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Transition-Metal Free Synthesis of Quinazolinones *via* Tandem Cyclization of 2-halobenzoic Acids with Amidines

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A simple protocol for the synthesis of quinazoline-4(3*H*)-ones by tandem cyclization of 2-halobenzoic acids with amidines has been firstly developed by using KOH as a base in DMSO at 120 °C. This protocol does not involve the use of any transition-metals or ligands or any coupling reagents. The present methodology is operationally simple, scalable and varieties of quinazolinone derivatives were obtained in good to excellent yields.

Introduction

Quinazolinone derivatives have wide applications in biological and medicinal activities such as hypnotic, sedative, analgesic, anticonvulsant, antitussive, antibacterial, antidiabetic, anti-inflammatory and antitumor agents.[1,2] For example, various molecules containing quinazolinone moieties *viz.*, compound **I** used as potent and selective inhibitor of Tankyrase,[3] compound **II** exhibits CNS depressant activity,[4] compound **III** is an inhibitor of the enzyme aldose reductase[5] and compound **IV** shows antihypertensive activity[6] (Fig. 1). Furthermore, quinazolinone derivatives also function as potent inhibitors for the epidermal growth factor (EGF) receptors of tyrosine kinase,[7] and some of them shows significant activity as antitubercular,[8] antiviral,[9] and anticancer agents.[10] Quinazolinones are very important basic structure of many naturally occurring alkaloids. They are isolated from a number of families of the plant kingdom, and from microorganisms, such as bouchardatine from *Bouchardatia neurococca*,[11] 2-methyl-4(3*H*)-quinazolinone from *Bacillus cereus*,[12] 2-(4-hydroxybutyl)quinazolin-4-one from *Dichroa febrifuga*,[13] and luotonin A from *Peganum nigellastrum*.[14]

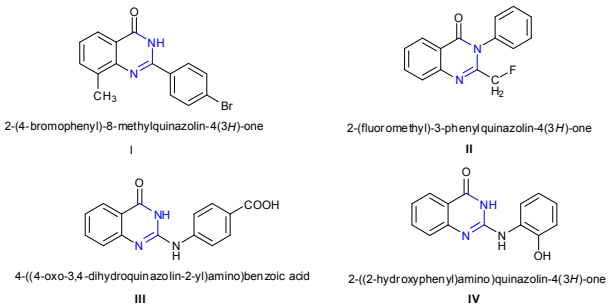

Fig. 1 Quinazolinone derivatives with biological and medicinal activity.

Traditionally, quinazolinone derivatives were synthesized by using *ortho*-amino or *ortho*-nitro benzoic acid derivatives.[1] In 1869, Griess[15] prepared the first quinazolinone derivative, by the action of cyanogens on the ethanolic solution of anthranilic acid. Next, von Niementowski[16] synthesized quinazolinone by fusion (130-150 °C) of anthranilic acid analogues with amides. Subsequently, Kabri *et al.*[17] reported microwave-assisted synthesis of new quinazoline derivatives from 2-aminobenzamide and chloroacetyl chlorides. Nevertheless, the feasibility of these methods was limited due to the difficult preparation of the starting materials, high temperature and longer reaction time. In the past few years, transition-metal catalyzed synthesis of quinazolinone derivatives *via* intermolecular cyclization of 2-halobenzoic acid or 2-halobenzoic esters derivatives with amidines has also been developed. However, the efficiency of these methods is highly dependent on the presence of transition metal-catalyst such as Cu[18] and Fe.[19] Moreover; these methods were limited by utilisation of ligand, support and microwave irradiation condition. Therefore, there is a need to develop an economically and environmentally benign method for the synthesis of quinazolinone derivatives under metal and ligand free conditions.

Recently, transition metal-free methods for the formation of C-N, C-C, C-S and C-O bonds have captured the interest of many research groups.[20] From this aspect, base promoted intermolecular cyclization has shown great potential for the organic synthesis.[21] Herein, we have firstly developed a simple transition metal-free, ligand-free, base mediated synthesis of quinazolinone derivatives from 2-halobenzoic acids and amidines under inert atmosphere. Notably, it employs simple KOH in DMSO, takes place at 120 °C. The results of our studies are described herein.

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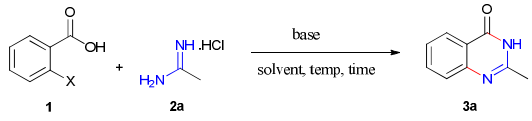
Results and discussion

Initially, 2-iodobenzoic acid (**1a**, 1.0 mmol) and acetamidine hydrochloride (**2a**, 1.1 mmol) were chosen as the model substrates for the optimization of the reaction conditions, which include solvent, base, temperature and time. As shown in Table 1, unfortunately, there was no formation of 2-methylquinazolin-4(3*H*)-one (**3a**) at 40 °C (Table 1, entry 1) and only trace amount of **3a** was found at 60 °C (Table 1, entry 2) in KOH (2.0 equiv)/DMSO system. To our delight, increase in temperature has significant effect on the yield of **3a** (Table 1, entries 3 and 4), and expected yield of 94% was obtained at 120 °C (Table 1, entry 5). Further increase in temperature didn't have significant effect on the yield of **3a** (Table 1, entry 6). Next, reaction time studies revealed that the reaction time could be reduced from 24 to 12 h giving 92% yield of **3a** (Table 1, entries 7-9). The use of 2.0 equiv of KOH proved to be essential. Decreasing the amount of the base to 1.0 equiv led to a significant reduction in yield of **3a** (Table 1, entries 10 and 11). To confirm that the presence of impurities such as Cu or Fe did not affect the reaction, the usually used KOH (Rankem 85%) was replaced by a sample with a purity of >99.99% (Alfa Aesar). Also in this case, the yield of **3a** was 92% (Table 1, entry 12), which confirmed that this factor was irrelevant here. When reaction was carried out under air atmosphere, very low yield of **3a** was observed (Table1, entry12). Another inorganic base K_2CO_3 was also found to give good yield 73% of **3a** (Table 1, entry 13). In the next set of experiments, solvents such as DMF and *o*-xylene were used, but they furnished low yields, 48% and 35% respectively (Table 1, entries 14 and 15). Finally, when iodo was changed with bromo, chloro and fluoro groups, a consistent decrease in the yield of **3a** was observed. The reactions of 2-iodo- and 2-bromobenzoic acids with **2a** produced **3a** in excellent to good yield and 2-chlorobenzoic acid gave very low yield of **3a**, whereas 2-fluorobenzoic acid didn't furnish **3a** under the same reaction conditions (Table 1, entries 16-18).

Based on these results, various quinazolinone derivatives were synthesized under our standard conditions: 2.0 equiv of KOH in DMSO at 120 °C for 12 h. As shown in Table 2, all the substrates examined provided excellent to good yields. It was found that 2-iodobenzoic acid reacts smoothly with different amidines providing corresponding products **3a-3c** in excellent yields (Table 2, entries 1-3). Furthermore, 2-bromobenzoic acid gave good yield of corresponding products **3a** and **3c** (Table 2, entries 4 and 6). Next, methyl-2-bromobenzoate (**1bb**) was also found to be effective for the synthesis of 2-phenylquinazolin-

Table 1 Optimization of reaction conditions[a]

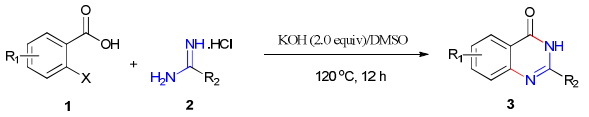


1 2a 3a

Entry	X	Base (equiv.)	Solvent	Temp(°C)/ Time (h)	Yield[b] (%)
1	I	KOH (2.0)	DMSO	40/24	-
2	I	KOH (2.0)	DMSO	60/24	trace
3	I	KOH (2.0)	DMSO	80/24	30
4	I	KOH (2.0)	DMSO	100/24	65
5	I	KOH (2.0)	DMSO	120/24	94
6	I	KOH (2.0)	DMSO	140/24	95
7	I	KOH (2.0)	DMSO	120/18	94
8	I	KOH (2.0)	DMSO	120/12	92
9	I	KOH (2.0)	DMSO	120/6	71
10	I	KOH(1.5)	DMSO	120/12	77
11	I	KOH (1.0)	DMSO	120/12	58
12	I	KOH (2.0)	DMSO	120/12	92[c],31[d]
13	I	K_2CO_3 (2.0)	DMSO	120/12	73
14	I	KOH (2.0)	DMF	120/12	48
15	I	KOH (2.0)	*o*-Xylene	120/12	35
16	Br	KOH (2.0)	DMSO	120/12	61,62[e]
17	Cl	KOH (2.0)	DMSO	120/12	< 10
18	F	KOH (2.0)	DMSO	120/12	-

[a] Reaction conditions: 2-halobenzoic acid (**1**, 1.0 mmol), acetamidine hydrochloride (**2a**, 1.1 mmol), solvent (2 mL) under inert atmosphere. [b] GC yield. [c] Use of KOH with a purity of > 99.99%. [d] Reaction was carried out in the presence of air. [e] Reaction was carried out at 140 °C for 24 h.

Table 2 The intermolecular tandem cyclization reaction for the synthesis of quinazolinone derivatives[a]



1 2 3

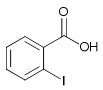
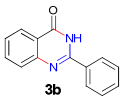
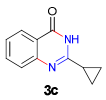
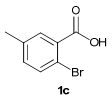
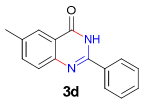
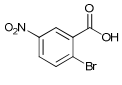
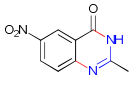
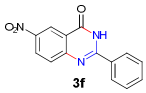
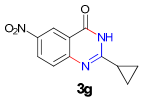
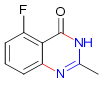
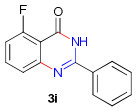
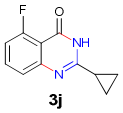
Entry	1	2	3	Yield[b] (%)
1	 1a	 2a	 3a	92
2	**1a**	 2b	 3b	94
3	**1a**	 2c	 3c	85
4	 1b	**2a**	**3a**	61
5	 1bb	**2b**	**3b**	63

Table 2 *(Contd.)*

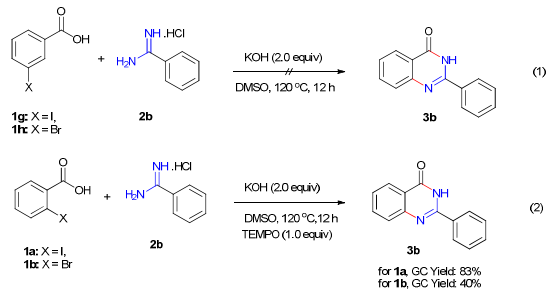
Entry	1	2	3	Yield[b] (%)
6	**1b**	**2c**	**3c**	58
7	 **1c**	**2b**	 **3d**	48
8	 **1d**	**2a**	 **3e**	67
9	**1d**	**2b**	 **3f**	71
10	**1d**	**2c**	 **3g**	50
11	 **1e**	**2a**	 **3h**	82
12	**1e**	**2b**	 **3i**	85
13	**1e**	**2c**	 **3j**	78
14	 **1f**	**2a**	**3h**	63
15	**1f**	**2b**	**3i**	68
16	**1f**	**2c**	**3j**	55

[a] Reaction conditions : **1** (1.0 mmol), **2** (1.1 mmol), KOH (2.0 equiv) in DMSO (2 mL) at 120 °C for 12 h under inert atmosphere. [b] Isolated Yield.

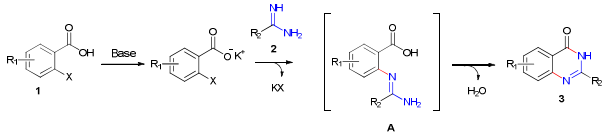
4(3*H*)-one (**3b**) in (Table 2, entry 5). Effect of electron donating and withdrawing group was also studied. It was found that electron donating substituent on **1b** produced corresponding 6-methyl-2-phenylquinazolin-4(3*H*)-one (**3d**) in 48% yield (Table 2, entry 7). Subsequently, the reaction of **1b** bearing electron withdrawing substituent with various amidines furnished the corresponding products **3e-3g** in good to moderate yields (Table 2, entries 8-10). We have also studied the effect of halo substituents on *o*-halobenzoic acids with amidines. It was found that reaction of 2-fluoro-6-iodobenzoic acid (**1e**) with amidines, afforded corresponding products **3h-3j** in excellent yields (Table 2, entries 11-13). Furthermore, 2-bromo-6-fluorobenzoic acid (**1f**) with amidines also furnished the respective products **3h-3j** in moderate yields (Table 2, entries 14-16).

To demonstrate the synthetic utility of this protocol, gram-scale reactions were carried out by employing substrates **1a** (2.0 g, 8.0 mmol) with **2b** (1.4 g, 8.8 mmol) and **1b** (2.0 g, 9.9 mmol) with **2b** (1.7 g, 10.9 mmol) under the standard reaction conditions. As per our expectation, reactions proceeded well to give **3b** in 93% and 61% isolated yields respectively.

In order to understand the reaction mechanism; some control experiments were carried out. To evaluate if the reaction proceeded *via* an aryne intermediate,[21i,22] *meta*-halo substrates **1g** and **1h** were reacted with **2b** under standard optimized reaction conditions. Surprisingly, no formation of expected product **3b** was observed, which eliminates the possibility of an aryne mechanism in the present protocol (Scheme 1, eq. 1). Also, experiments were performed in the presence of a known radical inhibitor TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) for both 2-iodo- and 2-bromobenzoic acids (Scheme 1, eq. 2). It was found that the reactions did not stop for 2-iodobenzoic acid, and for 2-bromobenzoic acid as there was not much decrease in the yield of **3b**, indicating that this reaction does not proceed through the formation of shortly lived radicals.[22,23] Based on our observations in the control experiments, a plausible reaction mechanism for this transformation is illustrated (Scheme 2). Taking all the results into account, these



Scheme 1 Control Experiments.



Scheme 2 Plausible mechanism for the intermolecular tandem cyclization reaction between 2-halobenzoic acids and amidines.

reaction may first proceeds with formation of an intermediate (**A**) *via* *N*-arylation under basic medium[24] *i.e.*, S_NAr[25] and then

followed by tandem cyclization providing corresponding product. The study of reaction mechanism is still under progress.

Conclusions

In summary, a new protocol for the synthesis of quinazolinone from 2-halobenzoic acids and amidines has been developed under simpler condition. The intermolecular tandem cyclization is mediated by inexpensive and easily available KOH base in DMSO at 120 °C. The various derivatives of quinazolinones were synthesized in good to excellent yields. Thus, the developed protocol could be an alternative for the academic as well as industrial applications.

Experimental Section

General

All chemicals and solvents were purchased with high purities and used without further purification. The progress of the reaction was monitored by gas chromatography (GC) Perkin Elmer Clarus 400. GC equipped with a flame ionization detector (FID) with a capillary column (30 m × 0.25 mm × 0.25 μm) and thin layer chromatography (using Merck silica gel 60 F-254 plates. The products were visualized with a 254 nm UV lamp. GC-MS-QP 2010 instrument (Rtx-17, 30 m × 25 mm ID, film thickness (df = 0.25 μm) (column flow 2 mL min^{-1}, 80 °C to 240 °C at 10 °C min^{-1} rise) was used for the mass analysis of the products. HRMS was recorded on a commercial apparatus (ESI Source, ion trap). Products were purified by column chromatography on 100-200 mesh silica gel. The ^{1}H NMR spectras were recorded on 400 MHz spectrometer in $CDCl_3$ and DMSO-d_6 using tetramethylsilane (TMS) as an internal standard. The ^{13}C NMR spectras were recorded on 100 MHz in $CDCl_3$ and DMSO-d_6. Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane as an internal standard. Coupling constant (J) values were reported in hertz (Hz). Splitting patterns of proton are described as s (singlet), d (doublet), dd (doublet of doublet), t (triplet) and m (multiplet). The products were confirmed by GCMS, HRMS, ^{1}H and ^{13}C NMR spectroscopic analysis.

General procedure for synthesis of quinazolinone derivatives

Substituted 2-halobenzoic acid (**1**, 1.0 mmol) and amidines hydrochloride (**2**, 1.1 mmol) and KOH (2.0 equiv) in DMSO (2 mL) were added under nitrogen atmosphere, and was stirred at room temperature for 10 min, then heated at 120 °C for 12 h. After completion of the reaction, the mixture was cooled to room temperature and water (2 mL) and ethyl acetate (4 mL) were added. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with brine (3 mL), dried with anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. The product was purified by silica gel column chromatography by using petroleum ether (PE)/ethyl acetate (EA).

Characterisation data of products

2-Methylquinazolin-4(3*H*)-one (3a).[18d,19] PE : EA (1 : 1). Yield 92% (2-iodobenzoic acid as the substrate); 61% (2-bromobenzoic acid as the substrate). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.75 (s, br, 1H), 8.30 (dd, 1H, J = 8 Hz, 4Hz,), 7.80 - 7.76 (m, 1H), 7.69 (d, 1H, J = 8 Hz) 7.48 (t, 1H, J = 8 Hz), 2.60 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.7, 153.3, 149.5, 135, 127.1, 126.5, 126.3, 120.4, 22 ppm; GCMS (EI, 70 eV): m/z (%): 160 (100, M^+), 118 (24), 44 (23), 39 (38).

2-Phenylquinazolin-4(3*H*)-one (3b).[18d,19] PE : EA (3 : 1). Yield 94% (2-iodobenzoic acid as the substrate); 63% (Methyl-2-bromobenzoate as the substrate). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.25 (s, br, 1H), 8.33 - 8.20 (m, 3H), 7.84-7.78 (m, 2H) 7.58-7.50 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 151.6, 149.4, 134.8, 132.8, 131.6, 129, 128, 127.2, 126.4, 120.9 ppm; GCMS (EI, 70 eV): m/z (%): 222 (63, M^+), 119 (100), 77 (19).

2-Cyclopropylquinazolin-4(3*H*)-one (3c).[18d,19] PE : EA (1 : 1). Yield 85% (2-iodobenzoic acid as the substrate); 58% (2-bromobenzoic acid as the substrate). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.59 (s, br, 1H), 8.24 (d, 1H, J = 8.0 Hz), 7.72-7.68 (m, 1H), 7.58 (d, J = 8, 1H), 7.40 - 7.36 (m, 1H), 1.99-1.93 (m, 1H), 1.33-1.29 (m, 2H), 1.14 - 1.10 (m, 2H) ppm; ^{13}C NMR (CDCl3, 100 MHz) δ 163.9, 157.9, 149.7, 134.8, 126.9, 126.2, 125.6,120.4, 14.7, 9.7 ppm; GCMS (EI, 70 eV): m/z (%): 186 (63, M^+), 185 (100), 119 (26), 92 (15).

2-Methyl-6-nitroquinazolin-4(3*H*)-one (3e).[18d] PE : EA (1 : 1). Yield 67%. Light yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12. 65 (s, br, 1H), 8.70 (s, 1H), 8.44 - 8.41 (dd, 1H, J = 8, 4 Hz), 7.67 (d, 1H, J = 8 Hz) 2.36 (s, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.3, 158.8, 153.6, 144.7, 128.7, 128.6, 122.3, 121, 22 ppm; GCMS (EI, 70 eV): m/z (%): 205 (100, M^+), 175 (33), 106 (28), 90 (69), 42 (54).

6-Nitro-2-phenylquinazolin-4(3*H*)-one (3f)[18d,25.] PE : EA (3 : 1). Yield 71%. Light yellow solid. ^{1}H NMR (DMSO-d6, 400 MHz) δ 13.00 (s, br, 1H), 8.81(d, 1H, J = 4 Hz), 8.50 - 8.47 (1H), 8.21 (d, 2H, J = 8 Hz), 7.8 (d, 1H, J = 8 Hz), 7.59 - 7.51 (m, 3H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.1, 157.1, 153.8, 144.7, 133.3, 132.4, 129.3, 129, 128.7, 128.5, 122, 121.4 ppm.

2-cyclopropyl-6-Nitro-4(3*H*)-one (3g).[18d] PE : EA (2 : 1). Yield 50%. White solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.88 (s, br, 1H), 8.68 (d, 1H, J = 4 Hz), 8.39 - 8.36 (m, 1H), 7.55 (d, 1H, J = 8 Hz), 1.99 - 1.95 (m, 1H), 1.13 - 1.07 (m, 4H) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ 163.9, 161.3, 153.8, 144.1, 128.5, 128.4, 122.5, 120.8, 14.3, 11 ppm; GCMS (EI, 70 eV): m/z (%): 230 (100), 231 (84, M^+), 184 (45), 90 (46), 41 (41).

5-Fluoro-2-methylquinazolin-4(3*H*)-one (3h).[19b] PE : EA (1 : 1). Yield 82 % (2-iodobenzoic acid as the substrate); 63% (2-bromobenzoic acid as the substrate). White solid. ^{1}H NMR ($CDCl_3$)

δ 11.16 (s, br, 1H), 7.70 - 7.65 (m, 1H), 7.45 (d, 1H, J = 8 Hz), 7.11 - 7.07 (m, 1H), 2.25 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.6, 159.7, 159.4 154.2, 151.3, 135.3, 122.9, 113.1, 112.9, 22.0 ppm; GCMS (EI, 70 eV): m/z (%): 178 (100, M^+), 163 (19), 110 (23), 108 (21), 42 (29).

5-Fluoro-2-cyclopropylquinazolin-4(3*H*)-one (3j). PE : EA (1 : 1).White solid. Yield 78% (2-iodobenzoic acid as the substrate); 55% (2-bromobenzoic acid as the substrate). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.51 (s, br, 1H), 7.64 - 7.58 (m, 1H), 7.36 (d, 1H, J = 4 Hz), 7.03 - 6.99 (m, 1H), 1.85 - 1.81 (m, 1H), 1.28 - 1.23 (m, 2H), 1.13 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz), δ 162.1, 161.1, 160, 154.2, 151.8, 135, 122.9, 112.9, 112, 14.5, 10 ppm; GCMS (EI, 70 eV): m/z (%): 203 (1000, M^+), 204 (65), 137 (20), 110 (14), 108 (16), 40 (39). HRMS (ESI-ion trap) m/z calcd [$(M+H)^+$] 205.0777, found 205.0767.

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