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One-pot preparation of *N,N′*-alkylidenebisamides promoted by $BF_3.SiO_2$

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ABSTRACT

A highly efficient procedure for the preparation of *N,N'*-alkylidenebisamides in the presence of $BF_3.SiO_2$ as a catalyst is described. *N,N'*-alkylidenebisamides have been prepared *via* one-pot three-component condensation reaction of various aldehydes and amides. All of the reactions proceeded in high yields and in moderately short reaction times.

***Keywords**: N,N'-Alkylidenebisamides, Aldehydes, Amides, $BF_3.SiO_2$.*

1. Introduction

Bisamides are of considerable interest in the synthesis of peptidomimetic compounds [1,2]. They are key constituents of many biologically active and pharmaceutical compounds such as introduction of gem-diaminoalkyl residues in retro-inverso pseudopeptide derivatives by treating the corresponding amide with iodobenzene bis(trifluoroacetate) [3,4].

Generally, symmetrical alkylidenebisamides are synthesized by the direct reaction of aldehydes with amides under suitable catalytic conditions. In this topic various conditions or catalysts such as triflic acid [5], *p*-toluene sulfonic acid [6], SiO_2-$MgCl_2$ [7], CC-activatd DMSO [8], sulfamic acid [9], phosphortungstic acid [10], boric acid [11], $ZnCl_2$ [12], $B(HSO_4)_3$ [13] and silica supported polyphosphoric acid (SiO_2-PPA) [14] have been examined. However, each method has certain restrictions with regards to scope and reaction conditions, such as, long reaction time, low yields, difficult work up and harsh reaction conditions.

$BF_3{\cdot}SiO_2$ [15-19] is a bench-top catalyst which has many advantages such as simple preparation, reusability, easy handling and environmental benignity.

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2. Experimental

2.1. General

The chemicals were used without any additional purification. Silica gel 60 (0.063-0.200 mm) for column chromatography (70-230 mesh ASTM) was used for preparation of $BF_3.SiO_2$. The products were characterized by FT-IR, ^{1}H-NMR, and a comparison of their physical properties with those reported in the literature. FT-IR spectra were run on a Bruker, Eqinox 55 spectrometer. A Bruker (DRX-400 Avanes) NMR was used to record the ^{1}HNMR spectra. The thermal gravimetric analysis (TGA) was done with "NETZSCH TG 209 F1 Iris" instrument. Melting points were determined by a Buchi melting point B-540 B.V.CHI apparatus. BANDELIN Sonopuls HD 3200 ultrasonic apparatus (20 kHz, 150 W) was used for sonication. The microwave oven Kenwood, 1300W and Mixer Mill (MM 400) in 25 Hz frequency were used for running the described reactions.

2.2. General procedure for the synthesis of $BF_3.SiO_2$

To a mixture of nano-silica gel (1 g) and $CHCl_3$ (5 ml), $BF_3.Et_2O$ (1.2 ml) was added dropwise. The resulting suspension was stirred for 1 h at room temperature, filtered, washed with chloroform, and dried at room temperature.

2.3. General procedure for the synthesis of N,N'-alkylidenebisamide

A mixture of aldehyde or 1,3,5-trioxane (1 mmol), amide (2 mmol), *n*-hexane (5 ml) and $BF_3.SiO_2$ (0.03 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 to isolation of product and catalyst. The catalyst was separated from product by boiling ethanol. The crude solid product was purified by recrystallization procedure in ethanol:water, 80:20.

2.4. Selected spectral data

N,N'-(Phenylmethylene) dibenzamide, (Table 2, Entry 1): 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*=7.1 Hz, 2H),7.49 (t, *J*=7.5 Hz, 6H), 7.39 (t, *J* =7.5 Hz, 2H),7.32 (t, *J*=7.1 Hz, 1H), 7.05 (t, *J*=7.7 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, Entry 2): FT-IR (ῡ, ATR, neat, cm^{-1}): 3242 (N-H, stretch.), 1664 (C=O, stretch.), 1628 (C=C, stretch.),1346 and 1528 (NO_2, 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*=1.7 Hz, 2H), 7.82 (d, *J*=7.8 Hz, 1H), 7.70 (t, *J*=8.0 Hz, 1H), 6.74 (t, *J*=7.5 Hz, 1H, CH), 6.35 (dd, *J*=17.1 and 10.2 Hz, 2H), 6.17 (dd, *J* = 17.1 and 1.8 Hz, 2H), 5.68 (dd, *J* = 10.2 and 1.8 Hz, 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, entry 3): FT-IR (ῡ, ATR, neat, cm^{-1}): 3256 (N-H, stretch.), 1649 (C=O, stretch.), 1343 and 1507 (NO_2, stretch.), 1546 (N-H, bend.), 852 (=C-H, bend.); ^{1}H NMR (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), 7.48-7.53 (m, 4H), 7.09 (brs, 1H, CH).^{13}C-NMR (DMSO-d_6, ppm) δ: 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, entry 4): FT-IR (ῡ, ATR, neat, cm^{-1}): 3306 (N-H, stretch.), 1706 (C=O, stretch.), 1600 (C=C, stretch.), 1349 and 1530 (NO_2, 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) δ: 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) dimethyl carboxamide (Table 2, entry 5): FT-IR (ῡ, ATR, neat, cm^{-1}): 3309 (N-H, stretch.), 1708 (C=O, stretch.), 1550 (N-H, bend.), 720, 699 (=C-H, bend.), 1050 (C-Cl, stretch.); ^{1}H NMR (DMSO-d_6, ppm) δ: 8.04 (sbr, 2H, N-H), 7.61 (d, *J*=8.2 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 6.24 (dd, *J* = 8.4 Hz, 1.9, 1H), 6.24 (t, *J* = 7.6 Hz, 1H, CH), 3.55 (s, 6H, OMe); ^{13}C-NMR (DMSO-d_6, ppm) δ: 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, entry 6): FT-IR (ῡ, ATR, neat, cm^{-1}): 3250 (N-H, stretch.), 1646 (C=O, stretch.),1340 (N-H, bend.), 1339, 1533 (NO_2,„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 and 1.4 Hz, 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, entry 7): 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.), 1051 (C-Cl, stretch.); ^{1}H NMR (DMSO-d_6, ppm) δ: 8.54 (d, *J*=7.2 Hz, 2H, N-H), 7.62 (d, *J*=7.6 Hz, 1H), 7.48-7.54 (m, 2H), 6.6 (t, *J*=7.6 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-*n*-propyl-methylene) dibenzamide (Table 2, entry 8): 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*=7.6 Hz, 2H, N-H), 7.86 (d, *J*=7.1 Hz, 4H), 7.55 (t, *J*=7.1 Hz, 2H), 7.47 (t, *J*=7.7 Hz, 4H), 5.84-5.86 (m, 1H, CH), 1.85 (td, *J*=7.7 and 7.4 Hz, 2H, CH_2), 1.32-1.40 (m, 2H, CH_2), 0.938 (t, *J*=7.3 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, entry 9): FT-IR (ῡ, ATR, neat, cm^{-1}): 3287 (N-H, stretch.), 1701 (C=O, stretch.), 1515 and 1343 (NO_2, stretch.), 1556 (N-H, bend.), 1255, 1032 (C-O, stretch.), 674, 783, 809 (=C-H, bend.); ^{1}HNMR (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-Phenylethyl-methylene) dibenzamide (Table 2, entry 10): 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*=7.2 Hz, 4H), 7.54 (t, *J*=7.3 Hz, 2H), 7.48 (t, *J*=7.7 Hz, 4H), 7.20–7.31 (m, 4H), 7.17 (m, 1H), 5.85 (m, 1H, CH), 2.69 (t, *J*=8.2 Hz, 2H, CH_2), 2.17 (dd, *J*=15.4 and 7.3 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-ethene-methylene) dibenzamide (Table 2, entry 11): 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*=7.4 Hz, 4H), 7.86 (t, *J*=7.9 Hz, 2H), 7.56 (t, *J*=7.2 Hz, 2H), 7.42-7.52 (m, 4H), 7.35 (m, 2H), 7.28 (t, *J*=7.3 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-propyl-methylene) dibenzamide (Table 2, entry 12): FT-IR (ῡ, ATR, neat, cm^{-1}): 3234 (N-H, stretch.), 1737 (C=O, stretch.), 1480, 1643 (C=C, stretch.), 1561 (N-H, bend.); ^{1}H NMR (DMSO-d_6, ppm) δ: 8.40 (d, *J*=8.2 Hz, 2H, N-H), 7.85(d, *J*=7.2 Hz, 4H), 7.54(t, *J*=7.2 Hz, 2H), 7.48 (t, *J*=7.8 Hz, 4H), 5.67 (q, *J*=8.2 Hz, 1H, CH), 2.15-2.3 (m, 1H, CH), 0.97(d, *J*=6.73 Hz, 6H, CH_3). Elemental analysis. Found (%): C 66.89; H 6.8; N 9.45. $C_{18}H_{20}N_2O_2$. Calculated (%): C 72.95; H 6.8; N 9.45.

N,N'-(2-Hydroxyphenyl-methylene) dibenzamide (Table 2, entry 14): 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-d_6, ppm) δ: 9.02 (d, *J*=7.4 Hz, 2H, N-H), 8.03 (d, *J*=7.3 Hz, 2H), 7.81 (d, *J*=7.3 Hz, 3H), 7.60-7.62 (m, 1H), 7.50-7.53 (m, 3H), 7.42-7.47 (m, 5H), 7.33-7.37 (m, 1H), 7.26 (t, *J*=7.3 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.

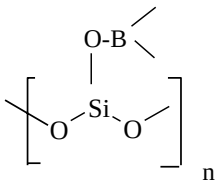
N-Benzylidene urea (Scheme 2): FT-IR (ῡ, ATR, neat, cm^{-1}): 3272 (N-H), 1670 (C=O), 1467, 1268, 1060, 868. ^{1}H NMR (DMSO-d_6, ppm) δ: 7.98 (d, *J*=5.7 Hz, 2 H), 7.6 (d, J= 6.5 Hz, 1 H), 7.5 (t, *J*=6.4 Hz, 2 H), 7.4 (d, *J*=6.5 Hz, 2 H), 6.45 (t, *J*=5.8 Hz, 1 H), 5.7 (brs., 2 H), 5.4 (brs., 2 H). Elemental analysis. Found (%): C 51.52; H 5.67; N 26.79. $C_9H_{12}N_4O_2$. Calculated (%): C 51.92; H 5.81; N 26.91.

N,N,N',N'-(1, 5-Pentylene) tetrabenzamide (Scheme 3): FT-IR (ῡ, ATR, neat, cm^{-1}): 3284 (N-H, stretch.), 1655 (C=O, stretch.), 1448, 1622 (C=C, stretch.), 1577 (N-H, bend.), 683, 774 (=C-H, bend.); ^{1}H NMR (DMSO-d_6, ppm) δ: 8.53 (d, *J*=7.7 Hz, 4H, N-H), 7.83(d, *J*=8.5 Hz, 8H), 7.53 (t, *J*=7.4 Hz, 4H), 7.44 (t, *J*=7.4 Hz, 8H), 5.84-5.87 (m, 2H, CH), 1.92-1.95 (m, 4H), 1.3-1.6 (m, 2H). Elemental analysis. Found (%): C 72.49; H 5.67; N 10.39. $C_{33}H_{32}N_4O_4$. Calculated (%): C 72.24; H 5.88; N 10.21.

N, N'-(Methylene) dibenzamide (Scheme 4): 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}H NMR (DMSO-d_6, ppm) δ: 9.03 (t, *J*=5.5 Hz, 2H, N-H), 7.9 (d, *J*=7.1 Hz, 4H), 7.55 (t, *J*=7.1 Hz, 2H), 7.48 (t, *J*=7.1 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.

3. Results and Discussion

In continuation of our investigations on the applications of solid acids in organic synthesis, we have investigated $BF_3{\cdot}SiO_2$ efficiency in the synthesis of *N,N'*-alkylidenebisamides under mild conditions. For identification of the structure of $BF_3{\cdot}SiO_2$, we studied FT-IR (ATR) spectra of $BF_3{\cdot}OEt_2$, $BF_3.SiO_2$, and SiO_2 (Fig. 1). In all of the spectrums, OH stretching band is observed and strong intermolecular hydrogen bonding occurs in the hydroxyl groups. Therefore, the resulting O-H absorption is very broad. The moisture in BF_3 causes presence of OH stretching bond in its infrared spectra. Comparison of the infrared spectra of $BF_3{\cdot}SiO_2$ and SiO_2 show that, in both of them, the absorbtion Si-OH and Si-O-Si bands are appeared in ~800 cm^{-1} and ~1100 cm^{-1}, respectively. In BF_3 pectrum, the absorbtion of B-F is observed in 700 and 900 cm^{-1}. In IR spectrum of $BF_3{\cdot}SiO_2$, the B-O, Si-OH and Si-O-Si are observed in 1520, 800 and 1100 cm^{-1}, respectively. The comparison of the infrared spectra of different percentage of $BF_3{\cdot}SiO_2$ shows that with increasing of percentage of BF_3, the intensity of B-O band in 1520 cm^{-1} is increased. Based on these results, we suggest the following structure for $BF_3{\cdot}SiO_2$ (Scheme 1).



Scheme 1. Structure of $BF_3{\cdot}SiO_2$.

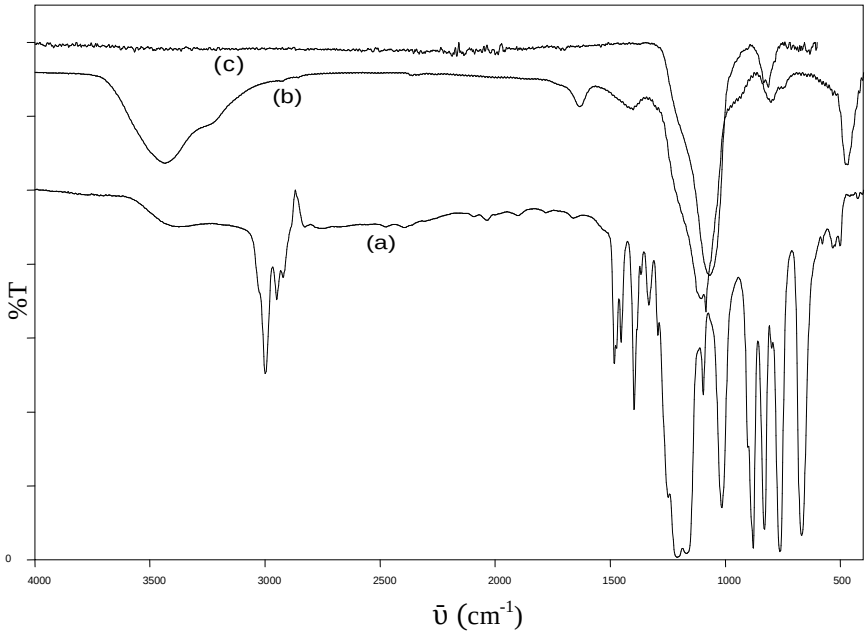


Fig. 1. FT-IR (ATR) spectrum of (a) $BF_3 \cdot Et_2O$, (b) $BF_3 \cdot SiO_2$, (c) SiO_2.

The X-ray diffraction (XRD) patterns of $BF_3.SiO_2$ is shown in Fig. 2. According to XRD pattern of catalyst, the values of 2θ and FWHM are shown in Table 1.

According to XRD pattern, the three signals in 2Θ equal to 14.54, 27.97 and 28.45 with FWHM equal to 0.2362, 0.2952 and 0.1771, respectively, is similar to HBO_2 and HBO_3 with B-O bonds. We can confirm the proposed structure for $BF_3.SiO_2$ in scheme 1.

Thermal gravimetric analysis (TGA) pattern of $BF_3.SiO_2$ was detected from 23.8 to 513 °C (Fig. 3). The catalyst is stable until 93.8 °C and only 3.34% of its weight was reduced in 93.8 °C. By heating of catalyst between 103 to 183 °C, the reducing amount of its weight is 25%. Only 2% of the catalyst weight was reduced between 183-513 °C. According to TGA diagram of $BF_3.SiO_2$, this catalyst is stable until 93.8 °C. This initial reducing mass (3.34%) of catalyst is related to removal of catalyst moisture.

Our aim is to develop new synthetic methods using heterogeneous catalysts to reduce risks to humans and the environment. To prepare *N,N'*-alkylidenebisamides and find the best reaction conditions, the reaction of benzamide and benzaldehyde was examined under various conditions and different quantities of $BF_3.SiO_2$ (Table 1). The reaction proceeded efficiently in *n*-hexane under reflux condition using 0.03 g of catalyst with 1mmol of aldehyde and 2 mmol of amide (Table 2, Entry 3).

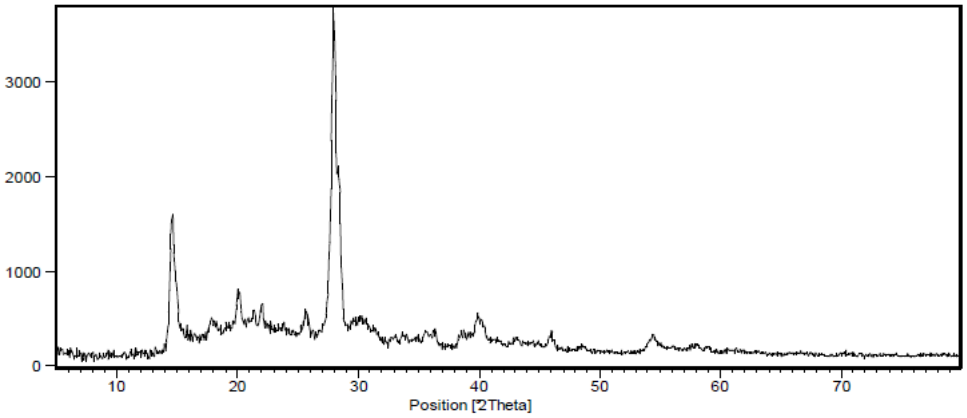


Fig. 2. X-ray diffraction (XRD) pattern of $BF_3.SiO_2$.

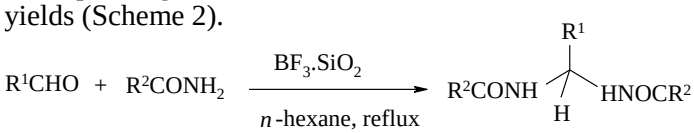
Table 1. $BF_3.SiO_2$ reflexes in XRD diffractogram.

No.	Pos. [2Θ]	FWHM [2Θ]
1	14.5404	0.2362
2	17.8055	0.5904
3	20.1006	0.3542
4	21.9895	0.1771
5	25.6686	0.2362
6	27.9718	0.2952
7	28.4516	0.1771
8	36.0281	0.7085
9	38.4628	0.4723
10	39.8824	0.2362
11	43.0838	0.7085
12	45.9974	0.4723
13	48.5913	0.7085
14	54.3613	0.5760

The reusability of catalyst in the reaction condition has been examined (Table 2, Entries 10 and 11). The obtained data have shown low reusability for catalyst in this protocol. Next, the scale of this procedure was explored using a wide range of aliphatic and aromatic aldehydes containing electron-donating or electron-withdrawing groups attaching to aromatic ring (Table 3). In all cases, aromatic aldehydes containing electron-withdrawing groups gave higher yield of products in shorter time than aromatic aldehydes containing electron-releasing groups (Table 3, Entries 3 and 14). In methyl carbamate, the nucleophilicity of nitrogen is higher than acetamide. Thus, methyl carbamate produces a good yield of product in shorter time than acetamide (Table 3, Entries 4 and 13).

Aromatic aldehydes have reacted in this protocol in lower times and higher yields than aliphatic aldehydes (Table 3, Entries 1, 8, 10, 11) specially aliphatic aldehydes with steric hinders (Table 3, Entry 10) or conjugated aliphatic aldehydes (Table 3, Entry 11). The OMe group in methyl carbamate caused higher yield of corresponding amide in lower time than acetamide (Table 2, Entry 5 and 7).

The reaction of benzaldehyde with urea produces corresponding bisamides and imines with different yields (Scheme 2).



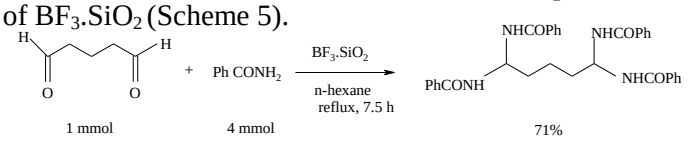
Scheme 2.

N,N,N′,N′-(1,5-Pentylene) tetrabenzamide was produced via reaction of 1 mmol of glutardialdehyde with 4 mmol of benzamide (Scheme 3).

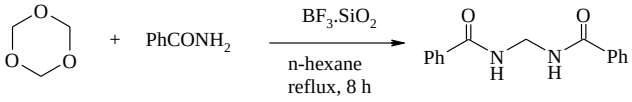
Bisacrylamides are cross-linking agents used during the formation of polymers such as polyacrylamide. *N,N′*-Methylenebisacrylamide is an electrophoresis matrix for size separation of proteins and nucleic acids, from biological industries. *N,N′*-(Methylene) dibenzamide was produced via reaction of 1,3,5-trioxane with benzamide in the presence of $BF_3.SiO_2$ (Scheme 4).

The chemo-selectivity of bisamide preparation was examined *via* reaction of 4-nitrobenzaldehyde with benzamide and acetamide in one vessel in the presence of $BF_3.SiO_2$. The preparation of mixed products approves no chemoselectivity 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 chemoselectivity between aromatic and aliphatic aldehydes.

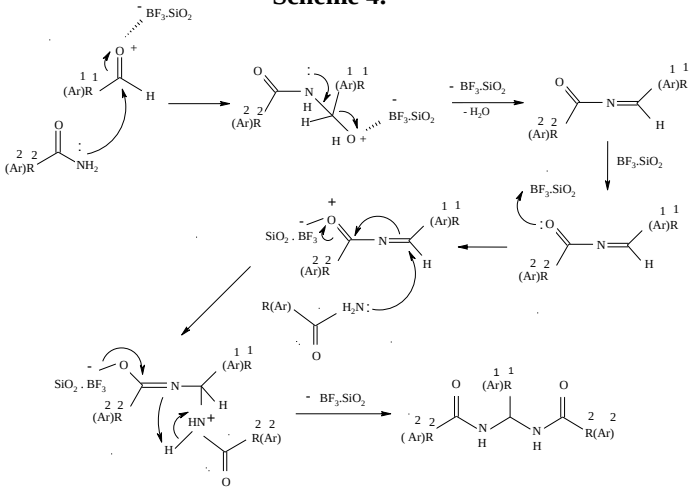
Previously, two types of mechanisms were reported for bisamide formation from aldehyde and amide [10, 11]. The best of our knowledge, we have proposed a mechanism for formation of bisamides in the presence of $BF_3.SiO_2$ (Scheme 5).



Scheme 3.



Scheme 4.



Scheme 5.

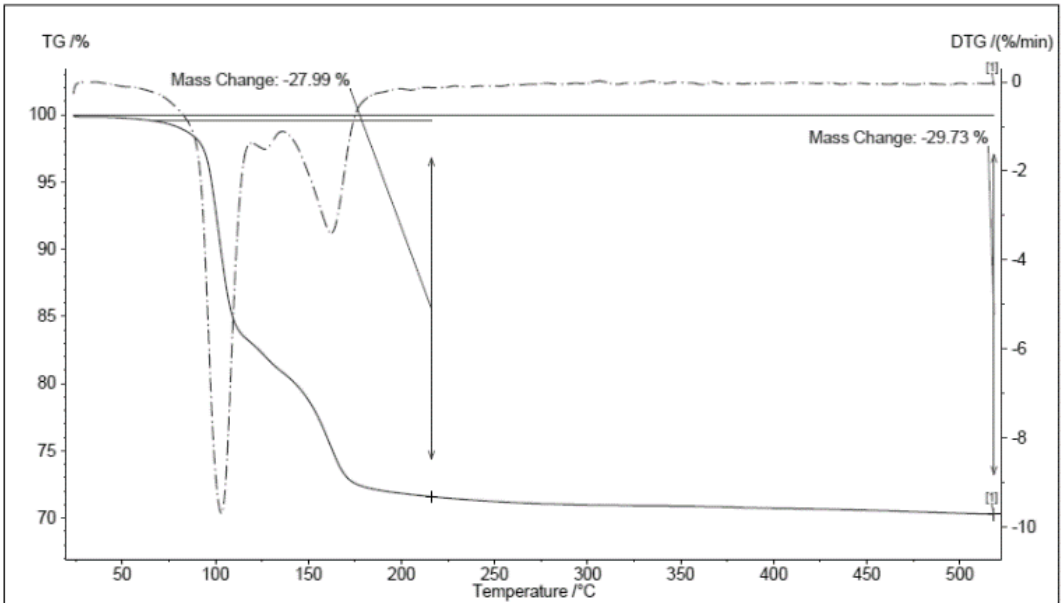


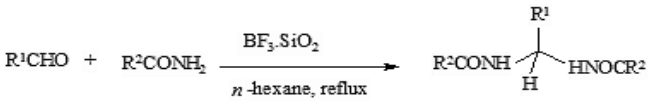
Fig. 3. TGA pattern of $BF_3.SiO_2$.

Table 2. Synthesis of *N*,*N*′-(phenylmethylene) dibenzamide.[a]

Entry	Catalyst (g)	Conditions	Time (h)	Yield (%)[b]	Ref.
1	$BF_3.SiO_2$ (0.07)	*n*-Hexane/reflux	1.3	81	-
2	$BF_3.SiO_2$ (0.05)	*n*-Hexane/reflux	1.3	84	-
3	$BF_3.SiO_2$ (0.03)	*n*-Hexane/reflux	1.3	87	-
4	$BF_3.SiO_2$ (0.02)	*n*-Hexane/reflux	1.3	83	-
5	$BF_3.SiO_2$ (0.03)	EtOAc/reflux	4	62	-
6	$BF_3.SiO_2$ (0.03)	$CHCl_3$/reflux	4.5	81	-
7	$BF_3.SiO_2$ (0.03)	S.F./Mixer Mill	1	-	-
8	$BF_3.SiO_2$ (0.03)	EtOAc/Sonication	0.5	25	-
9	$BF_3.SiO_2$ (0.03)	S.F./M.W.	0.03	50	-
10	$BF_3.SiO_2$ (0.03, 2nd run	*n*-Hexane/reflux	1.3	60	-
11	$BF_3.SiO_2$ (0.03), 3rd run	*n*-Hexane/reflux	1.3	43	-
12	SiO_2-$MgCl_2$(0.025)	Solvent-free/100 °C	3	73	7
13	CC(1.2 equiv)-activated DMSO (7.0 equiv)	Toluene/rt to 70 °C	1.5	71	8
14	Phosphotungstic acid (0.3 mmol)	Toluene/reflux	20	70	[10]
15	Boric acid (0.3 mmol)	Microwave	0.67	80	[11]

[a] 1 mmol of benzaldehyde and 2 mmol of benzamide was used.
[b] Isolated yield.

Table 3. Preparation of *N,N′*-alkylidenebisamides in the presence of $BF_3.SiO_2$[a].



Entry	R^1	R^2	Yield (%)[b]	Time (h)	m.p.°C (Lit.)	Ref.
1	C_6H_5	C_6H_5	87	1.3	210-211 (214-216)	[11]
2	3-NO_2-C_6H_4	CH_2=CH-	84	5.5	222-223 (224-226)	[11]
3	4-NO_2-C_6H_4	C_6H_5	90	2	239-240 (242-244)	[11]
4	4-NO_2-C_6H_4	OCH_3	81	0.9	196-198	-
5	2,4-di-Cl-C_6H_3	OCH_3	89	1	248-250 (252-254)	[7]
6	3-NO_2-C_6H_4	C_6H_5	83	1.6	236-237	-
7	2,4-di-Cl-C_6H_3	CH_3	60	5	264-265	-
8	CH_3-CH_2-CH_2-	C_6H_5	76	2.5	172-173	-
9	3-NO_2-C_6H_4	OCH_3	90	2.3	184-185	-
10	Ph-CH_2-CH_2-	C_6H_5	62	4.5	253-254 (248-249)	[6]
11	Ph-CH_2=CH_2-	C_6H_5	65	2.3	199-201	-
12	$(CH_3)_2$-CH-	C_6H_5	71	5.25	126-127	-
13	4-NO_2-C_6H_4	CH_3	97	5	264-265 (233-235)	[7]
14	2-OH-C_6H_4	C_6H_5	66	3.5	177-179	-

[a]Reaction conditions: Amide (2 mmol), aldehyde (1 mmol), $BF_3.SiO_2$ (0.03 g); refluxed in n-hexane as solvent.
[b]Isolated yields.

4. Conclusion

In conclusion, we have demonstrated a simple method for the synthesis of *N,N′*-alkylidenebisamides with using $BF_3.SiO_2$ as a eco-friendly and efficient catalyst. Short reaction times, high yields, a clean process, simple methodology, easy work-up and green conditions are advantages of this protocol.

Acknowledgment

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