ONE POT PREPARATIONS *N,N′*-ALKYLIDENE BISAMIDE DERIVATIVES CATALYZED BY NANO-$TiCL_4.SiO_2$ WITH ANTIMICROBIAL STUDIES OF SOME PRODUCTS

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ABSTRACT

Nano-$TiCl_4.SiO_2$ has been introduced to be an extremely efficient catalyst for the preparation of *N,N'*-alkylidene bisamides 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. 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, *N,N'*-Alkylidene bisamides, Antifungal, Antibacterial.

INTRODUCTION

Amide and bisamide compounds are main part of many peptidomimetic[1] and they play a major role in the expansion and composition of biological and pharmacological systems. They are of considerable interest in the synthesis of pharmacological materials such as peptidomimetic compounds[2,3] and gem-diaminoalkyl residues in retro-inverso pseudopeptide derivatives[4] by treating the corresponding amide with iodobenzene bistrifluoroacetate.[5] Generally symmetrical alkylidene bisamides are synthesized by the direct reaction of aldehydes with the corresponding amides under suitable catalytic condition. In this topic, let us examine the various conditions of the catalysts such as sulfuric acid[6], sulfonic acid[7], triflic acid[8], p-toluene sulfonic acid[9], SiO_2-$MgCl_2$[10], hydrochloric acid[11], CC- or DCMT activatd DMSO[12], phosphotungstic acid[13], boric acid [14], silica coated magnetic $NiFe_2O_4$ nanoparticle supported polyphosphoric acid[15] and *p*-toluenesulfonic acid.[16] Our studies towards the development of more efficient methods accompanied with higher yields for the synthesis of *N,N'*-Alkylidene bisamides in the presence of nano-$TiCl_4.SiO_2$. In addition, the antimicrobial and antifungal activities of some of the synthetic compounds were evaluated by broth microdilution methods.

EXPERIMENTAL

The chemicals were purchased 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. Spectrophotometer (Company BAUSCH & LOMB, US), Vortex mixer (Company Lab net), Tween 20 (Company Roche, Germany).

General experimental procedure for the synthesis of *N,N'*-alkylidene bisamide

A mixture of aldehyde (1 mmol), amide (2 mmol), *n*-hexane (5 ml) and nano-$TiCl_4.SiO_2$ (0.04 g) was refluxed for appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and filtered. The catalyst was separated from the reaction mixture by boiling ethanol. The crude solid product was purified by recrystallization procedure in ethanol:water, 80:20.

Biological study

Microorganisms

The antifungal activities of the synthetic compounds against some American Type Culture Collection (ATCC) strains of fungi, including *Candida albicans* (*ATCC 10261*), *Candida tropicalis* (*ATCC 750*), *Candida krusei* (*ATCC 6258*), *Candida glabarata* (*ATCC 90030*), *Candida dubliniensis* (*CBS 8501*), *Aspergillus flavus* (*ATCC 64025*), and *Aspergillus fumigatus* (*ATCC 14110*) as well as two clinical isolates of yeasts identified by PCR-RFLP were determined. The susceptibility of all clinical isolates of fungi against selected antibiotics was examined by microdilution and disk diffusion methods The antibacterial activities of the above compounds against standard species of *Staphylococcus aureus* (*ATCC 25923*), *Enterococcus faecalis (ATCC 11700*), *Escherichia coli* (*ATCC 25922*) and *Pseudomonas 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.[17,18]

Determination of minimum inhibitory concentration

MICs were determined using the broth microdilution method recommended by the CLSI with some modifications.[17,18] Briefly, for determination of antimicrobial activities against fungi, serial dilutions of the synthetic compounds (1–1024 μg/mL) were prepared in 96-well microtiter plates using RPMI-1640 media (Sigma, St. Louis, MO, USA) buffered with MOPS (Sigma). Stock inoculums were prepared by suspending three colonies of the examined yeast in 5 mL sterile 0.85% NaCl, and adjusting the turbidity of the inoculums to 0.5 McFarland standards at 530 nm wavelengths (this yields stock suspension of 1-5 × 106 cells/mL). For moulds (Aspergillus spp. and dermatophytes), conidia were recovered from the 7-day old cultures grown on potato dextrose agar by a wetting loop with tween-20. The collected conidia were transferred in sterile saline and their turbidity was adjusted to OD=0.09-0.11 that yields 0.4-5 × 106 conidia/mL. Working suspension was prepared by making a 1/50 and 1/1000 dilution with RPMI of the stock suspension for moulds and yeasts, respectively. Working inoculums (0.1 mL) were added to the microtiter plates, which were incubated in a humid atmosphere at 30ºC for 24–48 h. Uninoculated medium (200 μL) was included as a sterility control (blank). In addition, growth controls (medium with inoculums but without antibiotics or the synthetic compounds) were also included. The growth in each well was compared with that of the growth in the control well.

RESULTS AND DISCUSSION

$TiCl_4.SiO_2$[19-26] 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. In continue of our investigations on solid acid application in organic synthesis, we tried to develop new synthetic method to prepare *N,N'*-alkylidene bisamides and find the best reaction conditions. The reaction of benzamide and benzaldehyde was examined under various conditions and different quantities of $TiCl_4.SiO_2$ and nano-$TiCl_4.SiO_2$ (Table 1). According to our results, the best condition is the reaction in solvent free condition using 0.1 g of $TiCl_4.SiO_2$ or 0.04 g of nano-$TiCl_4.SiO_2$. The results showed an improved reaction rate and yield (Table 1, Entries 2, 11).

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 1).

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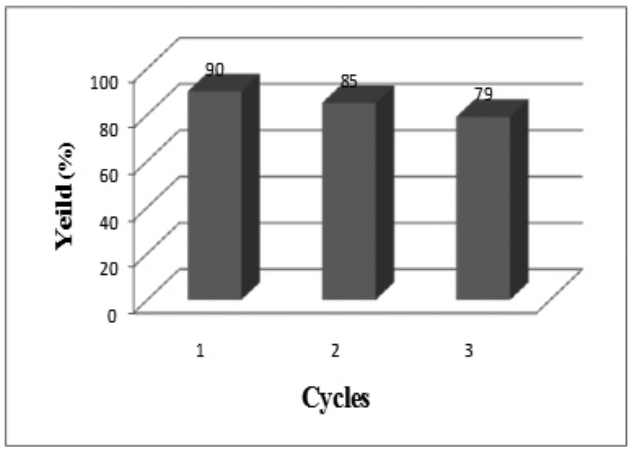


Fig. 1. Reusability of nano-$TiCl_4.SiO_2$ catalyst.

Table 1. Synthesis of *N, N'*-(4-nitrophenylmethylene) dibenzamide under various conditions

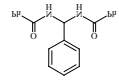
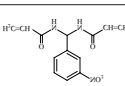
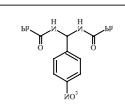
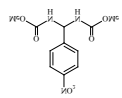
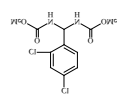
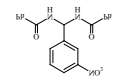
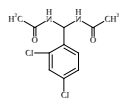
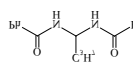
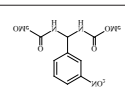
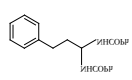
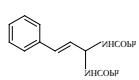
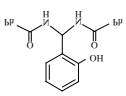
Entry	Catalyst (g)	Solvent/T °C	Yield(%)[a] / Time (h)	Reference
1	$TiCl_4.SiO_2$ (0.1)	Solvent-free/100	3/85	-
2	$TiCl_4.SiO_2$ (0.1)	n-Hexane/ reflux	2/89	-
4	$TiCl_4.SiO_2$ (0.1)	EtOAc/reflux	3.5/75	-
5	$TiCl_4.SiO_2$ (0.1)	$CHCl_3$/reflux	4/78	-
6	$TiCl_4.SiO_2$ (0.1)	Toluene/ reflux	5/30	-
7	$TiCl_4.SiO_2$ (0.1	S.F./mixer mill	2/0	-[b]
8	$TiCl_4.SiO_2$ (0.1)	EtOAc/ sonication	1/32	-[c]
9	$TiCl_4.SiO_2$ (0.1)	S.F./M.W.	0.5/50	-[d]
10	Nano-$TiCl_4.SiO_2$ (0.08)	*n*-Hexane/ reflux	1/90	-
11	Nano-$TiCl_4$. SiO_2(0.04)	*n*-Hexane/ reflux	1.5/90	-
12	Nano-$TiCl_4.SiO_2$ (0.04), 2nd run	*n*-Hexane/ reflux	1.5/85	-
13	Nano-$TiCl_4.SiO_2$ (0.04), 3rd run	*n*-Hexane/ reflux	1.5/79	-
14	SiO_2-$MgCl_2$ (0.025)	Solvent-free/100	2.5/73	10
15	CC(1.2 equiv)-DMSO(7.0 equiv)	Toluene/r.t. to 70	3/71	12
16	Phosphotungstic acid (0.3 mmol)	Toluene/ reflux	20-70	13
17	Boric acid (0.3 mmol)	Microwave	40 min/80	14

[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

Next, the scale of this procedure was explored using a wide range of aldehydes containing electron-donating or electron-withdrawing groups attaching to aromatic ring (Table 2).

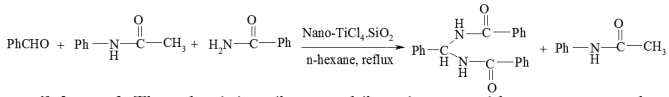
In all cases, aromatic aldehydes containing electron-withdrawing groups gave higher yield of products in shorter time than aromatic aldehydes containing electron-withdrawing groups (Table 2, entries 3 and 9). In methyl carbamate, the nucleophilicity of nitrogen is higher than acetamide. Thus, methyl carbamates produce a good yield of product in shorter time than acetamides (Table 2, entries 4).

Table 2. Preparation of *N,N'*-alkylidene bisamide derivatives in the presence of nano-$TiCl_4.SiO_2$[a]

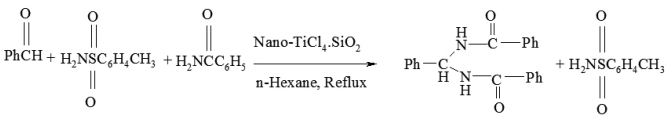
Entry	R^1	R^2	Products	M.P. °C (Lit)[Ref]	Yield(%)[b] /Time (h)
B1	Ph	Ph		210-211 (214-216)[13]	87/1.5
B2	3-NO_2-Ph	CH_2= CH		222-223 (224-226)[13]	90/5
B3	4-NO_2-Ph	Ph		239-240 (242-244)[13]	96/2
B4	4-NO_2-Ph	OCH_3		196-198	91/0.9
B5	2,4-Dichloro-ph	OCH_3		248-250	87/1
B6	3-NO_2-Ph	Ph		236-237	83/1.5
B7	2,4-Dichloro-ph	CH_3		264-265	72/5
B8	*n*-propyl	Ph		172-173	76/2.5
B9	3-NO_2-Ph	OCH_3		184-185	93/2.3
B10	$PhCH_2$-CH_2	Ph		253-254 (248-249)[9]	72/4.5
B11	PhCH=CH	Ph		199-201	68/2.3
B12	2-OH-phenyl	Ph		177-179	70/3.5

[a]Reaction conditions: amide (2 mmol), aldehyde (1 mmol), nano-$TiCl_4$. SiO_2 (0.04 g).
[b]Isolated yield.

This protocol is effective special for primary amides but secondary amides or primary sulfonamides (Scheme 1and 2).

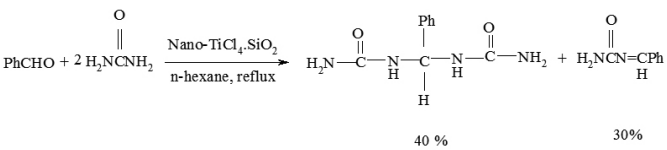


Scheme 1. The selectivity of protocol for primary amides versus secondary amides



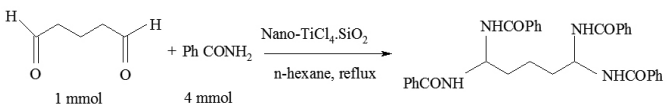
Scheme 2. The selectivity of protocol for primary amides versus sulfonamides

Nano-$TiCl_4.SiO_2$ catalyzes the reaction of benzaldehyde with urea to produce corresponding bisamides and imines with different yields (Scheme 3).



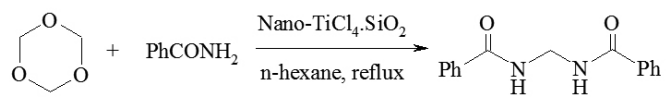
Scheme 3. Reaction of benzaldehyde with urea

N,N,N′,N'-(1, 5-pentylene)tetrabenzamide was also produced *via* the reaction of 1 mmol of glutardialdehyde with 4 mmol of benzamide in the presence of Nano-$TiCl_4.SiO_2$ (Scheme 4).



Scheme 4. Synthesis of *N,N,N′,N'*-(1, 5-pentylene)tetrabenzamide from glutardialdehyde and benzamide

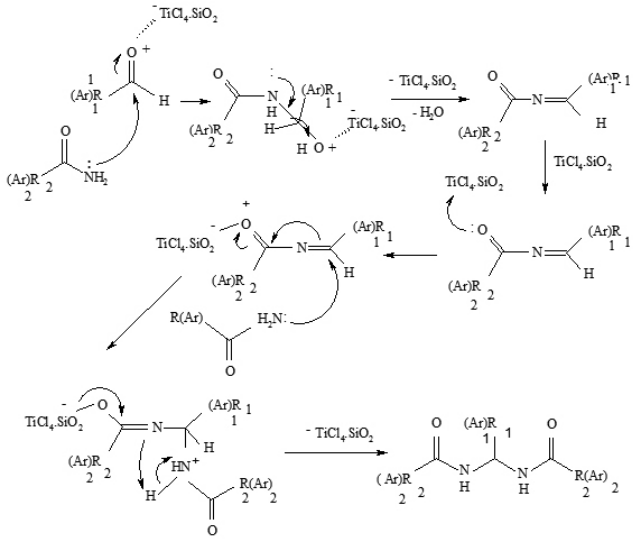
N,N'-(methylene)dibenzamide was produced *via* the reaction of 1, 3, 5-trioxane with benzamide in the presence of nano-$TiCl_4.SiO_2$ (Scheme 5).



Scheme 5. Synthesis of *N,N'*-(methylene)dibenzamide from 1, 3, 5-trioxane with benzamide

The chemo-selectivity of bisamide preparation was examined *via* reaction of 4-nitrobenzaldehyde with benzamide and acetamide in one vessel in the presence of nano-$TiCl_4.SiO_2$. The preparation of mixed products approves no chemo selectivity between aromatic and aliphatic amides. Reaction of benzamide with 3-phenylpropione aldehyde and benzaldehyde in one vessel and producing a mixture of corresponding bisamides show no chemo selectivity between aromatic and aliphatic aldehydes. Previously, two types of mechanisms were reported for bisamide formation from aldehyde and amide.[13,14]

According to our knowledge, we have proposed a mechanism for formation of bisamides in the presence of nano-$TiCl_4.SiO_2$ (Scheme 6).



Scheme 6. The suggested mechanism for bisamide formation from aldehyde and amide

None of the selected compounds exhibited antifungal activity against the examined fungi at the tested concentrations (Table 3). 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 (Table 4). Further studies still needed to investigate other biological activities of these compounds.

SPECTROSCOPIC DATA

N,N'-(phenylmethylene)dibenzamide (Table 2, B1)

FT-IR: ῡ (ATR, neat, cm^{-1}): 3275 (N-H stretch), 1650 (C=O stretch), 1480 (N-H bend), 715, 799 (C-H bend); ^{1}H NMR (DMSO-d_6, ppm): δ 9.01 (d, *J*=7.7 Hz, 2H, N-H),7.92 (d, *J*=7.8 Hz, 4H),7.56 (t, *J*=7.09 Hz, 2H),7.49 (t, *J*=7.5 Hz, 6H),7.39 (t, *J*=7.5 Hz, 2H),7.32 (t, *J*=7.07 Hz, 1H), 7.05 (t, *J*=7.72 Hz, 1H, CH).

Elemental analysis. Found, %: C 76.55; H 5.38; N 8.38. $C_{21}H_{18}N_2O_2$. Calculated, %: C 76.34; H 5.49; N 8.48.

N,N'-(3-nitrophenylmethylene)diacrylamide (Table 2, B2):

FT-IR: ῡ (ATR, neat, cm^{-1}): 3242 (N-H stretch), 1664 (C=O stretch), 1628 (C=C stretch), 1346, 1528 (N=O stretch), 1520 (N-H bend), 966, 703, 667 (C-H bend); ^{1}H NMR (DMSO-d_6, ppm): δ 9.22 (d, *J*=7.4 Hz, 2H, N-H), 8.20 (d, *J*=1.74 Hz, 2H), 7.82 (d, *J*=7.78 Hz, 1H), 7.70 (t, *J*=8.03 Hz, 1H), 6.74 (t, *J*=7.49 Hz, 1H, CH), 6.35 (dd, *J*=17.09 Hz, 10.19, 2H), 6.17 (dd, *J*=17.10 Hz, 1.73, 2H), 5.68 (dd, *J* =10.17 Hz, 1.78, 2H). Elemental analysis. Found, %: C 56.56; H 4.58; N 15.38. $C_{13}H_{13}N_3O_4$. Calculated, %: C 56.72; H 4.76; N 15.27.

N,N'-(4-nitrophenylmethylene)dibenzamide (Table 2, B3):

FT-IR: ῡ (ATR, neat, cm^{-1}): 3256 (N-H stretch), 1649 (C=O stretch), 1343, 1507 (N=O stretch), 1546 (N-H bend), 852 (C-H bend); ^{1}HNMR (DMSO-d_6, ppm): δ 9.2 (d, *J*=5.0 Hz, 2H, N-H), 8.26(d, *J*=6.9 Hz, 2H), 7.93(d, *J*=5.6 Hz, 4H), 7.75(d, *J*=6.9 Hz, 2H), 7.58(s, 2H), 7.50(m, 4H), 7.09 (brs, 1H, CH).^{13}C-NMR (DMSO-d_6, ppm): 166.7, 134.41, 132.62, 129.21, 128.91, 128.47, 124.38. Elemental analysis, Found, %: C 66.99; H 4.78; N 11.15. $C_{21}H_{17}N_3O_4$. Calculated, %: C 67.19; H 4.56; N 11.19.

***N,N'-(4-nitrophenylmethylene)dimethylcarboxamide (Table 2, B4)*:**

FT-IR: ῡ (ATR, neat, cm^{-1}): 3306 (N-H stretch), 1706 (C=O stretch), 1600 (C=C stretch), 1349, 1530 (N=O stretch), 1550 (N-H bend), 1251, 1195 (C-O stretch), 871 (C-H bend); ^{1}H NMR (DMSO-d_6, ppm): δ 8.2(d, *J*=7.5 Hz, 2H), 8.1 (brs, 2H, N-H), 7.6(d, *J*=7.6 Hz, 2H), 6.24(brs, 1H, CH), 3.58 (s, 6H, OMe); ^{13}C-NMR (DMSO-d_6, ppm): 156.6, 148.1, 147.9, 128.7, 124.3, 61.9, 52.5. Elemental analysis, Found, %: C 46.50; H 4.70; N 14.90. $C_{11}H_{13}N_3O_6$. Calculated, %: C 46.65; H 4.63; N 14.84.

***N,N'-(2,4-dichlorophenylmethylene)dimethylcarboxamide (Table 2, B5)*:**

FT-IR: ῡ (ATR, neat, cm^{-1}): 3309 (N-H stretch), 1708 (C=O stretch), 1550 (N-H bend), 720, 699 (C-H bend), 643 (C-Cl stretch); ^{1}H NMR (DMSO-d_6, ppm): δ 8.04 (sbr, 2H, N-H), 7.61 (d, *J*=2 Hz, 1H), 7.57 (d, *J*=8.45 Hz, 1H), 6.24 (dd, *J*=8.42 Hz, 1.9, 1H), 6.24(t, *J*=7.55 Hz, 1H, CH), 3.55(s, 6H, OMe); ^{13}C-NMR (DMSO-d_6, ppm): 156.3, 137.5, 134.1, 133.8, 130.3, 129.5, 128.1, 59.8, 52.4. Elemental analysis, Found, %: C 42.92; H 3.90; N 9.08; Cl 23.02.

$C_{11}H_{12}N_2O_4Cl_2$. Calculated, %: C 43.02; H 3.94; N 9.12; Cl 23.09.

N,N'-(3-nitrophenylmethylene)dibenzamide (Table 2, B6):

FT-IR: ῡ (ATR, neat, cm^{-1}): 3250 (N-H stretch), 1646 (C=O stretch),1340 (N-H bend), 1339, 1533 (N=O stretch), 1505 (C=C stretch), 715, 695 (C-H bend);^{1}H NMR (DMSO-d_6, ppm): δ 9.2 (d, *J*=7.4 Hz, 2H, N-H), 8.35 (sbr, 1 H), 8.2 (dd, *J*=6.9 Hz, 1.37, 1H), 7.96(s, IH), 7.93(d, *J*=8.4 Hz, 4H), 7.71(t, *J*=7.9 Hz, 1 H), 7.58(t, *J*=7.2 Hz, 2H), 7.5(t, *J*=7.8 Hz, 4H), 7.09 (t, *J*=7.3 Hz, 1H, CH). Elemental analysis, Found, %: C 66.89; H 4.67; N 11.39. $C_{21}H_{17}N_3O_4$. Calculated, %: C 67.19; H 4.56; N 11.19.

N,N'-(2,4-dichlorophenylmethylene)diacetamide (Table 2, B7):

FT-IR: ῡ (ATR, neat, cm^{-1}): 3285 (N-H stretch), 1665 (C=O stretch), 1425 (C=C stretch), 1518 (N-H bend), 856, 749 (C-H bend), 643 (C-Cl stretch); ^{1}H NMR (DMSO-d_6, ppm): δ 8.54 (d, *J*=7.19 Hz, 2H, N-H), 7.62 (d, *J*=1.6 Hz, 1H), 7.5 (m, 2H), 6.6 (t, *J*=7.55 Hz, 1H, CH), 1.84(s, 6H, CH_3). Elemental analysis, Found, %: C 47.90; H 4.48; N 10.08; Cl 25.62. $C_{11}H_{12}N_2O_2Cl_2$. Calculated, %: C 48.02; H 4.40; N 10.18; Cl 25.77.

N,N'-(1-butylene)dibenzamide (Table 2, B8):

FT-IR: ῡ (ATR, neat, cm^{-1}): 3232 (N-H stretch), 1643 (C=O stretch), 1484, 1600 (C=C stretch), 1530 (N-H bend); ^{1}H NMR (DMSO-d_6, ppm): δ 8.52 (d, *J*=7.62 Hz, 2H, N-H), 7.86 (d, *J*=7.12 Hz, 4H), 7.55 (t, *J*=7.12 Hz, 2H), 7.47(t, *J*=7.7 Hz, 4H), 5.85(m, 1H, CH), 1.85 (td, *J*=7.65 Hz, 7.42, 2H, CH_2), 1.37(m, 2H, CH_2), 0.938(t, *J*=7.33 Hz, 3H, CH_3). Elemental analysis, Found, %: C 73.09; H 6.57; N 9.39. $C_{18}H_{20}N_2O_2$. Calculated, %: C 72.95; H 6.80; N 9.45.

N,N'-(3-nitrophenyl-methylene)dimethylcarboxamide (Table 2, B9):

FT-IR: ῡ (ATR, neat, cm^{-1}): 3287 (N-H stretch), 1701 (C=O stretch), 1515, 1343 (N=O stretch), 1556 (N-H bend), 1255, 1032(C-O stretch), 674, 783, 809 (C-H bend); ^{1}H NMR (DMSO-d_6, ppm): δ 8.24(s, 1H), 8.17 (d, *J*=8.3 Hz, 1H), 8.15(sbr, 2H, NH), 7.82 (d, *J*=7.6 Hz, 1H), 7.67 (t, *J*=7.9 Hz, 1H), 6.25 (t, *J*=7.9 Hz, 1H, CH), 3.61(s, 6H, OMe). Elemental analysis, Found, %: C 46.82; H 4.56; N 14.28. $C_{11}H_{13}N_3O_6$. Calculated, %: C 46.65; H 4.63; N 14.84.

N,N'-(3-phenyl-propylene)dibenzamide (Table 2, B10):

FT-IR: ῡ (ATR, neat, cm^{-1}): 3299 (N-H stretch), 1637 (C=O stretch), 1508, 1579 (C=C stretch), 1545 (N-H bend), 690, 756 (C-H bend); ^{1}H NMR (DMSO-d_6, ppm): δ 8.64 (d, *J*=7.5 Hz, 2H, N-H), 7.88 (d, *J*=7.22 Hz, 4H), 7.54(t, *J*=7.31 Hz, 2H), 7.48 (t, *J*=7.69 Hz, 4H), 7.28 (m, 4H), 7.17 (m, 1H), 5.85 (m, 1H, CH), 2.69 (t, *J*=8.15 Hz, 2H, CH_2), 2.17 (dd, *J*=15.4 and 7.31 Hz, 2H, CH_2). Elemental analysis, Found, %: C 76.89; H 6.24; N 7.95. $C_{23}H_{22}N_2O_2$. Calculated, %: C 77.07; H 6.19; N 7.82.

N,N'-(3-phenyl-2-ene-propylene)dibenzamide (Table 2, B11):

FT-IR: ῡ (ATR, neat, cm^{-1}): 3274(N-H stretch), 1647 (C=O stretch), 1484,1504 (C=C stretch), 1543 (N-H bend), 690, 756 (C-H bend); ^{1}H NMR (DMSO-d_6, ppm): δ 8.87 (d, *J*=6.8 Hz, 2H, N-H), 7.92 (d, *J*=7.36 Hz, 4H), 7.86 (t, *J*=7.92 Hz, 2H), 7.56 (t, J=7.2 Hz, 2H), 7.48 (m, 4H), 7.35 (m, 2H), 7.28 (t, *J*=7.32 Hz, 1H), 6.69 (d, *J*=14.7 Hz, 1H, CH), 6.65 (m, 2H). Elemental analysis, Found, %: C 77.99; H 5.37; N 7.59. $C_{23}H_{20}N_2O_2$. Calculated, %: C 77.51; H 5.66; N 7.86.

N,N'-(2-hydroxyphenyl-methylene)dibenzamide (Table 2, B12):

FT-IR: ῡ (ATR, neat, cm^{-1}): 3406-3268(O-H and N-H stretch), 1639 (C=O stretch), 1425 (C=C stretch), 1126 (C-N bend), 758 (C-H bend);^{1}H NMR (DMSO-d6, ppm): δ 9.02 (d, *J*=7.39 Hz, 2H, N-H), 8.03 (d, *J*=7.27 Hz, 2H), 7.81(d, *J*=7.31 Hz, 3H), 7.69 (m, 1H), 7.52 (m, 3H), 7.45 (m, 5H), 7.35 (m, 1H), 7.26 (t, *J*=7.34 Hz, 1H, CH). Elemental analysis, Found, %: C 72.99; H 5.17; N 7.99. $C_{21}H_{18}N_2O_3$. Calculated, %: C 72.82; H 5.24; N 8.09.

N,N'-(methylene)dibenzamide (Scheme 5):

FT-IR: ῡ (ATR, neat, cm^{-1}): 3308 (N-H stretch), 1634 (C=O stretch), 1487, 1578 (C=C stretch), 1526 (N-H bend), 1448 (CH_2 bend); ^{1}HNMR (DMSO-d_6, ppm): δ 9.03 (t, *J*=5.5 Hz, 2H, N-H), 7.9 (d, *J*=7.14 Hz, 4H), 7.55 (t, *J*=7.15 Hz, 2H), 7.48(t, *J*=7.14 Hz, 4H), 4.84(t, *J*=5.5 Hz, 2H, CH_2). Elemental analysis, Found, %: C 69.99; H 4.97; N 11.48. $C_{15}H_{14}N_2O_2$. Calculated, %: C 70.85; H 5.55; N 11.02.

CONCLUSION

We have demonstrated simple methods for the synthesis of preparation of *N,N'*-alkylidene bisamides 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 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 bisamides with different biological activities.

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REFERENCES

1. C. Aleman, J. Puiggali, *J. Org. Chem.*, **60**, 910, (1995).
2. T. Yamazaki, K.I. Nunami, M. Goodman, *Biopolymers*, **31**, 1513, (1991).
3. M. Goodman, H. Shao, *Pure & Appl. Chem*., **68**, 1303, (1996).
4. P.V. Pallai, R.S. Struthers, M. Goodman, L. Moroder, E. Wunsch, W. Vale, *Biochem*., **24**, 1933, (1985).
5. M. Rodriguez, P. Dubreuil, J.-P. Bali, J. Martinez, *J. Med. Chem*., **30**, 758, (1987).
6. E.E. Magat, B.F. Faris, J.E. Reith, L.F. Salisbury, *J. Am. Chem. Soc.*, **73,** 1028, (1951).
7. S. Zhu, G. Xu, Q. Chu, Y. Xu, C. Qui, *J. Fluor. Chem.*, **93**, 69, (1999).
8. J. Pernak, B. Mrowczynski, J. Weglewski, *Synthesis*, **12**, 1415, (1994).
9. M.H. Mosslemin, M. Anary- Abbasinejad, A. Hassanabadi, S. Tajic, *Synth. Commun.*, **40**, 2209, (2010).
10. R.M. Mohammad-Shafiee, *Lett. Org. Chem.*, **8**, 562, (2011).
11. N.O. Brace, G.J. Mantell, *J. Org. Chem.*, **26**, 5170, (1961).
12. Q. Wang, L. Sun, Y. Jiang, C. Li, L. Chunbao, *Beilstein J. Org. Chem.*, **4**, 51, (2008).
13. G. Harichandran, S.D. Amalraja, P. Shanmugam, *Indian J. Chem.*, **50 B (1)**, 77, (2011).
14. G. Harichandran, S.D. Amalraja, P. Shanmugam, *J. Iran. Chem. Soc.*, **8**, 298, (2011).
15. B. Maleki, M. Baghayeri, *RSC Adv.*, **5**, 79746, (2015).
16. R. Pyrzehi-Bakhshani, A. Hassanabadi, *J. Chem. Res*., **3**, 35, (2016).
17. Clinical and Laboratory Standards Institute (CLSI). Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; approved standard. (2006), 2th edition. Wayne, PA: Clinical and Laboratory Standards Institute; CLSI M27-A7.
18. 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).
19. B.F. Mirjalili, A. Bamoniri, L. Zamani, *Scientia Iranica*, **C 19**, 565, (2012).
20. B.F. Mirjalili, A. Bamoniri, L. Zamani, *Lett. Org. Chem*., **9**, 338, (2012).
21. B.F. Mirjalili, L. Zamani, *S. Afr. J. Chem.*, **67**, 21, (2014).
22. L. Zamani, B.F. Mirjalili, M. Namazian, *Chemija* **24**, 312, (2013).
23. L. Zamani, B.F. Mirjalili, K. Zomorodian, S. Zomorodian, *S. Afr. J. Chem*., **68**, 133, (2015).
24. L. Zamani, B.F. Mirjalili*, Chem. Heterocycl. Compd*., **51**, 578, (2015).
25. L. Zamani, B. F.Mirjalili, K. Zomorodian, M. Namazian, S. Khabnadideh, E. FaghihMirzaei, *Farmacia*, **62**, 467, (2014).
26. B.F. Mirjalili, L. Zamani, K. Zomorodian, S. Khabnadideh, Z. Haghighijoo, Z. Malakotikhah, S.A. Ayatollahi Mousavi, Sh. Khojasteh, *J. Mol. Struct.,* **1116**, 102 (2016).
27.

Table 3. Minimum inhibitory and fungicidal concentrations of the synthetic compounds (μg/mL) against the examined fungi.

		B1		B2		B3		B5		B6		B7		B9		B10		B12		Fluconazole	
		MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
	C. albicans ATCC10261	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	3.3	84.44
	C. ropicalis ATCC750	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	8	256
Fungi	C. krusei ATCC6258	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	16	32
	C. glabrata ATCC90030	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	2.8	32
	C. dubliniensis CBS8501	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	1.4	8
	A. flavus ATCC64025	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	128	128
	A. fumigatus ATCC14110	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	128	256

Table 4. MIC and MFC (μg/mL) values for the synthetic compounds against bacteria.

	B1		B2		B3		B5		B6		B7		B9		B10		B12	
	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MFC
S.aureus ATCC25923	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
E.fecalis ATCC1299	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
E. coli ATCC25922	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256
P.aeruginosa ATCC27853	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256	>256