A Facile, Catalyst-Free, Microwave-Assisted Access towards the Synthesis of 2-Aryl/Alkyl-3-(1H-benzo[*d*]imidazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-ones

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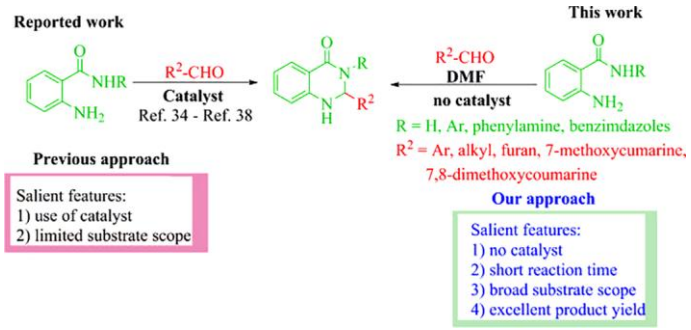
Abstract

An efficient, catalyst free, microwave assisted approach has been developed for the synthesis of 2-aryl/alkyl-3-(1*H*-benzo[*d*]imidazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one derivatives by condensing 2-aminobenzamides with various aliphatic, aromatic and heterocyclic aldehydes. This catalyst free approach exhibited good functional group compatibility and produced the desired products in good to excellent yields in just 10-20 minutes. This approach can be seen as a better alternative of the metal catalyzed protocols used for the synthesis of this class of compounds. The formation of desired compound has also been confirmed by X-ray analysis.

GRAPHICAL ABSTRACT



KEYWORDS: Catalyst free; Microwave irradiation; Substrate scope; Short reaction time; 2,3-dihydroquinazolinone

INTRODUCTION

The modern era of synthetic organic chemistry has witnessed a rapid expansion in the development of efficient protocols that involve the use of transition metal catalysts or Lewis acid catalysts for the generation of industrially significant heterocyclic molecules.[1-4] Although, different catalytic approaches have shown high efficiency in providing rapid access to a large number of heterocyclic compounds, however from an economic and chemical standpoint, they present some serious problems such as high cost, contamination of the product, waste production, involvement of harsh reaction conditions, etc. Therefore, the exploration of novel, catalyst free pathways is presently an issue of significance in order to expand the frontiers of heterocyclic chemistry.

The quinazolinone structure is a prevalent synthetic as well as natural scaffold that has been extensively employed as drug like template in medicinal chemistry.[5-11] Amongst the leading derivatives of quinazolinones, 2,3-dihydroquinazolin-4(1*H*)-ones in particular have become the most attractive targets in organic synthesis, as they are an integral part

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of many bioactive molecules that exhibit a broad spectrum of pharmacological properties (Figure 1)[12-15], such as anti-malarial[16], anti-cancer[17], anti-microbial[18, 19], anti-hypertensive[20-23], anti-oxidant[24, 25], anti-inflammatory.[26-28] They also function as inhibitors of several key enzymes e.g. dihydrofolate reductase[29-31], poly(ADP-ribose)polymerase[32] and human microsomal prostaglandin synthase 1 (mPGES 1).[33]

Considering the significance of the quinazolinone scaffold, several methods have been reported for the synthesis of 2-aryl/alkyl-3-(1*H*-benzo[*d*]imidazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-ones using 2-aminobenzamides and benzaldehydes as starting material under the influence of various catalytic systems like cyanuric chloride[34], CuI[35], ,Poly(VPyPS)-PW[36], Co-CNTs[37], 2-morpholinoethanesulfonic acid[38], indion ina 225H resin[39], Amberlyst-15[40], ionic liquid[41,42] boehmite-SSA[43], boehmite-Si-DSA[44], *L*-proline nitrate[45], NH_4Cl[46], $TiCl_4$-Zn[47], Cellulose-SO3H[48] etc, (Scheme 1). Although these synthetic methodologies lead to the generation of the targeted quinazolinones, however a number of challenges need to be addressed as they intrinsically suffer from some serious limitations such as limited substrate scope, employment of a toxic and expensive catalyst that invariably leads to product contamination, moisture-sensitivity of catalysts make their use difficult, need for prior synthesis of catalyst which is unfavorable in terms of both atom economy and requirement of high energy consuming instruments for their characterization, etc.

The challenges associated with metal catalyzed synthesis of this highly significant scaffold encouraged us to investigate more expedient methods for the construction of 2,3-

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dihydroquinazolin-4(1*H*)-ones. Recently, our group has reported a base-mediated synthesis of benzimidazo[1,2-*a*]quinazolines as our first step towards the direction of catalyst free synthesis.[49] While investigating its reaction mechanism, interestingly we found that 2,3-dihydroquinazolin-4(1*H*)-ones could be obtained under catalyst free reaction conditions. Encouraged by this observation and as an extension of our previous work, we decided to carry out the synthesis of 2,3-disubstituted-2,3-dihydroquinazolin-4(1*H*)-one derivatives by condensing 2-aminobenzamides with various aldehydes without use of any catalyst under microwave irradiation. To the best of our knowledge there is no report of catalyst free synthesis of 2-aryl/alkyl-2,3-dihydroquinazolin-4(1*H*)-ones using 2-aminobenzamides and aldehydes as starting materials. The structure of the key compound was confirmed using X-ray crystal structure analysis.

RESULT AND DISCUSSION

Our investigation started with the condensation of 2-amino-*N*-(1*H*-benzo[*d*]imidazol-2-yl)benzamide (**1a**) and 2-chlorobenzaldehyde (**2a**) in DMF under irradiation with microwaves at 80 W maximum power for 10 minutes at a ceiling temperature of 130 ^{o}C. To our great satisfaction, the desired product was obtained in 83% yield (Table 1, entry 1). However, drop in the product yield was observed when reaction was prolonged (Table 1, entry 2). When the reaction was performed under conventional heating at 130 ^{o}C, the reaction was completed in 4 hours and the desired product was obtained in 65% yield (Table 1, entry 3).

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Encouraged by these outcomes we further screened various solvents like toluene, 1,4-dioxane, ethanol, acetonitrile and water under the microwave conditions. It was observed that the aprotic solvents provided better product yields as compare to the protic solvents. Out of these screened solvents, except water where no product formation was observed even after irradiation for 30 min (Table 1, entry 8), all solvents yielded the desired product **3a** in relatively moderate to good yields. It was also found that the reaction did not proceed to completion when it was irradiated in toluene for 30 min (Table 1, entry 4). Moreover, no product formation was observed when the reaction was performed in the absence of any solvent (Table 1, entry 9).

Firstly, substrate scope of this newly optimized protocol with a wide range of aliphatic, heterocyclic and aromatic aldehydes with 2-amino-*N*-(1*H*-benzo[*d*]imidazol-2-yl)benzamide was explored. All the employed aldehydes reacted efficiently with 2-amino-*N*-(1*H*-benzo[*d*]imidazol-2-yl)benzamide and furnished the desired products in good to excellent yields (Table 2).

During the course of this investigation, it was observed that the electronic nature and the positions of the substituents on the aromatic ring of the benzaldehyde significantly affect the outcome of the reaction. Benzaldehydes with electron withdrawing group at *ortho* position yielded the desired product in lower yields (Table 2, entries **3a** and **3b**), however significant decrease in product yield was observed when electron withdrawing group was present at the *para* position (Table 2, entries **3g-3i**) as compared to the unsubstituted benzaldehyde (Table 2, entry **3d**). Moreover, higher product yield was obtained when

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electron donating group was present at *para* position of the benzaldehyde analogues (Table 2, entries **3e** and **3f**). Substantially lower yield in case of -NO_2 group (Table 2, entry **3c**) may be attributed to strong electron withdrawing nature of -NO_2 group. Nevertheless, aliphatic and heterocyclic aldehydes also furnished the corresponding products in good yields (Table 2, entries **3n-3r**). The structure of compound **3a** has been confirmed by single crystal X-ray analysis (Figure 2). The details of data collection, structure solution and refinement for compound **3a** are listed in Table 3 (see supporting information).

Substrate scope was further explored with other reaction partner i.e. 2-aminobenzamide. Various 2-aminobenzamides were allowed to react with benzaldehyde. Much to our delight, all the employed benzamides resulted in good to excellent product yields (Table 4).

Initially, to examine whether any change in the starting material would cause variation in the reaction yields, we performed competitive experiments (Scheme 2). When 2-amino-*N*-(1*H*-benzo[*d*]imidazol-2-yl)benzamides (**1**) was allowed to react with an equimolar mixture of *p*-methoxybenzaldehyde (**2f**) and *p*-nitrobenzaldehyde (**2i**), products **3f** and **3i** were obtained in 1:1.4 ratio. Likewise, when equal amount of 2-amino-*N*-(6-methyl-1*H*-benzo[*d*]imidazol-2-yl)benzamide (**4c**) and 2-amino-*N*-(6-chloro-1*H*-benzo[*d*]imidazol-2-yl)benzamide (**4d**) was subjected to a reaction with benzaldehyde, products **5c** and **5d** were obtained in 1:1.1 ratio. These experiments revealed that when the substrates bearing electron donating group were made to react individually, they provided better yields than

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substrates bearing electron withdrawing group. However in the mixture, substrates with electron withdrawing group not only reacted faster, but also resulted in higher yields in comparison to substrates containing electron donating group.

CONCLUSION

We have developed an efficient catalyst free approach for the synthesis 2-aryl/alkyl-3-(1*H*-benzo[*d*]imidazol-2-yl)-2,3-dihydroquinazolin-4(1*H*)-one derivatives starting from 2-aminobenzamides and benzaldehydes. This methodology was found to show good functional group tolerance and a wide range of differently substituted derivatives could be synthesized in good to excellent yields. Substrate scope and product yields of this approach are excellent. Further, to evaluate functional group compatibility competitive experiment was carried out and found that substrates bearing electron withdrawing groups reacts faster than containing electron releasing groups. This catalyst free approach can been seen as an attractive and alternative pathway to the previously reported metal-catalyzed synthesis of this medicinally important class of compounds.

EXPERIMENTAL

General Procedure For The Synthesis Of 3-(1H-Benzo[D]Imidazol-2-Yl)-2-(2-Chlorophenyl)-2,3-Dihydroquinazolin-4(1H)-One (3a)

A mixture of the *N*-(2-benzimidazolyl)-2-aminobenzamides (0.79 mmol) and aldehydes (0.95 mmol) in DMF (2 mL) was taken in a microwave transparent glass vial equipped with a small magnetic stirring bar, and the vial was tightly sealed with a Teflon crimp cap. The mixture was then irradiated for the appropriate time at 130 ^{o}C and 80 W maximum

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power. Completion of the reaction was monitored by TLC (20 % ethyl acetate in hexane). The reaction mixture was then cooled to room temperature and then poured onto crushed ice. The precipitated crude product was filtered and finally purified by column chromatography over silica gel using 15% ethyl acetate in hexane to give **3a** (129 mg, 83%) as a yellow solid; mp 247-249 ^{o}C; Rf = 0.40 (30% EtOAc-Hexane).

It was obtained as light yellow solid having m. p. 247-249 ^{o}C in 83% yield. IR ($CHCl_3$) ν_{max} (cm^{-1}): 3363, 3066, 2925, 1658, 1614, 1527, 1448, 1237, 751. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.70 (1H, s), 8.03 (1H, d, *J* = 8.39Hz), 7.73 (1H, d, *J* = 3.05 Hz), 7.57-7.55 (2H, m), 7.41-7.39 (1H, m), 7.31 (1H, t, *J* = 7.63 Hz), 7.20-7.16 (3H, m), 7.13-7.11 (1H, m), 7.07-7.03 (1H, m), 6.87 (1H, d, *J* = 7.63 Hz), 6.63 (1H, d, *J* = 8.39 Hz), 5.71 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.97, 147.15, 145.13, 135.93, 135.33, 131.94, 130.54, 129.91, 128.88, 126.94, 126.55, 122.21, 119.74, 118.21, 115.28, 114.91, 110.71, 66.47. HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{21}H_{15}ClN_4O$: 375.1016; found: 375.1019.

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SUPPORTING INFORMATION

Full experimental detail, ^{1}H and ^{13}C NMR spectra have been provided in supporting information. This material can be found via the "Supplementary Content" section of this article's webpage.

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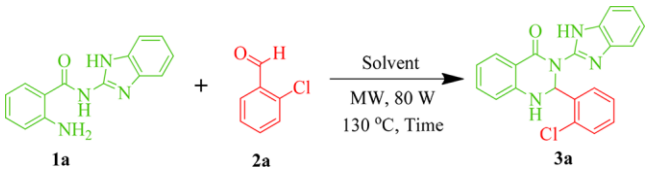
Table 1. Optimization of reaction conditions.[a]



Entry	Solvent	Time (min)	Yield (%)[b]
1	DMF	10	83
2	DMF	15	75
3	DMF	4 hour	65[c]
4	PhMe	30	65[d]
5	1,4-Dioxane	10	73
6	CH_3CN	10	67
7	EtOH	20	53
8	H_2O	30	-[e]
9	Neat	30	-[e]

[a]Reaction conditions: a mixture of 2-amino-*N*-(1*H*-benzo[*d*]imidazol-2-yl)benzamide (**1a**) (1.0 mmol), 2-chlorobenzaldehyde (**2a**) (1.2 mmol) in DMF (2 mL) was irradiated at 80W maximum power, at a ceiling temperature of 130 °C; [b]isolated yield; [c]reaction was performed under conventional heating at 130 °C; [d]reaction was incomplete even after 30 min of irradiation under microwave condition; [e]reaction could not proceed and only starting materials were isolated.

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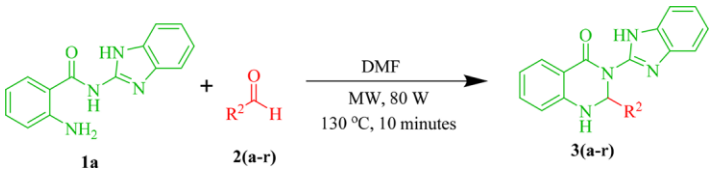
Table 2. Optimization of substrate scope of aldehydes.[a]



1a 2(a-r) 3(a-r)

S. No.	Compound	R^2	Yield (%)[b]
1	**3a**	2-Cl-phenyl	83
2	**3b**	2-Br-pheny	74
3	**3c**	2-NO_2-phenyl	57
4	**3d**	phenyl	89[c]
5	**3e**	4-CH_3-phenyl	93[d]
6	**3f**	4-CH_3O-phenyl	98[d]
7	**3g**	4-Cl-phenyl	71[c]
8	**3h**	4-Br-phenyl	63[c]
9	**3i**	4-NO_2-phenyl	84
10	**3j**	4-Br-2-F-phenyl	88
11	**3k**	2,6-dichlorophenyl	89
12	**3l**	3,4-dichlorophenyl	69
13	**3m**	2,6-difluorophenyl	85
14	**3n**	ethyl	74
15	**3o**	cyclohexyl	72
16	**3p**	furan	66
17	**3q**	7-methoxycoumarin-4-yl	64[c]
18	**3r**	7,8-dimethoxycoumarin-4-yl	71[c]

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[a]Reaction conditions : a mixture of 2-amino-*N*-(1*H*-benzo[*d*]imidazol-2-yl)benzamides (**1a**) (1.0 mmol), aldehydes (**2)** (1.2 mmol) in DMF (2 mL) was irradiated at 80W maximum power, at a ceiling temperature of 130 °C; [b]isolated yield; [c]reaction was carried out for 15 minutes; [d]reaction was carried out for 20 minutes.

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Table 3. Important crystal data of compounds **3a**.

Parameters	3a
CCDC deposition number	1440320
Empirical Formula	$C_{21}H_{15}ClN_4O$
Formula weight	374.82
Temperature (K)	298.15
Crystal System	monoclinic
Space Group	$P2_1/n$
Unit Cell Dimension	a/Å = 11.5108(8)
	b/Å = 9.1933(6)
	c/Å = 16.3785(11)
	α/° = 90
	β/° = 97.978(6)
	γ/° = 90
Volume $Å^3$	1716.4(2)
Z	4
Density Calculated g/cm^3	1.450
Absorption coefficient(μ) mm^{-1}	0.242
F(000)	776.0
Crystal size/mm^3	0.11 × 0.06 × 0.03
Radiation	MoKα (λ = 0.71073)

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2Θ range for data collection/°	6.02 to 52.038
Index ranges	$-11 \leq h \leq 14$
	$-6 \leq k \leq 11$
	$-20 \leq l \leq 14$
Reflection Collected	7247
Independent Reflections	3373 [R_{int} = 0.0394, R_{sigma} = 0.0682]
Data/Restraints/parameters	3373/0/304
Goodness of fit on F^2	1.074
Final R indices [I>=2sigma(I)]	R_1 = 0.0539, wR_2 = 0.1006
R indices (all data)	R_1 = 0.0899, wR_2 = 0.1250
Largest difference peak and hole [e $Å^{-3}$]	0.19/-0.26

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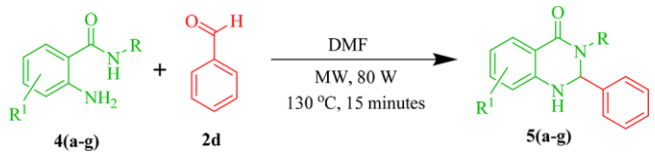
Table 4. Optimization of substrate scope of 2-aminobenzamides.[a]



S. No.	Compound	R	R^1	Yield (%)[b]
1	**5a**	Benzimidazol-2-yl	4-F	62
2	**5b**	Benzimidazol-2-yl	5-I	64
3	**5c**	6-methylbenzimidazol-2-yl	-	87
4	**5d**	6-cholrobenzimidazol-2-yl	-	83
5	**5e**	Phenyl amino	-	87
6	**5f**	phenyl	-	67
7	**5g**	H	-	89

[a]Reaction conditions : a mixture of **4** (1.0 mmol), benzaldehyde (**2d**) (1.2 mmol) in DMF (2 mL) was irradiated at 80W maximum power, at a ceiling temperature of 130 °C;

[b]isolated yield.

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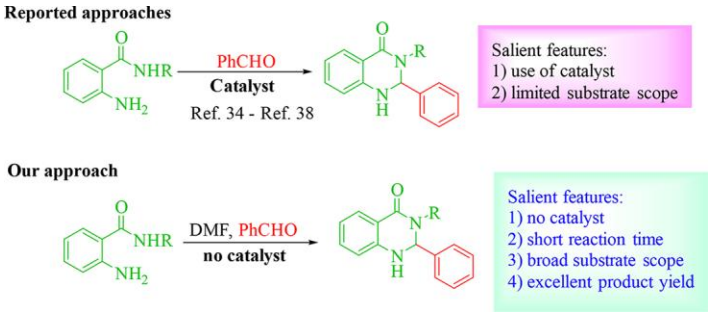
Scheme 1. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones from 2-aminobenzamides.



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Scheme 2. Competitive experiments **a**) between benzaldehydes and **b**) between 2-aminobenzamides.

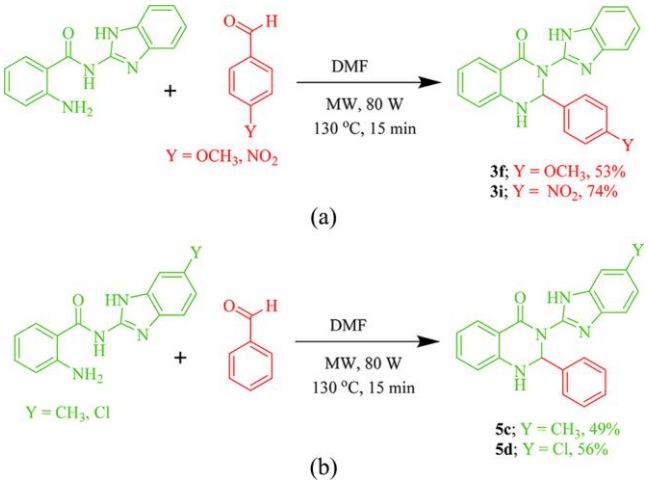

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Figure 1. Some representative biologically important 2,3-dihydroquinazolinone scaffolds.

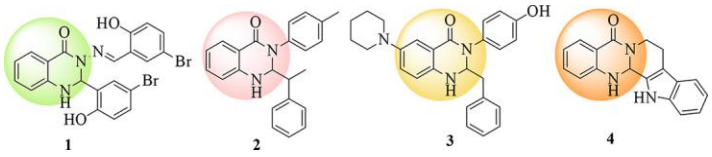

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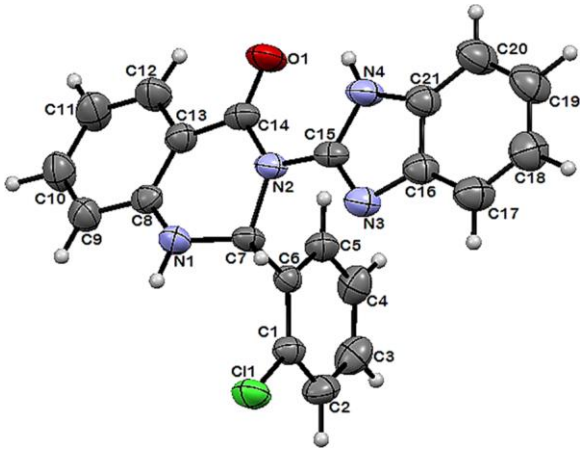
Figure 2. ORTEP diagram of compound **3a** with atomic numbering scheme at 30% probability level.



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