	3-pyridyl	CH_3		100	98	192-194	-
N7	C_6H_5	Ph		40	92	251-252	230-232[29]

N8	4-MeC_6H_4	Ph		41	92	226-228	204-205[29]
N9	4-$O_2NC_6H_4$	Ph		28	97	236-238	228-229[29]
N10	2,6-$Cl_2C_6H_3$	Ph		55	98	215-217	-

[a]The ratio of 2-naphthol (mmole): aldehydes (mmole): amide (mmole): 50% nano $TiCl_4.SiO_2$ (g) is 1:1:1.2:0.05.
[b]Isolated yield.

CONCLUSION

We have demonstrated simple methods for the synthesis of preparation of 1-amidoalkyl-2-naphthols with using nano-$TiCl_4.SiO_2$ as eco-friendly and efficient catalyst in a one-pot procedure that has been developed. Short reaction times, high yields, a clean process, simple methodology, easy work-up and green conditions are advantages of this protocol. Even at this time our new compounds didn't show antifungal and antibacterial activity but we suppose these negative results probably related to undesirable pharmacokinetic properties. Maybe some structural modifications could improve the pharmacokinetic properties of our compounds. We hope in future studies we could be able to synthesize some effective derivatives of naphthols with different biological activities.

ACKNOWLEDGEMENTS

The Research Council of Yazd University is gratefully acknowledged for the financial support of design and synthesis of compounds. The antifungal activities of the synthetic compounds were evaluated in Shiraz University of Medical Sciences by grant number 90-01-43-3451. We gratefully acknowledge generous allocations of computing from the Australian National Computational Infrastructure.

REFERENCES

1. Dingermann T, Steinhilber D, Folkers G. Molecular Biology in Medicinal Chemistry. Wiley-VCH, Verlag GmbH & Co. KGaA, Weinheim, 2004.
2. Shen AY, Tsai CT, Chen CL. Synthesis and cardiovascular evaluation of N-substituted aminonaphthols. Eur J Med Chem. 1999; 34: 877-882.
3. Shen AY, Chen CL, Lin CI. Electrophysiological basis for the bradycardic effects of 1-(1-pyrrolidinylmethyl)-2-naphthol in rodents. Chin J Physiol. 1992; 35: 45–54.
4. Damodiran M, Selvam NP, Perumal PT. Synthesis of highly functionalized oxazines by Vilsmeier cyclization of amidoalkyl naphthols. Tetrahedron Lett. 2009; 50:5474–5478.
5. Wani MC, Taylor HL, Wall ME. Plant antitumor agents: Colubrinol acetate and colubrinol, antileukaemic ansa macrolides from Colubrina texensis. J Chem Soc Chem Commun. 1973; 390.
6. Lesher GY, Surrey AR. A new method for the preparation of 3-substituted-2-oxazolidones. J Am Chem Soc. 1955; 77: 636–641.
7. Mosher HS, Frankel MB, Gregory M. Heterocyclic Diphenylmethane Derivatives. J Am Chem Soc. 1953; 75: 5326–5328.
8. Benedini F, Bertolini G, Cereda R, Doná G, Gromo G, Levi S, Mizrahi J, Sala A. New anti-angina nitro esters with reduced hypertensive activity. Synthesis and pharmacological evaluation of 3-[(nitrooxy)alkyl]-2H-1,3-benzoxazin-4(3H)-ones. J Med Chem. 1995; 38: 130-136.
9. Clark RD, Caroon JM, Kluge AF, Repke DB, Roszkowski AP, Strosberg AM, Baker S, Bitter SM, Okada MD. Synthesis and antihypertensive activity of 4'-substituted spiro[4H-3,1-benzoxazine-4,4'-piperidin]-2(1H)-ones. J Med Chem. 1983; 26: 657–661.
10. Peglion JL, Vian J, Gourment B, Despaux N, Audinot V, Millan M. Tetracyclic analogues of [+]-S 14297: Synthesis and determination of affinity and selectivity at cloned human dopamine D_3 vs. D_2 receptors. Bioorg Med Chem Lett. 1997; 7: 881–886.
11. Matsuoka H, Ohi N, Mihara M, Suzuki H, Miyamoto K, Maruyama N, Tsuji K, Kato N, Akimoto T, Takeda Y, Yano K, Kuroki T, Antirheumatic Agents: Novel Methotrexate Derivatives Bearing a Benzoxazine or Benzothiazine Moiety. J Med Chem. 1997; 40: 105–111.
12. Ren H, Grady S, Gamenara D, Heinzen H, Moyna P, Croft S, Kendrick H, Yardley V, Moyna G, The structure of minimycin, a novel carbon-linked nucleoside antibiotic related to pseudouridine. Bioorg Med Chem Lett. 2001; 11: 1851–1854.
13. Haneishi T, Okazaki T, Hata T, Tamura C, Nomura M, Naito A, Seki I, Arai M, Design, synthesis, and biological evaluation of a series of simple and novel potential antimalarial compounds J. Antibiot. 1971; 24: 797–799.
14. Sasaki K, Kusakabe Y, Esumi S. Oxazinomycin, a new carbon-linked nucleoside antibiotic. J. Antibiot. 1972; 25: 151–154.
15. Kusakabe Y, Nagatsu J, Shibuya M, Kawaguchi O, Hirose C, Shirato S. Minimycin, a new antibiotic. J. Antibiot. 1972; 25: 44-47.
16. Dorehgiraee A, Khabazzadeh H, Saidi K. Heteropoly acid catalyzed synthesis of 1-amidoalkyl-2-naphthols in the presence of molten tetraethylammonium chloride. Arkivoc 2009; 7: 303-310.
17. Supale AR, Gokavi GS. An environmentally benign three component one-pot synthesis of amidoalkyl naphthols using $H_4SiW_{12}O_{40}$ as a recyclable catalyst. J Chem Sci. 2010; 122:189-192.
18. Cai X-H, Guo H, Xie B. One-pot Multi-component Synthesis of Amidoalkyl Naphthols with Potassium Hydrogen Sulfate as Catalyst under Solvent-free Condition. Int J Chem 2011; 3: 119-122.
19. Nandi GC, Samai S, Kumar R, Singh MS. Atom-efficient and environment-friendly multicomponent synthesis of amidoalkyl naphthols catalyzed by P_2O_5. Tetrahedron Lett. 2009; 50: 7220-7222.
20. Mahdavinia GH, Bigdeli MA, Heravi MM. Silica supported perchloric acid ($HClO_4$–SiO_2): A mild, reusable and highly efficient heterogeneous catalyst for the synthesis of amidoalkyl naphthols. Chinese Chem Lett. 2008; 19: 1171–1174.
21. Lei M, Maa L, Hu L. Thiamine hydrochloride as an efficient catalyst for the synthesis of amidoalkyl naphthols. Tetrahedron Lett. 2009; 50: 6393-6397.
22. Clinical and Laboratory Standards Institute (CLSI), "Performance standards for antimicrobial disk susceptibility tests; approved standard." 9th Ed., Wayne, PA: Clinical and Laboratory Standards Institute, CLSI M2-A9, 2006.
23. Clinical and Laboratory Standards Institute (CLSI), "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard." 7th ed., Wayne, PA: Clinical and Laboratory Standards Institute, CLSI M7-A7, 2006.
24. Clinical and Laboratory Standards Institute (CLSI), "Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi; Approved Standard," Wayne, PA: Clinical and Laboratory Standards Institute, CLSI M38-A, 2006.
25. Clinical and Laboratory Standards Institute. (CLSI), "Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard," Wayne, PA: Clinical and Laboratory Standards Institute, CLSI document M27-A7, 2006.
26. Mirjalili B F, Bamoniri A, Zamani L. One-pot synthesis of 1,2,4,5-tetrasubstituted imidazoles promoted by Nano-$TiCl_4.SiO_2$. Scientica Iranica C. 2012; 19: 565-569.
27. Mirjalili BF, Bamoniri A, Zamani L. Nano-$TiCl_4/SiO_2$: An Efficient and Reusable Catalyst for the Synthesis of Tetrahydrobenzo[a]xanthenes-11-ones. Lett Org Chem. 2012; 9: 338-343.

28. Hajipour AR, Ghayeb Y, Sheikhan N, Ruoho AE. Brønsted acidic ionic liquid as an efficient and reusable catalyst for one-pot synthesis of 1-amidoalkyl 2-naphthols under solvent-free conditions. Tetrahedron Lett. 2012; 50: 5649-5651.
29. Mirhendi H, Makimura K, Khoramizadeh M, Yamaguchi HA. A one-enzyme PCR-RFLP assay for identification of six medically important candida species. Nippon Ishinkin Gakkai Zasshi. 2006; 47: 225-229.

Source of support: Research Council of Yazd University & Shiraz University of Medical Sciences, Conflict of interest: None Declared

QUICK RESPONSE CODE	ISSN (Online) : 2277 –4572
	Website http://www.jpsionline.com

How to cite this article:
Leila Zamani, Kamiar Zomorodian, Bi Bi Fatemeh Mirjalili, Soghra Khabnadideh. One pot preparations 1-amidoalkyl-2-naphthols derivative catalyzed by nano-$TiCl_4.SiO_2$ with antimicrobial studies of some products. J Pharm Sci Innov. 2014;3(3):208-216 http://dx.doi.org/10.7897/2277-4572.033141