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HBF_4: SiO_2: An efficient heterogeneous catalyst for the one step synthesis of 4(3*H*)-quinazolinones under solvent free conditions

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ABSTRACT

The one pot synthesis of 3-Substituted quinazolinones derivatives prepared from anthranalic acid, substituted amines and triethylorthoformate in presence of $HBF_4.SiO_2$ as catalyst has been described. The reaction proceeded with in few minutes with excellent yields. The simple experimental procedure and reusability of the catalyst are significant advantages of this protocol.

Keywords: 4(3H)-quinazolinones, $HBF_4.SiO_2$, Heterogeneous catalyst, Solvent free conditions.

INTRODUCTION

In regards to importance of quinazoline derivatives, especially 4(3H)-quinazolinones have gained more importance in recent years because of their biological activities such as anti-inflammatory, anti-malarial, anti-cancer, anti-convulsant, anti-hypertensive, anti-parkinsonin, analgesic activities [1-7]. Several bioactive natural products containing quinazolinone skeleton have also been reported from natural sources [8-11]. Some of these compounds were reported as anti-hyperlipidemic active compounds [12]. The common method for the preparation of quinazolinones involves the amidation of 2-aminobenzoic acid or 2-aminobenzonitrile followed by oxidative ring closure under basic conditions [13-16] and aza Wittig reactions of α-azido substituted aromatic imides [17-18]. There are different one-pot synthesis of these compounds have also been reported [19-30]. However most of these methods have significant drawbacks such as harsh reaction conditions, long reaction times, low yields, difficult work-up procedures, expensive reagents and difficulty in recovery and reusability of the catalysts. Therefore there is need for development of simple and efficient catalyst to prepare (3H)-quinazolinones.

MATERIALS AND METHODS

Melting points were measured on a Buchi 510 apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer RX 1 FT-IR spectrophotometer, the ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra on a Brucker-400 MHz spectrometer and the mass spectra on a API-2000, LCMS-MS system. Column chromatography was performed over silica gel (BDH 100-200 mesh) and TLC with silica gel GF 254.

General Procedure for the preparation of 4(3H)-Quinazolinones 4(a-o)

To a mixture of substituted anthranillic acid (**1**) (1 mmol), triethyorthoformate **(2)** (1.2 mmol) and substituted amine **(3)** (1.2 mmol), silica gel supported HBF_4 (100 mg) was added. The mixture was stirred at room temperature for an appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, 10 ml of Chloroform was added to the reaction mixture and the catalyst was recovered by filtration. The filtrate was concentrated under vacuum and the obtained residue was chromatographed through silica gel using chloroform: methanol as eluent to obtain 4(3H)-quinqzolinones **4 (a-o)** in pure form.

4a: (R=H and R_1= Ph); Yield: 94%; Reaction time: 6 min; Reaction temperature: RT; m. p: 136-138 ^{0}C; I.R (KBr) cm^{-1}: 1671, 1595, 1498, 1323, 1262; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.33 (1H, s), 8.19 (1H, d, *J*= 8.0 Hz), 7.85 (1H, t, *J*=8.0 Hz), 7.72 (1H, dd, *J*=8.0, 1.9 Hz), 7.59-7.49 (5H, m); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 160.3, 148.0, 147.4, 137.9, 134.9, 129.6, 127.8, 126.8, 122.2; MS *m/z:* 223 $[M+H]^{+\cdot}$

4b: (R=H and R_1= 2-F-Ph); Yield: 91%; Reaction time; 10 min; Reaction temperature: RT; m. p: 119-121.5^{0}C; I.R (KBr) cm^{-1}: 3054.8, 1674.7, 1500, 1472, 1311, 1265, 771; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.39 (1H, s), 8.22 (1H, dd, *J*=7.9, 1.9 Hz), 7.85 (1H, td, *J*=8.0, 1.3 Hz), 7.78 (1H, d, *J*=8.0 Hz), 7.64 (1H, t, *J*=8.0 Hz), 7.62-7.38 (4H, m); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 159.7, 158.7, 156.2, 148.0, 147.4, 135.3, 131.8, 130.3, 128.0, 126.7, 125.6, 125.3, 121.9, 116.8, 116.6;MS *m/z*: 241.4 $[M+H]^{+\cdot}$

4c: (R=H and R_1= 2-Cl-Ph); Yield: 89%; Reaction time; 15 min; Reaction temperature: RT; m. p: 160.1-163.2^{0}C; I.R (KBr) cm^{-1}: 3062.5, 1676.7, 1607.2, 1472.6, 1302, 1266; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.31 (1H, s), 8.20 (1H, dd, *J*= 8.0, 2.0 Hz), 7.85 (1H, t, *J* =8.0 Hz), 7.78-7.70 (3H, m), 7.61-7.56 (3H, m); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 159.8, 148.1, 147.3, 135.3, 131.8, 131.0, 130.4, 128.8, 128.0, 127.8, 126.8, 122.1,
MS *m/z:* 157.3 $[M+H]^{+\cdot}$

4d: (R=H and R_1= 3-Cl-Ph); Yield: 93%; Reaction time; 15 min; Reaction temperature: RT; m. p; 164.7-166.3 ^{0}C; I.R (KBr) cm^{-1}: 3072, 1678, 1610, 1469, 1311, 1248; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.31 (1H, s), 8.21 (1H, dd, *J* = 8.0, 2.0 Hz), 8.19 (1H, t, *J*=8.0 Hz), 7.91-7.70 (3H, m), 7.62-7.56 (3H, m); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 159.8, 148.1, 147.3, 135.3, 131.8, 130.9, 128.8, 128.0, 127.8, 126.8, 122.09; MS *m/z:* 157.3$[M+H]^{+\cdot}$..

4e: (R=H and R_1= 3,4-Cl-Ph); Yield: 91%; Reaction time; 10 min; Reaction temperature: RT; m. p; 213.7-215.4 ^{0}C; I.R (KBr) cm^{-1}: 3067, 1677, 1610, 1470, 1305, 1245; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.36 (1H, s), 8.20 (1H, dd, *J*=8.0, 2.0 Hz), 7.97 (1H, d, *J*= 1.9 Hz), 7.89-7.84

(2H, m), 7.74 (1H, dd, *J*=8.0, 2.0 Hz), 7.62-7.59 (2H, m); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 160.2, 147.9, 146.9, 137.6, 135.2, 132.0, 131.3, 130.2, 128.5, 127.7, 126.8, 122.1; MS *m/z:* 291$[M+H]^{+\cdot}$

4f: (R=H and R_1= 4-bromo pyridine); Yield: 92%; Reaction time; 20 min; Reaction temperature: RT; m. p; 211.8-214.6 ^{0}C; I.R (KBr) cm^{-1}: 3060, 1680, 1614, 1576, 1474, 1371, 1306, 1255; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.81 (1H, d, *J*=1.9 Hz), 8.56 (1H, s), 8.33 (1H, dd, *J*=8.0, 2.0 Hz), 8.23 (1H, d, *J*=8.0 Hz), 7.91-7.75 (3H, m), 7.63 (1H, t, *J*= 8.0 Hz); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 159.9, 150.2, 148.8, 147.6, 145.7, 141.4, 135.5, 128.1, 127.8, 126.9, 124.3, 121.9, 120.4; MS *m/z:* 302 $[M+H]^{+\cdot}$

4g: (R=H and R_1= 3-Br-Ph); Yield: 96%; Reaction time; 10 min; Reaction temperature: RT; m. p; 186.4-187.9 ^{0}C; I.R (KBr) cm^{-1}: 3061, 1677, 1606, 1470, 1301, 1265. 122.2. ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.28 (1H, s), 8.20 (1H, dd, *J*=8.0, 2.0 Hz), 7.93-7.87 (2H, m), 7.77 (1H, d, *J*=8.0 Hz), 7.70 (1H, m), 7.63-7.50 (3H, m); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 159.8, 148.1, 147.3, 137.0, 135.3, 133.5, 131.7, 129.3, 128.0, 127.8, 126.8; MS *m/z:* 301 $[M+H]^{+\cdot}$

4h: (R=H and R_1= 4-CH_3-Ph); Yield: 97%; Reaction time; 15 min; Reaction temperature: RT; m. p; 139.8-143.2 ^{0}C; IR (KBr) cm^{-1}: 1690, 1600, 1515, 1472, 1260; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.30 (1H, s), 8.19 (1H, d, *J*=8.0 Hz), 7.87 (1H, t, *J*=8.0 Hz), 7.73 (1H, d, *J*=8.0 Hz), 7.59 (1H, t, *J*=8.0 Hz), 7.41-7.34 (4H, m), 2.49 (3H, s); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 160.4, 148.1, 147.6, 138.6, 1354.4, 134.9, 130.0, 127.6, 126.7, 122.2, 21.0; MS *m/z:* 237 $[M+H]^{+\cdot}$

4i: (R=H and R_1= 3-CH_3-Ph); Yield: 94%; Reaction time; 20 min; Reaction temperature: RT; m. p: 125.5-128.1 ^{0}C; I.R (KBr) cm^{-1}: 1671, 1608, 1470, 1260; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.30 (1H, s), 8.18 (1H, d, *J*=8.0 Hz), 7.87 (1H, t, *J*=8.0 Hz), 7.84 (1H, d, *J*=8.0 Hz), 7.72 (1H, t, *J*=8.0 Hz), 7.59 (1H, t, *J*=8.0 Hz), 7.43-7.30 (3H, m), 2.37 (3H, s); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 160.3, 148.0, 147.4, 139.2, 137.8, 135.0, 129.7, 128.2, 127.6, 124.8, 122.2, 21.1; MS *m/z:* 237$[M+H]^{+\cdot}$

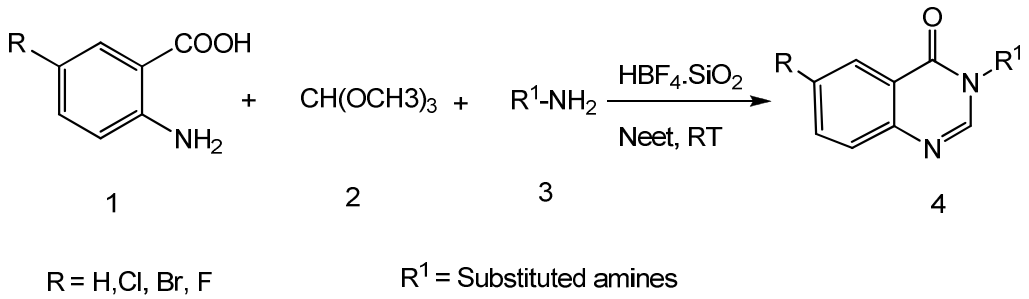
4j: **(R=H and R_1= 3-OCH_3-Ph)**; Yield: 90%; Reaction time; 15 min; Reaction temperature: RT; m. p: 155.1-156.8 ^{0}C; I.R (KBr) cm^{-1}: 3050, 1686, 1596, 1459, 1308, 1260; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.33 (1H, s), 8.19 (1H, d, *J*=8.0 Hz), 7.83 (1H, t, *J*=8.0 Hz), 7.64 (1H, d, *J*=8.0 Hz), 7.48 (1H, t, *J*=8.0 Hz), 7.44 (1H, t, *J*=8.0 Hz), 7.18-7.03 (3H, m), 3.80 (3H, s); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 160.2, 160.1, 148.0, 147.4, 139.0, 135.0, 130.3, 127.6, 122.2, 115.0, 113.7, 55.8; MS *m/z:* 253$[M+H]^{+\cdot}$

4k: (R=H and R_1= 4-COOH-Ph); Yield: 81%; Reaction time; 20 min; Reaction temperature: Reflux; m. p: Above 260 ^{0}C**;** I.R (KBr) cm^{-1}: 3368, 3072, 1694, 1601, 1480, 1313, 1263; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 13.1 (1H, brs), 8.31 (1H, s), 8.18 (1H, dd, *J*=8.0, 1.8 Hz), 8.05 (1H, dd, *J*=7.8, 1.8 Hz), 7.92-7.85 (1H, t, *J*= 8.0 Hz), 7.82-7.71 (2H, m), 7.69-7.52 (3H, m); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 166.2, 160.6, 148.3, 147.5, 137.5, 133.8, 131.4, 130.1, 129.5, 127.6, 126.7, 122.2; MS *m/z:* 267$[M+H]^{+\cdot}$

4l: (R=H and R_1= 4-$COOCH_2CH_3$-Ph); Yield: 79%; Reaction time; 25 min; Reaction temperature: Reflux; m. p: 199.6-201.3 ^{0}C; I.R (KBr) cm^{-1}: 3359, 2903, 1692, 1596, 1473, 1369, 1280, 1109; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.40 (1H, s), 8.22 (1H, dd, *J*=8.0, 2.0 Hz), 8.13 (1H, d, *J*= 8.0 Hz), 7.89 (1H, t, *J* = 8.0 Hz), 7.79-7.70 (3H, m), 7.62 (1H, m), 4.38-4.35 (2H, q, *J*= 7.0 Hz), 1.36-1.32 (3H, t, *J*=7.0 Hz); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 165.4, 160.1, 147.9, 146.9, 141.8, 135.2, 130.3, 128.2, 127.7, 126.8, 122.1, 61.4, 14.4; MS *m/z:* 295 $[M+H]^{+\cdot}$

4m: (R=H and R_1= 4-Br-Ph); Yield: 79%; Reaction time; 25 min; Reaction temperature: Reflux; m. p: 178.6-180.2 ^{0}C; I.R (KBr) cm^{-1}: 3065.6, 1674.75, 1592, 1466, 1399, 1268.32, 1175.6, 749.19 ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 8.39 (1H, s), 8.25 (1H, d, *J*= 8.0 Hz), 8.0 (1H, t, *J*=8.0 Hz), 7.69 (1H, dd, *J*=8.0, 1.9 Hz), 7.59-7.53 (5H, m); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 159.30, 148.16, 147.10, 137.7, 129.63, 129.29, 128.83, 127.79, 123.94, 120.22. I.R (KBr) cm^{-1}: 3065.6, 1674.75, 1592, 1466, 1399, 1268.32, 1175.6, 749.19; MS *m/z:* 301.0 $[M]^{+\cdot}$

RESULTS AND DISCUSSION



Scheme 1

In the present work we reported one pot synthesis of 4(3H)-quinazolines using silica-supported $HBF_4.SiO_2$ as catalyst. The catalyst prepared from the readily available ingredients such as HBF_4 and silica gel finer than 200 mesh [31]. The reaction of substituted anthranalic acid **1(a-0)** with substituted amines **3 (a-o)** in triethylorthoformate and catalytic amount of **HBF4.SiO2** at room temperature under solvent free conditions to give the 4(3H)-quinazoline **4(a-o).** The reaction procedure is simple and proceeded at room temperature within few minutes (6-25 min) in excellent yields after addition of the catalyst. The substituted amines containing both electrons withdrawing as well as electron donating groups reaction proceeds the smoothly. The reaction with amine having electron withdrawing groups (entry k, l) required reflux conditions and prolonged reaction times (20, 25 min). The reusability of the recovered catalyst was tested with 4-methyl aniline (entry h)**.** The first time when the fresh catalyst was used the yield of the product 3-p-tolylquinazolin-4(3H)-one was 97%, while with the recovered catalyst in three subsequent recycles the yields were mentioned in the Table-1.

CONCLUSION

In conclusion we have developed a simple and efficient synthesis of 4(3H)-quinqzolinones by coupling of substituted anthranalic acid, triethyorthoformate and substituted amines using $HBF_4.SiO_2$ as a heterogeneous catalyst under solvent free conditions. The simple experimental

procedure, environmentally clean technology, comprising and ease of handling, fast reaction conditions, with excellent yields. The reusability of the catalyst are notable advantages of the present protocol.

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