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SYNTHESIS OF 2-SUBSTITUTED 4(3H)-QUINOZOLINONES DERIVATIVES USING BORON TRIBROMIDE AS A EFFICIENT CATALYST

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ABSTRACT

A highly efficient synthesis of 2-substituted 4(3H)-quinazolinones is elucidated using BBr_3 catalyzed coupling of isatoic anhydride and benzamidine derivatives at room temperature. This reaction proceeds under mild conditions. This method was found to be better method giving high yields. The present method shows some advantages such as short reaction times and enhanced selectivity. The Structures of the Compounds are confirmed by ^{1}H NMR & ^{13}C NMR, Mass spectral data.

KEY WORDS: Isatoic anhydride, benzamidine, *2-substituted 4(3H)-quinazolinones.*

INTRODUCTION

Quinazolinones are fused heterocyclic compounds that possessing an extensive array of biological activities. Quinoxalinone and its derivatives have gained much attention in the recent past as an important pharmacore in the family of numerous biologically active heterocyclic compounds. Its derivatives have been used as synthetic precursors for many antihypertensive and analgesic drugs[1-9]. Moreover, quinazolinone derivatives are associated with several important biological activities such as, anti-cancer[10], anti-inflammation[11], anti-bacterial[12], anti-virus[13] anti-tuberculosis[14], anti-malarial[15], anti-hypertensive[16], anti-obesity, anti-psychotic, anti-diabetes[17].

Quinazolinones represent a class of privileged scaffolds that occur in approximately 150 naturally occuring alkaloids, some of which exhibit a wide range of biological and pharmacological activities, such as rutaecarpine, luotonin A, luotonin F, sildenafil, bouchardatine and raltitrexed[18]. Although numerous methods have been developed[19], the previously reported conditions required to effect the synthesis include metal catalysts, organic solvents and/or specific oxidants.

A number of synthetic protocols have been developed for the preparation of 2-substituted 4(3H)-quinozolinones. The most classical and general protocols for the synthesis of quinazolinones are still through the condensation between *o*-aminobenzamides and aldehydes followed by the oxidation of the resulting aminal intermediates[20]. One OF the most common approaches is the cyclization of anthranilamides with aldehyde in the presence of various promoting agents, such as $NaHSO_3$[21], p-toluenesulfonic acids/DDQ[22], I_2[23], $CuCl_2$ (3.0

equiv)[24], and $FeCl_3$ (2.0 equiv)[25]. The most common synthetic method involved condensation of aryl-1,2-diamines with 1,2-dicarbonyl compounds[26]. Other noteworthy syntheses of quinoxaline and related compounds include multicomponent reaction (MCR) [27] etc. Despite these remarkable efforts, development of an efficient methodology for the synthesis of highly functionalized 2-substituted 4(3H)-quinozolinones derivatives is still an important challenge for organic chemists. Herein we report BBr_3 catalyzed simple and efficient method for the preparation of 2-substituted quinazolinones from isatoic anhydride and aryl imidamides in high yield (**Scheme 1**).

EXPERIMENTAL SECTION

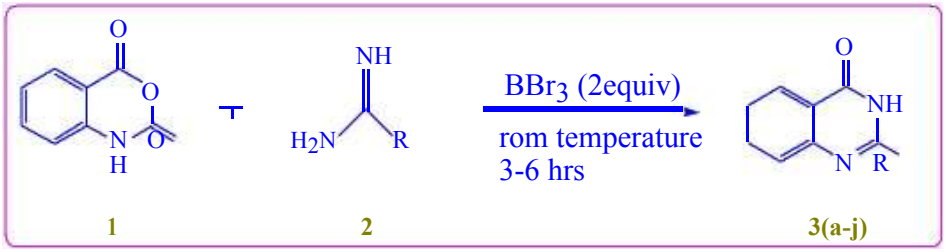
Melting points were determined in open-end capillaries and are uncorrected. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by iodine vapors. ^{1}H NMR spectra were recorded on BRUKER ADVANCE II 400 NMR Spectrometer using TMS as internal standard. The mass spectra were obtained on a JEOL 5x102/DA-6000 mass spectrometer. The IR spectra were recorded on Perkin-Elmer spectrum RX IFT-IR System using KBr pellets. Elemental analyses of the newly synthesized compounds were carried out on Perkin Elmer model 2400 C H N analyzer. All the compounds gave satisfactory elemental analysis within ±0.4% of theoretical values. All reactions were carried out under argon in oven dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium benzophenone ketyl and degassed thoroughly with dry argon directly before use. Unless otherwise noted, organic extracts were dried with anhydrous Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 Torr). Flash chromatography was performed with silica gel (200–300 mesh) by using the mobile phase indicated. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz, for 1H for 13C, respectively, in $CDCl_3$ solution with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ) and are referenced to the residual proton resonances of the solvents. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$-*d* or DMSO-*d*6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.26 ppm, DMSO at 2.50 ppm;
^{13}C NMR: $CDCl_3$ at 77.16 ppm, DMSO at 40.00 ppm.

General Procedure for the Synthesis of 2-substituted 4(3H)-quinozolinones 3(a-j):

To a solution of isatoic anhydride (1 mmol) in 1,4-dioxane (10 vol) was added benzimidamide(1.1 mmol) followed by BBr_3 (2 equiv). The reaction mixture was stirred at room temperature for 3-6 hrs. After completion of reaction (monitored by TLC), the reaction mixture was quenched with water (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The crude compound was purified through the silica gel column chromatography using ethyl acetate and hexane (30:70) as eluent affords the product in 75-86% yield.

Scheme I: The synthetic route was depicted in Scheme I

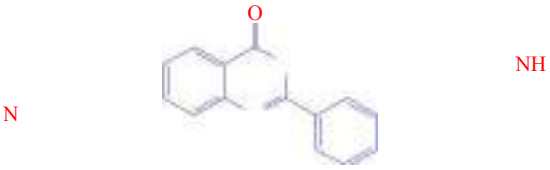
Scheme I



Synthesis of 2-Substituted Quinazolinone derivatives

Spectral data for selected compounds:

2-Phenylquinazolin-4(3*H*)-one (3a):

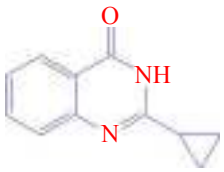


Yellow solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 11.94 (1H, s), 8.04 (1H, d, *J* = 7.2 Hz), 7.99-7.98 (2H, m),

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 152.3, 149.2, 134.3, 132.9, 131.2, 129.5, 128.6, 128.1,

m/z=223 (M+H), positive mode.

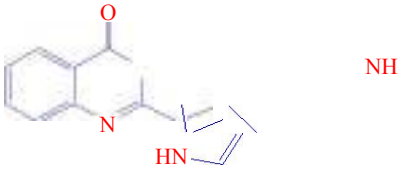
2-Cyclopropylquinazolin-4(3*H*)-one (3b):



White solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 11.59 (s, br, 1H), 8.24 (d, 1H, *J* = 8.0 Hz), 7.71-7.68 (m, 1H), 7.58 (d, *J* = 8, 1H), 7.40-7.37 (m, 1H), 1.99-1.93 (m, 1H),1.33-1.29 (m, 2H), 1.14 - 1.10 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 157.9, 149.7, 134.8, 126.9, 126.2, 125.6, 120.4, 14.7,

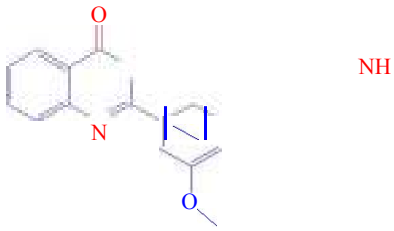
GCMS (EI, 70 eV): m/z (%): 186 (63, M+), 185 (100), 119 (26), 92 (15).

2-(1*H*-Pyrrol-2-yl)quinazolin-4(3*H*)-one (3c):



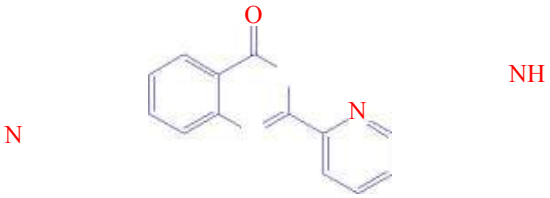
Brown powder.
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.18 (1H, s), 11.70 (1H, s),8.08 (1H, d, *J* = 7.6 Hz), 7.77 (1H, t, *J* = 7.6 Hz), 7.62 (1H, d, *J* =8.0 Hz), 7.41 (1H, t, *J* = 7.2 Hz), 7.29 (1H, s), 7.05 (1H, s), 6.21(1H, s).
^{13}C NMR(100 MHz, $CDCl_3$): δ 162.4, 149.7, 146.8,135.0, 126.8, 126.4, 125.7, 124.7, 124.3,

m/z=212 (M+H), positive mode.
2-(3-Methoxyphenyl)quinazolin-4(3*H*)-one (3d):



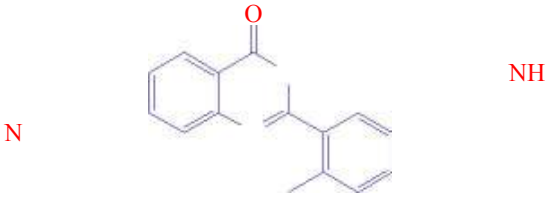
White solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.39 (1H, s, br), 8.19 (2H, d, *J* = 8.5 Hz), 8.12(1H, d, *J* = 7.0 Hz), 7.82 (1H, t, *J* = 6.5 Hz), 7.71 (1H, d, *J* = 8.0Hz), 7.48 (1H, t, *J* = 7.0 Hz), 7.09 (2H, d, *J* = 9.0 Hz), 3.85 (3H, s).
C NMR (100 MHz, $CDCl_3$): δ 162.7, 162.3, 152.3, 149.4,134.9, 129.9, 127.7, 126.5, 126.3,

m/z=253 (M+H), positive mode.
2-(Pyridin-2-yl)quinazolin-4(3*H*)-one (3e):



White crystalline solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 11.82 (1H, s, br), 8.74 (1H, d, *J* =4.4 Hz), 8.42 (1H, d, *J* = 8.0 Hz), 8.17 (1H, d, *J* = 8.0 Hz), 8.07 (1H, t, *J* = 8.0 Hz), 7.86 (1H, t, *J* = 8.0 Hz), 7.79 (1H, d, *J* = 8.0Hz), 7.65-7.61 (1H, m), 7.56 (1H, t, *J* = 7.6 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ 161.2, 150.3, 149.4, 149.0, 148.8, 138.5,135.2, 128.1, 127.8,

m/z=224(M+H), positive mode.
2-(o-Tolyl)quinazolin-4(3*H*)-one (3f):

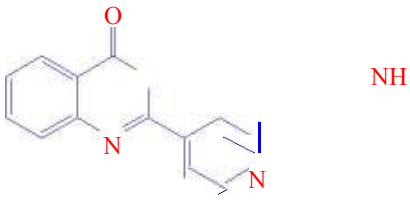


White solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.49 (1H, s, br), 8.33 (1H, d, *J* = 7.6 Hz), 8.15 (2H, d, *J* = 8.0 Hz), 7.82 (2H, t, *J* = 8.0Hz), 7.51 (1H, t, *J* = 8.0 Hz), 7.38 (2H, d, *J* = 2.0 Hz), 2.47 (3H, s).
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 151.9, 149.7, 142.1, 134.8,130.0, 129.7, 127.9, 127.4,

m/z=237 (M+H), positive mode.

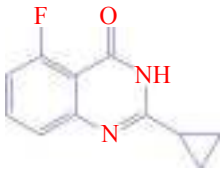
2-(Pyridin-4-yl)quinazolin-4(3*H*)-one (3g):



White solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 12.77 (1H, s), 8.78 (2H, d, *J* =4.0 Hz), 8.18 (1H, d, *J* = 7.6 Hz), 8.12 (2H, d, *J* = 4.5 Hz), 7.88(1H, t, *J* = 7.5 Hz), 7.79 (1H, d, *J* = 7.9 Hz), 7.58 (1H, t, *J* = 7.2Hz).
C NMR (100 MHz, $CDCl_3$): δ 162.5, 151.0, 150.7,140.4, 135.3, 128.2, 127.9, 126.4, 122.0,

HRMS (ESI-MS): m/z cald. for $C_{13}H_9N_3O$ (M+H) 224.0824, found 224.0820.

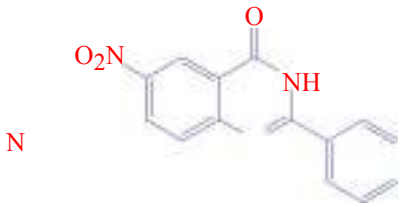
5-Fluoro-2-cyclopropylquinazolin-4(3*H*)-one (3h):



White solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.51 (s, br, 1H), 7.64 - 7.58 (m, 1H), 7.36 (d, 1H, *J* = 4 Hz),
^{13}
C NMR (100 MHz, $CDCl_3$): δ 162.1, 161.2, 160, 154.2, 151.8, 134, 122.9, 112.9, 112, 14.5,

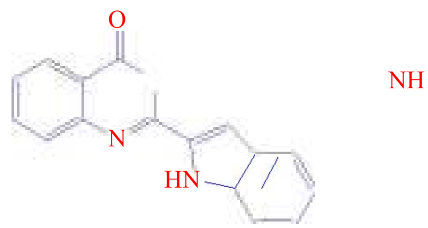
HRMS (ESI-ion trap): m/z calcd [(M+H)+] 205.0777, found 205.0767.

6-Nitro-2-phenylquinazolin-4(3*H*)-one (3i):



Light yellow solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 13.00 (s, br, 1H), 8.81(d, 1H, *J* = 4 Hz), 8.50-8.47 (1H), 8.22 (d,2H, *J* = 8 Hz), 7.8 (d, 1H, *J* = 8 Hz), 7.59 - 7.51 (m, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 157.2, 153.8, 144.7, 133.2,132.4, 129.3, 129, 128.7,

2-(1*H*-Indol-2-yl)quinazolin-4(3*H*)-one (3j):



Yellow solid.

H NMR (400 MHz, $CDCl_3$): δ 12.62 (1H, s), 11.81 (1H, s), 8.17 (1H, d, *J* = 8.0 Hz), 7.88-

7.2 Hz), 7.24 (1H, t, *J*= 8.4 Hz), 7.07 (1H, t, *J* = 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 149.2, 147.0, 138.1, 135.2, 130.5, 127.9, 127.4,

HRMS (ESI-MS): m/z cald. for $C_{16}H_{11}N_3O$ (M+H) 262.0980, found 262.0980.

RESULTS AND DISCUSSION

A series of 2-substituted Quinazolinone derivatives **3(a-j)** synthesised from isatoic anhydride and benzimidamide using BBr_3. This method was found to be better method giving high yields. A series of aldehydes with either electron-donating or electron withdrawing groups attaching to aromatic ring were investigated. The substitution groups on the aromatic ring had no obvious effect on the yield.

CONCLUSION

In conclusion, we have developed a simple methodology for the preparation of 2-substituted Quinazolinone derivatives from isatoic anhydride and benzimidamide using BBr_3 at room temperature. The reaction proceeds under mild conditions with good to excellent yields. Thus, the developed methodology could be an alternative for the academic as well as industrial applications.

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