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Silica-Supported Boron Trifluoride (BF_3-SiO_2): An Efficient, Environment Friendly and Recyclable Catalyst for The One-Pot Synthesis of 4(3*H*)-quinazolinones

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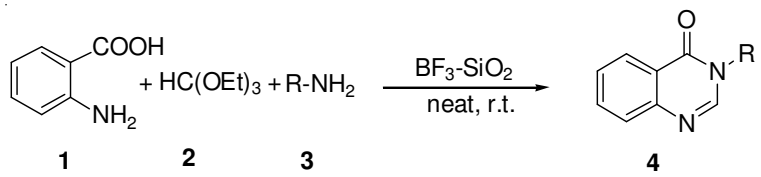
A simple and efficient synthesis of 4(3*H*)-quinazolinones has been accomplished by the one-pot condensation of anthranilic acid, triethylorthoformate and primary amines under solvent-free conditions in the presence of BF_3-SiO_2.

Key Words: BF_3-SiO_2, Anthranilic acid, 4(3*H*)-Quinazolinones, Solvent-free.

INTRODUCTION

The synthesis of 4(3*H*)-quinazolinones has been considered of great interest to organic chemists because of their pharmacological and therapeutic properties such as antimalarial, anticancer, anticonvulsant, antiinammatory activities[1]. The most common methods for synthesis of 4(3*H*)-quinazolinones are the condensation reaction of anthranilic acid or isatoic anhydride with orthoesters and primary amines in the presence of $SnCl_4$[2a], silica gel/$FeCl_3$[2b], H-Y-zeolites[2c], $La(NO_3)_3$[2d], *p*-TsOH[2d], $Bi(TFA)_3$-[nbp]$FeCl_4$[2e], $NaHSO_4$-SiO_2[2f], Amberlyst-15[2f], $Yb(OTf)_3$[2g], Nafion-H[2h]. However, most of these procedures have signicant drawbacks such as long reaction times, low yields, harsh reaction conditions, difficult work-up and use of environmentally toxic reagents or media. Thus, there is still need of a simple and general procedure for one-pot synthesis of 4(3*H*)-quinazolinones under mild conditions.

BF_3-SiO_2 as an efficient, environment friendly and recyclable catalyst, has been widely used in organic synthesis[3]. The silica supported form of the catalyst is a bench-top catalyst which is easy to handle and enables better accessibility of the reactants to the active sites[4]. BF_3-SiO_2 is a solid superacid has surface species such as Al-OBF_2, Si-OBF_2 and the ion pairs[5] Al-OBF_3-H^+ or Si-OBF_3-H^+. We now report a simple and efficient route to synthesis of 4(3*H*)-quinazolinones using BF_3-SiO_2 as a efficient and environmentally benign catalyst under solvent-free conditions (**Scheme-I**).



1 **2** **3** **4**

Scheme-I

EXPERIMENTAL

NMR spectra were determined on Bruker AV-300 spectrometer at room temperature using TMS as internal standard, coupling constants (*J*) were measured in Hz; elemental analysis were performed by a Vario-III elemental analyzer; melting points were determined on a XT-4 binocular microscope and were uncorrected. The commercially available reagents were used throughout without further purification unless otherwise stated.

General procedure for the preparation of BF_3-SiO_2: A mixture of BF_3·OEt (0.57 g, 4 mmol) and preheated silica gel (0.5 g) in MeOH (5 mL) was prepared and was stirred for 1 h at room temperature. The slurry was dried slowly on a rotary evaporator at 40 ºC. The obtained solid was dried in an ambient temperature for 2 h and then was stored under dry atmosphere in a container for months.

General procedure for the preparation of compound 4: To a mixture of anthranillic acid (1 mmol), triethylorthoformate (1.2 mmol) and an amine (1.2 mmol) BF_3-SiO_2 (100 mg) was added. The mixture was stirred at room temperature for an appropriate time (Table-1). After completion of the reaction, 10 mL CH_2Cl_2 was added to the reaction mixture and the catalyst was recovered by filtered. The organic layer was dried over $MgSO_4$, the solvent was evaporated and crystallized from ethanol to afford pure 4(3*H*)-quinazolinones in 84-96 % yields.

3-Phenyl-4(3*H*)-quinazolinone (4a): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.37 (d, 1H, *J* = 7.8 Hz), 8.04 (s, 1H), 7.75-7.65 (m, 2H), 7.45 (t, 1H, *J* = 7.5 Hz), 7.30-7.22 (m, 5H); MS m/z: 222 (M^+); Anal. calcd. (%) for $C_{14}H_{10}N_2O$: C 75.66, H 4.54, N 12.60; found (%): C 75.79, H 4.37, N 12.68.

3-*o*-Tolylquinazolin-4(3*H*)-one (4b): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.33 (d, 1H, *J* = 7.5 Hz), 8.00 (s, 1H), 7.80-7.68 (m, 2H), 7.60-7.25 (m, 4H), 7.20 (d, 1H, *J* = 7.1 Hz), 2.37 (s, 3H); MS m/z: 236 (M^+); Anal. calcd. (%) for $C_{15}H_{12}N_2O$: C 76.25, H 5.12, N 11.86; found (%): C 76.51, H 4.99, N 11.95.

3-*p*-Tolylquinazolin-4(3*H*)-one (4c): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.30 (d, 1H, *J* = 7.8 Hz), 8.09 (s, 1H), 7.75-7.68 (m, 2H), 7.45 (t, 1H, *J* = 7.2 Hz), 7.30 (d, 2H *J* = 7.8 Hz), 7.12 (d, 2H, *J* = 7.8 Hz), 2.30 (s, 3H); MS m/z: 236 (M^+); Anal. calcd. (%) for $C_{15}H_{12}N_2O$: C 76.25, H 5.12, N 11.86; found (%): C 76.47, H 5.07, N 11.85.

3-(2-Chlorophenyl)quinazolin-4(3*H*)-one (4d): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.36 (d, 1H, *J* = 8.1 Hz), 8.05 (s, 1H), 7.80-7.76 (m, 2H), 7.64-7.40 (m, 5H); MS m/z: 256 (M^+); Anal. calcd. (%) for $C_{14}H_9N_2OCl$: C 65.51, H 3.53, N 10.91; found (%): C 65.69, H 3.30, N 11.06.

3-(4-Chlorophenyl)quinazolin-4(3*H*)-one (4e): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.28 (d, 1H, *J* = 7.5 Hz), 8.10 (s, 1H), 7.75-7.69 (m, 2H), 7.42 (t, 1H, *J* = 7.2 Hz), 7.28 (d, 2H, *J* = 7.8 Hz), 7.12 (d, 2H, *J* = 7.5 Hz); MS m/z: 256 (M^+); Anal. calcd. (%) for $C_{14}H_9N_2OCl$: C 65.51, H 3.53, N 10.91; found (%): C 65.74, H 3.42, N 11.12.

3-(4-Bromophenyl)quinazolin-4(3*H*)-one (4f): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.25 (d, 1H, *J* = 7.5 Hz), 8.12 (s, 1H), 7.72-7.68 (m, 2H), 7.45 (t, 1H, *J* = 7.2 Hz), 7.22 (d, 2H, *J* = 7.8 Hz), 7.12 (d, 2H, *J* = 7.8 Hz); MS m/z: 300 (M^+); Anal. calcd. (%) for $C_{14}H_9N_2OBr$: C 55.84, H 3.01, N 9.30; found (%): C 56.02, H 3.14, N 9.24.

3-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (4g): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.25 (d, 1H, *J* = 7.8 Hz), 8.10 (s, 1H), 7.77-7.70 (m, 2H), 7.47 (t, 1H, *J* = 7.5 Hz), 7.30 (d, 2H, *J* = 7.8 Hz), 7.10 (d, 2H, *J* = 7.8 Hz), 3.80 (s, 3H); MS m/z: 252 (M^+); Anal. calcd. (%) for $C_{15}H_{12}N_2O_2$: C 71.42, H 4.79, N 11.10; found (%): C 71.63, H 4.91, N 11.19.

3-(2,4-Dibromophenyl)-4(3*H*)-quinazolinone (4h): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.22 (d, *J* = 8.1 Hz, 1H), 7.99 (s, 1H), 7.88-7.61 (m, 2H), 7.64 (t, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 1H); MS m/z: 380 (M^+); Anal. calcd. (%) for $C_{14}H_8N_2OBr$: C 44.25, H 2.12, N 7.37; found (%): C44.51, H 2.02, N 7.45.

3-(3,4-Dichlorophenyl)-4(3*H*)-quinazolinone (4i): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.28 (d, *J* = 8.1 Hz, 1H), 8.25 (s, 1H), 7.91-7.81 (m, 2H), 7.58 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 1H); MS m/z: 380 (M^+); Anal. calcd. (%) for $C_{14}H_8N_2OBr$: C 44.25, H 2.12, N 7.37; found (%): C44.46, H 2.18, N 7.22.

3-Benzylquinazolin-4(3*H*)-one (4j): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.34 (d, 1H, *J* = 7.8 Hz), 8.12 (s, 1H), 7.77-7.72 (m, 2H), 7.51 (dd, 1H, *J* = 7.8, 7.2 Hz), 7.40-7.32 (m 5H), 5.21 (s, 2H); MS m/z: 236 (M^+); Anal. calcd. (%) for $C_{15}H_{12}N_2O$: C 76.25, H 5.12, N 11.86; found (%): C 75.29, H 5.05, N 11.92.

3-Butylquinazolin-4(3*H*)-one (4k): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.30 (d, 1H, *J* = 7.8 Hz), 8.08 (s, 1H), 7.75-7.70 (m, 2H), 7.49 (t, 1H, *J* = 7.8 Hz), 3.96 (t, 2H, *J* = 7.5 Hz), 1.85-1.79 (m, 4H), 0.93-0.90 (m, 3H); MS m/z: 202 (M^+); Anal. calcd. (%) for $C_{12}H_{14}N_2O$: C 71.26, H 6.98, N 13.85; found (%): C 71.43, H 6.90, N 13.59.

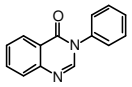
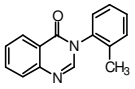
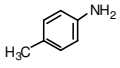
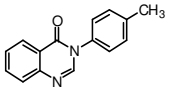
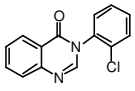
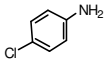
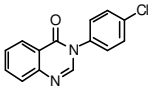
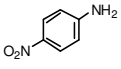
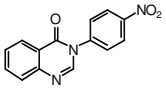
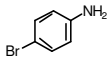
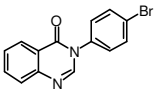
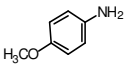
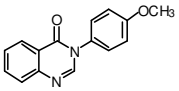
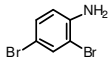
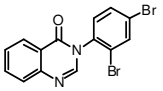
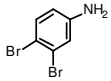
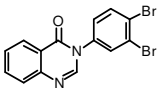
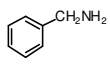
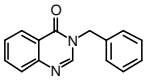
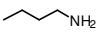
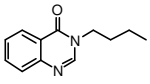
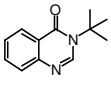
3-*t*-Butylquinazolin-4(3*H*)-one (4l): ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.26 (d, 1H, *J* = 7.8 Hz), 8.02 (s, 1H), 7.75-7.68 (m, 2H), 7.47 (t, 1H, *J* = 7.8 Hz), 1.35 (s, 9H); MS m/z: 202 (M^+); Anal. calcd. (%) for $C_{12}H_{14}N_2O$: C 71.26, H 6.98, N 13.85; found (%): C 71.52, H 6.88, N 13.74.

RESULTS AND DISCUSSION

The experimental condensation reaction has been examined by the amount of catalyst for the reaction involving anthranilic acid (1 mmol) with triethylorthoformate (1.2 mmol) and aniline (1.2 mmol) to afford the product 3-phenylquinazolin-4(3*H*)-one under solvent-free conditions at room temperature. The best result was obtained with 100 mg/mmol BF_3-SiO_2. Higher amounts of catalyst did not improve the result to any greater extent.

A range of 4(3*H*)-quinazolinones derivatives was synthesized by the one-spot condensation of anthranilic acid **1**, triethylorthoformate **2** and primary amines **3**.

TABLE-1
PREPARATION OF 4(3*H*)-QUINAZOLINONES CATALYZED BY BF_3-SiO_2[a]

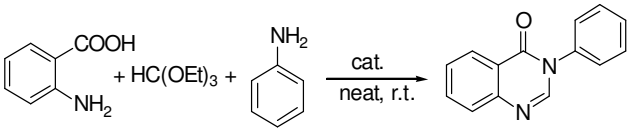
Entry	3	4	Time (min)	Yield (%)	m.p. (ºC)	
					Found	Reported
a			15	95 (92, 89, 86, 80)[b]	134-135	136-138 [2c]
b			15	93	134-135	137-138 [2g]
c			15	96	147-148	145 [2c]
d			20	91	182-183	180-181 [2g]
e			20	88	176-177	178-180 [2c]
f			20	85[c]	164-165	165-166 [2g]
g			20	89	188-189	188-190 [2g]
h			15	94	182-183	180 [2c]
i			20	91	240-242	–
j			20	90	171-173	–
k			20	89	118-119	116 [2c]
l			15	93	70-72	70-71 [6]
m			15	84	65-66	68-74 [6]

[a]All the products were characterized from their spectral (^{1}H NMR) and element analysis.
[b]Isolated yields after recycling of catalyst. [c]The reaction was carried out at 60 ºC.

The reaction proceeded at room temperature within 20 min in excellent yields after the addition of the acid catalyst BF_3-SiO_2 (Table-1). After completion of the reaction, CH_2Cl_2 was added to the reaction mixture and the catalyst was recovered by filtered. The efficiency of the recovered catalyst was verified with the reaction of anthranilic acid, triethylorthoformate and aniline (entry a). Using the fresh catalyst the yield of the products, 3-phenyl-4(3*H*)-quinazolinone (**4a**) was 95 %, while with the recovered catalyst in the four subsequent recyclization the yields were 92, 89, 86, 80 %.

In order to show the merit of the presented protocol, we have compared some of the results obtained by the other catalysts such as $NaHSO_4$-SiO_2, Amberlyst-15, $FeCl_3$-SiO_2, $La(NO_3)_3$, *p*-toluene sulfonic acid, which have been reported recently for the reaction of anthranilic acid, triethylorthoformate and aniline (Table-2). It revealed that BF_3-SiO_2 is an equally efficient, cost-effective and environmentally benign catalyst useful in the synthesis of 4(3*H*)-quinazolinones derivatives.

TABLE-2
COMPARISON OF THE EFFECT OF CATALYSTS IN SYNTHESIS OF 3-PHENYL-4(3*H*)-QUINAZOLINONE



Entry	Catalysis	Time (min)	Yield (%)	Reference
1	$NaHSO_4$-SiO_2	5	89	15
2	Amberlyst-15	5	90	15
3	$FeCl_3$-SiO_2	5	94	8
4	$La(NO_3)_3$	5	92	10
5	*p*-Toluene sulfonic acid	5	96	10
6	BF_3-SiO_2	15	95	–

In conclusion, we have developed a simple and highly efficient practical method for one-pot synthesis of 4(3*H*)-quinazolinones using BF_3-SiO_2 under solvent-free conditions. The notable features of this procedure are mild reaction conditions, simple experimental procdure and excellent yields (84-96 %), which make it a useful and attractive process for the synthesis of 4(3*H*)-quinazolinones. We believe that this methodology will be a valuable addition to the existing methods in the field of synthesis of 4(3*H*)-quinazolinones.

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