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INCREDIBLY PRODUCTIVE ONE-POT SYNTHESIS OF QUINAZOLIN-4(3*H*)-ONES USING TRIS(PENTAFLUOROPHENYL)BORANE AS AN EFFECTIVE CATALYST

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ABSTRACT
Using isatoic anhydride, ammonium acetate, and aldehydes in DMF at mild conditions, a series of quinazolin-4(3H)-ones have been synthesized in good to exceptional yields with high selectivity in a one-pot procedure. $B(C_6F_5)_3$ effectively stimulated the reaction. Some particular benefits of the current approach are its mildness, short reaction times, and enhanced selectivity.

KEYWORDS: Quinazolin-4(3H)-ones, one-pot reaction, $B(C_6F_5)_3$.

INTRODUCTION
Quinazolinone core and its derivatives are a significant class of chemicals with a wide range of pharmacological and biological properties[I-IV] such as anti-inflammatory,[V] anti-bacterial,[VI] anti-tumor,[VII] anti-HIV,[VIII] anti-fungal,[IX] anti-cancer,[X] anti-tumor,[XI] anti-inflammatory,[XII] anti-inflammatory,[XIII] anti-hypertensive, and antimalarial properties.[XIV] and so forth. Moreover, derivatives of quinazolinone core substituted at positions two and three are essential to the hypotensive action.[XV-XVI] There are quinazolinone moieties in several bioactive natural compounds, including febrifugine and isofebrifugine, which may have anti-malarial properties.[XVII] Many alkaloids, including 2-methyl-4(3*H*)-quinazolinone,[XVII] the essential structural units of the pharmacophores of bouchardatine, [XVIII] luotonin (A, B, E),[XIX] auranthine,[XX] circumdatin (C, F),[XXI] and sclerotigenin[XXII] are these heterocycles (**Figure 1**). Organic chemists are interested in the synthesis of quinazolinones because of their broad range of applications and derivatives.

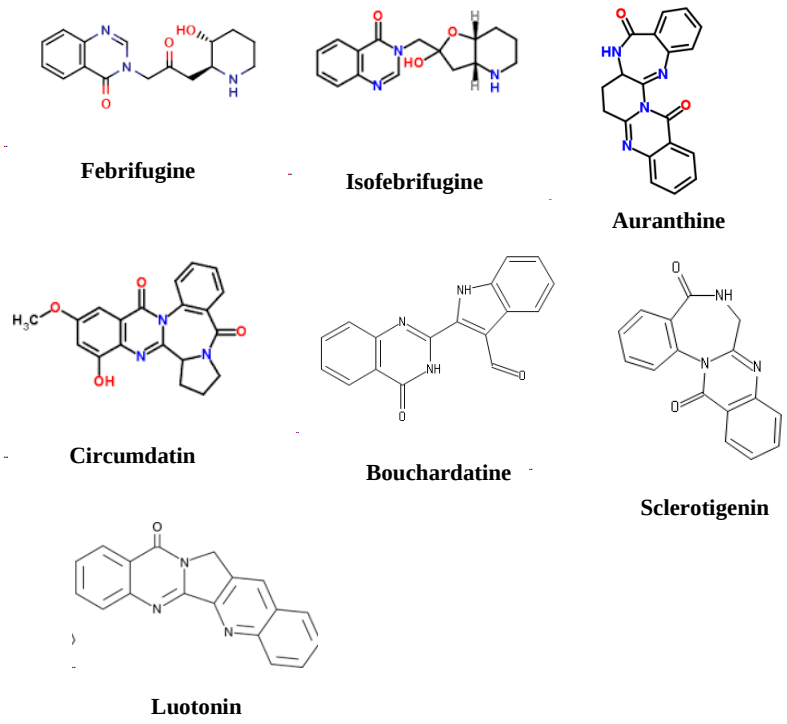


Figure 1

Quinazolin-4(3*H*)-ones are also crucial building blocks used in the pharmaceutical and natural product industries. In recent years, several methods for synthesizing derivatives of quinazolin-4(3*H*)-one have been investigated. The most popular method involves cyclizing anthranilamides with aldehyde while various promoting agents tural and pharmacological compounds. Various approaches toward the synthesis of quinazolin-4(3*H*)-one's derivatives have been explored during the past years. One of the most common approaches is the cyclization of anthranilamides with aldehyde in the presence of various promoting agents, such as $NaHSO_3$,[XXIII] p-toluenesulfonic acids/DDQ,[XXIV] I_2,[XXV] $CuCl_2$[XXVI] and $FeCl_3$.[XXVII] Some other methods include cyclization reaction of 2-amino benzamides with substituted benzoyl chlorides in ionic liquid[XXVIII] and cyclization of *o*-acylamino benzamides,[XXIX] 2-amino-benzonitrile,[XXX] N-arylorthanilamides,[XXXI] nitrones, [XXXII] and aza-Wittig reactions of a-azido-substituted aromatic imides. [XXXIII] Using Nafion-H as a heterogeneous catalyst and microwave irradiation, Rao has reported a one-pot three-component coupling of isatoic anhydride/anthranilic acid, orthoesters, and amines[XXXIV] and also Harikrishna has reported the synthesis of 2-substituted derivatives using various catalysts in one-pot diverse method.[XXXV] Unfortunately, there are several disadvantages to both conventional and microwave techniques, including limitations on reaction conditions, reagent availability, and chemical risks. Of the developed protocols, the majority of the synthetic pathways suffer from multistep reactions, generally severe reaction conditions, and low yields. Thus, there is still a need for innovative quinazolinone synthesis techniques. Silver triflates have been successfully included in many reactions recently. Due to our strong interest in organic reactions catalyzed by Lewis acids, we provide here a workable approach that uses aldehydes, ammonium acetate, and isatoic anhydride to selectively synthesize quinazolin-4(3*H*)-ones in a single pot.

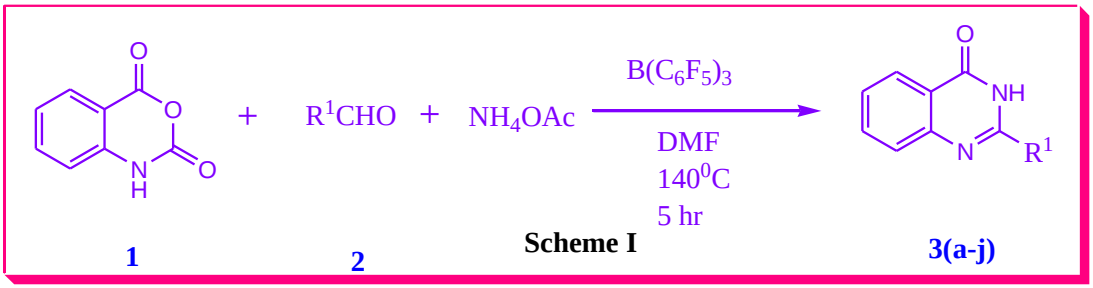
MATERIALS AND METHODS

Uncorrected melting points were found in open-end capillaries. Spots on silica gel G plates were located using iodine vapors, and the chemicals' purity was assessed using TLC. The NMR spectra were measured with a 400 MHz Bruker Avance spectrometer at 400.1 and 100.6 MHz. Chemical shifts are given in ppm (δ) and 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. The IR spectra were recorded on the Perkin-Elmer spectrum RX IFT-IR System using KBr pellets.

General Procedure for the Synthesis of 2-Substituted Quinazolinone Derivatives 3(a-j):

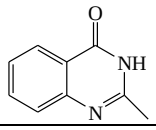
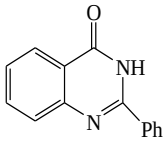
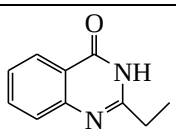
$B(C_6F_5)_3$ (102.2 mg (0.2 mmol) was added to a solution of isatoic anhydrides **1** (5.5 mmol), ammonium acetate (6.0 mmol), and aldehydes **2** (5 mmol) in DMF (5 mL). For five hours, the mixed solution was agitated at 140^{0}C. TLC was used to track the reaction's development. Following completion, 12 mL of water was added and the system was allowed to cool to room temperature. After a straightforward filtration process, the solid product **3** was recovered and recrystallized from ethanol. Using spectral (IR, ^{1}H NMR, ^{13}C NMR, and mass) and analytical data, all of the products were identified.

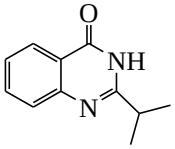
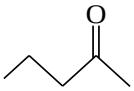
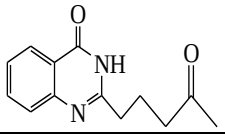
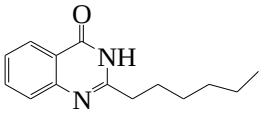
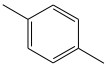
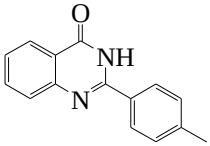
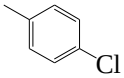
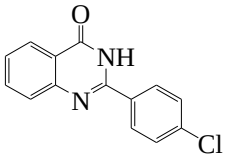
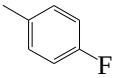
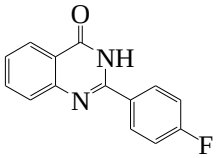
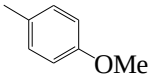
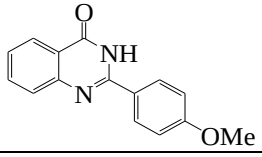
Scheme I: The synthetic route was depicted in Scheme I



Scheme I

Table 1: Synthesis of 2-Substituted Quinazolinone derivatives 3(a-j):

Entry	Aldehyde (R^1)	Product	Yield(%)
1	Methyl-		83
2	Ph-		85
3	Ethyl-		81

4	Isopropyl-		83
5			82
6	Hexyl-		86
7			87
8			84
9			83
10			87

Spectral data for selected compounds:

2-methylquinazolin-4(*3H*)-one (3a):
White solid, mp: 176-177°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.19 (s, 1H), 8.29 (dd, *J*1 =8.0 Hz, *J*2 = 1.2 Hz, 1H), 7.76 (dt, *J1* = 8.4 Hz, *J2* = 1.6 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.47 (dt, *J1* = 8.4 Hz, *J2* = 1.2 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.1, 120.2, 126.2, 126.4, 127.0, 134.9, 149.4, 153.2, 164.4.

2-phenylquinazolin-4(*3H*)-one (3b):
White solid, mp: 122-123°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.66 (s, 1H), 8.33 (d, *J*=7.6 Hz, 1H), 8.15 -8.17 (m, 2H), 7.78-7.86 (m, 2H), 7.59-7.60 (m, 3H), 7.52 (dt, *J1* = 8.0 Hz, *J2* = 1.6 Hz, 1H): ^{13}C NMR ($CDCl_3$, 100 MHz): δ 126.5, 126.9, 127.1, 128.1, 129.2, 131.8, 132.8, 134.9, 149.4,151.4, 163.1.

2-ethylquinazolin-4(*3H*)-one (3c):
White solid, mp: 232-233°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.80 (s, 1H), 8.27 (d, *J* 7.6 Hz, 1H), 7.78 (dt, *J1* = 8.0 Hz, *J2* =1.2 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 2.83 (q, *J* = 7.6 Hz,2H), 1.47 (t, *J* = 7.6 Hz, 3H): ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.5, 29.2, 120.5, 126.1, 126.8, 127.2, 134.7, 149.7, 157.1,164.2.

2-isopropylquinazolin-4(*3H*)-one (3d):
White solid, mp: 232-233°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.96 (s,1H), 8.28 (d, *J* = 7.6Hz, 1H), 7.71-7.79 (m, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 2.98-3.08 (m, 1H), 1.47 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.5, 35.0, 120.8, 126.3, 126.4, 127.4, 134.7, 149.4, 160.5,163.7.

2-(4-oxopentyl)quinazolin-4(*3H*)-one (3e):
White solid, mp: 145-146°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.54 (s, 1H), 8.28 (dd, *J*1 = 8.0 Hz, *J*2 =1.2 Hz, 1H), 7.87 (dt, *J1* = 8.0 Hz, *J2* = 1.6 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.48 (dt, *J1* = 8.0 Hz, *J2* = 1.2 Hz, 1H), 2.17 (s, 3H), 2.81 (t, *J* = 7.2 Hz, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.13-2.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.2, 30.0, 34.7, 42.3, 120.6, 126.2, 126.5, 127.22, 134.8, 149.1,155.8, 163.7, 208.2.

2-hexylquinazolin-4(3H)-one (3f):
White solid. Mp: 145 – 146°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.12 (s, 1H), 8.05 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.77 – 7.69 (m, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.46 – 7.38 (m, 1H), 2.61 – 2.51 (m, 2H), 1.75 – 1.63 (m, 2H), 1.27 (d, *J* = 15.2 Hz, 6H), 0.81 (t, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.28, 157.97, 149.43, 134.69, 127.24, 126.31, 126.12, 121.24, 34.97, 31.38, 28.64, 27.19, 22.40, 14.34.

2-(p-tolyl)quinazolin-4(3H)-one (3g):
White solid. Mp: 245 – 246°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.43 (s, 1H), 8.15 – 8.05 (m, 3H), 7.83 – 7.76 (m, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.47 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.72, 152.69, 149.30, 141.92, 135.01, 130.36, 129.65, 128.15, 127.87, 126.84, 126.31, 121.37, 21.45.

2-(4-chlorophenyl)quinazolin-4(3H)-one (3h):
White solid. Mp: 298 – 299°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.57 (s, 1H), 8.21 – 8.16 (m, 2H), 8.13 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.83 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.54 – 7.49 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.78, 151.96, 149.01, 136.74, 135.10, 132.13, 130.11, 129.15, 127.91, 127.21, 126.35, 121.47.

2-(4-fluorophenyl)quinazolin-4(3H)-one (3i):
White solid. Mp: 257 – 259°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.54 (s, 1H), 8.26 – 8.20 (m, 2H), 8.13 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.83 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H),7.50 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 7.40 – 7.33 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.76, 162.97, 151.84, 149.13, 135.10, 130.84, 129.70, 127.93, 127.08, 126.32, 121.37, 116.09.

2-(4-methoxyphenyl)quinazolin-4(3H)-one* (*3j):
White solid. Mp: 240 – 241°C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 12.38 (s, 1H), 8.23 – 8.08 (m, 3H), 7.84 – 7.76 (m, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.07 (dd, *J* = 6.8, 5.0 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.84, 162.35, 152.41, 149.34, 134.99, 129.93, 127.67, 125.58, 126.30, 125.31, 121.15, 114.47, 55.94.

RESULTS AND DISCUSSION

As we planned, this reaction proceeded smoothly, and outstanding yields of the desired products were achieved. A set of aldehydes that attached to an aromatic ring by either electron-donating or electron-withdrawing groups were studied. The yield was not significantly impacted by the replacement groups on the aromatic ring (**Table 1**). In the

development of new synthetic methodologies, we herein report an efficient, facile protocol for the synthesis of 2-substituted Quinazolinone derivatives **3(a-j)** catalyzed by $B(C_6F_5)_3$ in DMF at 140°C in 5hrs (**Scheme 1**). This method was found to be better method giving high yields.

CONCLUSION

In summary, we have created a straightforward process for the synthesis of 2-substituted quinazolinone derivatives in DMF under mild conditions, utilizing $B(C_6F_5)_3$ as an effective catalyst in a one-pot reaction. This method's fast reaction time, excellent yield, and incredibly gentle reaction conditions are its advantages.

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