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ORIGINAL PAPER

A practical and versatile approach toward a one-pot synthesis of 2,3-disubstituted 4(3*H*)-quinazolinones

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Abstract An effective one-pot three-component route to 4(3*H*)-quinazolinones from commercially available starting materials is reported. Thus, isatoic anhydride reacted with ammonium acetate or primary amines and aldehydes in the presence of iodine to produce the corresponding quinazolinone derivatives in moderate to good yields.

Keywords Quinazolinone · Heterocycle · Iodine · Multicomponent reaction · Aldehyde · Amine

Introduction

The construction of complex molecules through multicomponent reactions (MCRs) constitutes a very attractive strategy in organic synthesis [1]. In a multicomponent reaction three or more reactants are involved in a cascade of bond-forming individual steps to provide a complex molecule without isolation of intermediates or modification of the reaction conditions. Attractive features of MCRs are simplicity of operation, reduction of isolation and purification steps, and minimization of costs, time, energy, solvents, and waste production. Moreover, by employing an array of diverse reagents, molecular diversity is efficiently generated. In fact, MCRs have been extensively employed in combinatorial and parallel diversity oriented synthesis [2, 3].

The quinazolinone moiety is a building block for approximately 150 naturally occurring alkaloids [4], such as glycosminine [5], luotonin [6], deoxyvasicinone [7], and drugs like methaqualone [8, 9] and piriqualone [10] (Fig. 1).

In addition, quinazolinone analogues are an important class of heterocyclic compounds and used as antimalarial [11], anticonvulsant [12], antibacterial [13], antidiabetic [14], and anticancer drugs [15].

According to the valuable biological and diverse range of the pharmacological activities of quinazolinones, their synthesis is in demand. Consequently many research groups work on synthesis of this priceless heterocycles [16–18]. The most common synthesis route involves the amidation of 2-aminobenzoic acid or its derivatives, i.e. 2-aminobenzonitrile, 2-aminobenzoate, and 2-arylnitrilium salts, followed by ring closure with carboxylic acid derivatives [19, 20] or orthoesters [21–25]. Other synthesis pathways include the cyclization–oxidation of anthranilamides with aldehydes [26–30], which is only useful for the synthesis of 2-substituted quinazolinones, and reductive cyclization of nitro-aromatic compounds [31]. Reports on solid-phase synthesis [32], palladium-catalyzed cyclocarbonylation of *o*-iodoanilines [33], base-promoted ring closure of *o*-fluorobenzoylguanidines [34], ring closure of the N-protected guanidines [35], and α-functionalization reaction of cyclic amines [36] are some additional inputs to explore the quinazolinone multifaceted importance. However, there are few reports on one-pot synthesis of 2,3-disubstituted quinazolinones using aldehydes as a starting material in which only preparation of 2-substituted analogues has been reported [26–30]. In this contribution, we

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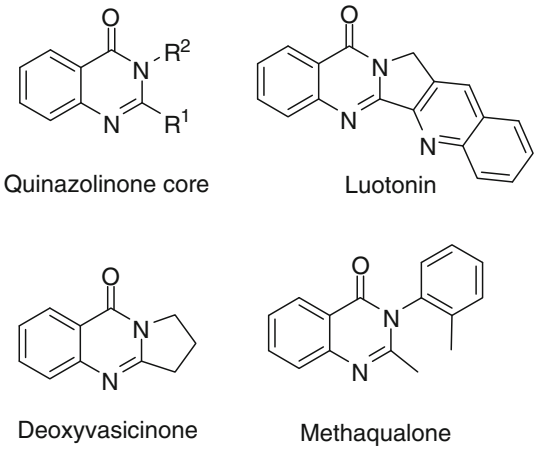


Fig. 1 Quinazolinone core and some well-known quinazolinone derivatives

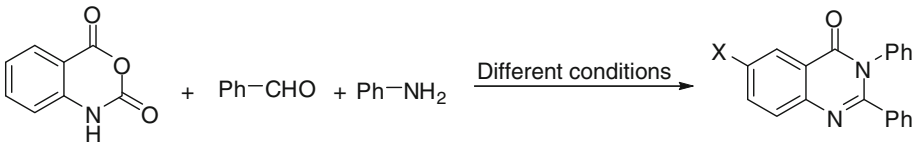
report the one-pot three-component synthesis of 2,3-disubstituted quinazolinones starting from aldehydes for the first time. This will allow the method to be used for the production of ensembles, as different isatoic anhydrides, amines, and aldehydes could be used in the reaction.

The use of molecular iodine in organic synthesis has been known for a long time, such as in the Grignard reaction. In recent years, molecular iodine has received considerable attention as an inexpensive and readily available catalyst for various organic transformations under very mild and convenient conditions to afford the corresponding products in excellent yields with high selectivity [37].

Results and discussion

Isatoic anhydride, benzaldehyde, and aniline were chosen as the model substrates to optimize the reaction conditions including the solvents, amount of iodine, and catalyst. As shown in Table 1, five different solvents were tested under reflux conditions using 1 equivalent of iodine and 10 mol% of acetic acid as the catalyst (relative to the amount of isatoic anhydride) (Table 1, entries 1–5). As can be seen, acetonitrile was the best choice (Table 1, entry 2). No quinazolinone **4** was formed in the absence of acetic acid (Table 1, entry 6), and no improvement in yield was observed using higher amounts of the acid (Table 1, entry 7). When the reaction was run in the presence of lower amounts of iodine the yield of product decreased and increasing the amount of iodine had no obvious effect on

Table 1 Optimization of reaction conditions



Entry	Solvent	Iodine (eq)	AcOH (mol%)	Time (h)	Yield (%)[a]
1	$CHCl_3$	1	10	12	10
2	CH_3CN	1	10	12	62
3	CH_3OH	1	10	12	50
4	C_2H_5OH	1	10	12	50
5	$C_6H_5CH_3$	1	10	12	–
6	CH_3CN	1	–	12	–
7	CH_3CN	1	20	12	61
8	CH_3CN	–	10	12	–
9	CH_3CN	0.5	10	12	30
10	CH_3CN	2	10	12	62
11	CH_3CN:H_2O (3:1)	1	10	10	60
12	CH_3CN:H_2O (2:1)	1	10	8	61
13	CH_3CN:H_2O (1:1)	1	10	5	60
14	CH_3CN:H_2O (1:2)	1	10	12	50
15	CH_3CN:H_2O (1:3)	1	10	12	30

Reaction conditions: a mixture of isatoic anhydride (1 mmol), benzaldehyde (1 mmol), aniline (1.1 mmol), I_2, acetic acid, and 5 cm^3 solvent was stirred in a round bottom flask under reflux

[a] Isolated yield

conversion (Table 1, entries 8–10). Based on our knowledge in using water in the synthesis of quinazolinones [38–40], a mixture of water and acetonitrile was utilized as the solvent (Table 1, entries 11–15). Different ratios were examined and in 1:1 ratio the best result was provided (Table 1, entry 13). A wide range of structurally diverse amines **3**, aldehydes **2**, and isatoic anhydrides **1** were reacted under the optimum conditions (Scheme 1). The results are summarized in Table 2. In all cases, the three-component reaction proceeded smoothly to afford the corresponding quinazolin-4(3*H*)-ones in good yields. Anilines having an electron-donating group (methyl) gave a higher yield (65%) (Table 2, entry 3) due to the increased electron density of the aromatic system, whereas electron-withdrawing groups (Cl) gave a lower yield (54%) (Table 2, entry 6). Heteroaromatic aldehydes also underwent cyclocondensation reaction successfully (Table 2, entries 11, 20). The results also showed that aliphatic aldehydes were cyclized to give the corresponding quinazolinone in lower yields and longer reaction time. Using ammonium acetate instead of amine in the reaction produced 2-substituted quinazolinones successfully in higher yield and shorter time compared to disubstituted analogues. It was found that by using ammonium acetate there was no need to use acetic acid in the reaction (Table 2, entries 18–24). Although the 2-substituted quinazolinone nucleus has been synthesized via condensation of anthranilamides with aldehydes followed by oxidation reaction using

Scheme 1

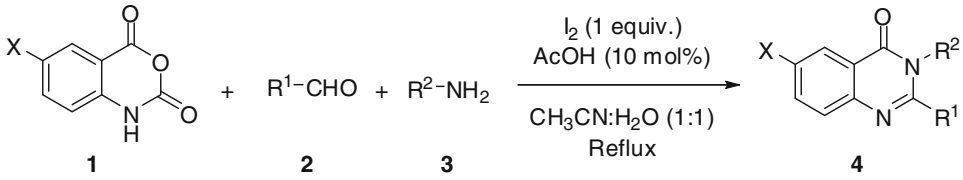


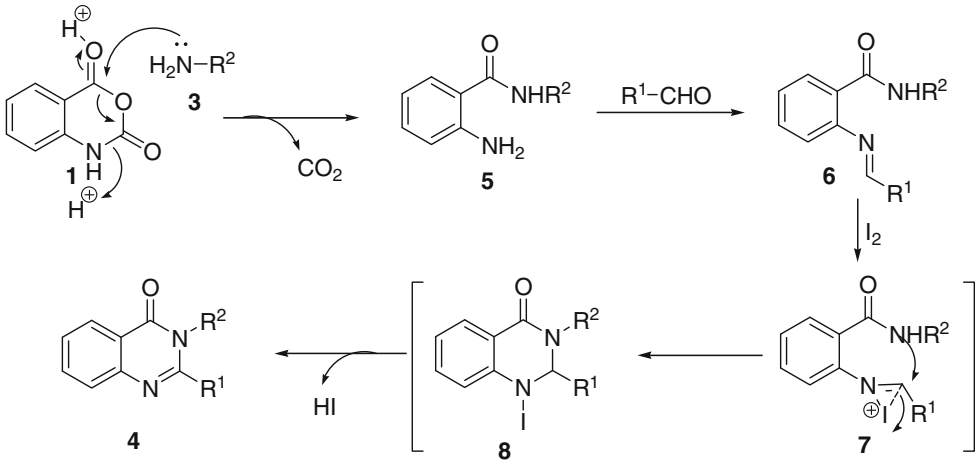
Table 2 Synthesis of quinazolinone derivatives

Entry	Product	X	R^1	R^2	Time (h)	Yield (%)[a]	Mp (°C) [Ref.]
1	**4a**	H	Ph	Ph	7	60	156–157 [33]
2	**4b**	H	Ph	4-$CH_3OC_6H_4$	5	71	198–200 [33]
3	**4c**	H	Ph	4-$CH_3C_6H_4$	7	65	178–179 [33]
4	**4d**	H	4-$CH_3C_6H_4$	Ph	7	63	171–173 [33]
5	**4e**	H	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	7	60	168–169 [33]
6	**4f**	H	Ph	4-ClC_6H_4	7	54	198–200 [33]
7	**4g**	H	4-ClC_6H_4	Ph	6	58	175–176 [33]
8	**4h**	H	4-ClC_6H_4	4-ClC_6H_4	6	60	182–183 [33]
9	**4i**	H	Ph	*i*-Pr	6	70	130–131 [33]
10	**4j**	H	Ph	*n*-Bu	7	73	114–115 [33]
11	**4k**	H	2-Furyl	Ph	6	57	202–204 [33]
12	**4l**	Cl	Me	Me	10	45	231–232 [42]
13	**4m**	H	4-HOC_6H_4	4-$CH_3C_6H_4$	7	68	172–174
14	**4n**	H	Ph	$PhCH_2$	7	71	137–139 [43]
15	**4o**	H	4-BrC_6H_4	4-$CH_3C_6H_4$	7	65	176–178
16	**4p**	Cl	3-$O_2NC_6H_4$	4-$CH_3C_6H_4$	10	40	252–254
17	**4q**	H	2-Pyridyl	4-$CH_3C_6H_4$	8	45	206–207 [20]
18[b]	**4r**	H	4-HOC_6H_4	H	5	65	302–303 [30]
19[b]	**4s**	H	Me	H	5	50	335–337 [22]
20[b]	**4t**	H	2-Furyl	H	5	55	220–221 [30]
21[b]	**4u**	Cl	4-$CH_3C_6H_4$	H	5	74	247–248 [44]
22[b]	**4v**	Cl	Ph	H	5	72	208–210 [44]
23[b]	**4w**	Cl	4-ClC_6H_4	H	5	74	213–215 [44]
24[b]	**4x**	Cl	4-$O_2NC_6H_4$	H	5	60	230–232 [44]

[a] Isolated yield

[b] The reaction was carried out using NH_4OAc instead of AcOH and amine

Scheme 2



different oxidant [26–30] in good yields, our present method has the capability to adapt for the synthesis of 2,3-disubstituted quinazolinones which are important compounds in biological and pharmaceutical chemistry (Fig. 1) [8–15].

In view of these results, we assume the reaction mechanism to be working as shown in Scheme 2. At first, the reaction starts through condensation of isatoic anhydride **1** and amine followed by decarboxylation to yield the corresponding 2-aminobenzamide **5** [21–25]. Condensation of the aromatic aldehyde with the amino group of **5** then gives imine **6** [26–30]. Electrophilic activation of imine via a cyclic iodonium ion [8, 9, 41] opens the way for nucleophilic cyclization of the amide. Finally, when the intermediate **8** loses HI [37], the quinazolinone **4** is formed.

In conclusion, we developed a general and efficient method for the synthesis of quinazolinone derivatives via iodine-catalyzed cyclization–oxidation coupling of isatoic anhydride with aldehydes and amines under mild conditions. The present method shows simple, economical, and practical advantages over the previous methods, so it can provide a procedure for one-pot synthesis of diverse molecules for organic and medicinal chemistry.

Experimental

Melting points were measured on an Electrothermal 9200 apparatus. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-300 Avance spectrometer at 300.13 and 75.47 MHz. The structures of the isolated products were confirmed by elemental analyses and from spectral data (mass, ^{1}H, and ^{13}C NMR spectra) and by comparison of their melting points with those of authentic samples.

General procedure for the one-pot synthesis of 2,3-disubstituted quinazolin-4(3H)-ones

Isatoic anhydride (1 mmol, 0.16 g), 1.2 mmol primary amine or 0.1 g ammonium acetate (1.2 mmol), 1 mmol aldehyde, and 5 cm^3 solvent (CH_3CN:H_2O/1:1) were mixed in a round bottom flask. Then 0.25 g iodine (1 mmol) and 6 cm^3 AcOH (10 mol%) were added and the mixture was stirred under reflux condition for the appropriate time (see Table 2). After completion of the reaction confirmed by TLC (eluent: ethyl acetate/*n*-hexane: 1/2), the solvent was evaporated. To the resulting solid was added 15 cm^3 H_2O and the mixture was stirred for 10 min. The resulting precipitate was filtered and washed with 10% aqueous $Na_2S_2O_3$ solution, water, and cold MeOH. Finally, the crude quinazolinone was recrystallised from ethanol.

2-(4-Hydroxyphenyl)-3-(4-methylphenyl)quinazoline-4(3H)-one (**4m**, $C_{21}H_{16}N_2O_2$)

Pale yellow solid; m.p: 172–174 °C; ^{1}H NMR (300.13 MHz, DMSO-d_6): $\delta = 2.29$ (s, 3H), 3.47–3.40 (m, 1H), 6.59 (d, $J = 7.4$ Hz, 2H), 7.21–7.15 (m, 6 H), 7.58–7.56 (m, 1H), 7.73 (d, $J = 7.5$ Hz, 1H), 7.87–7.85 (m,1 H), 8.17 (d, $J = 7.5$ Hz, 1H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6): $\delta = 21.1$, 114.8, 120.9, 126.9, 127.2, 127.7, 129.5, 129.6, 131.2, 135.1, 136.1, 137.8, 147.8, 155.8, 158.4, 162.1 ppm; IR (KBr): $\bar{\nu} = 1{,}678$ [(C=O)] cm^{-1}; MS (70 eV): $m/z = 328$ (M$^+$ 60), 327 (100), 256 (25), 221 (20), 192 (20), 160 (40), 128 (35), 96 (25), 64 (75).

2-(4-Bromophenyl)-3-(4-methylphenyl)quinazoline-4(3H)-one (**4o**, $C_{21}H_{15}BrN_2O$)

White solid; m.p.: 176–178 °C; ^{1}H NMR (300.13 MHz, DMSO-d_6): $\delta = 2.27$ (s, 3H), 7.14 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.36 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 8.4$ Hz, 2H), 7.63–7.58 (m, 1H), 7.77 (d, $J = 8.1$ Hz, 1H), 7.92–7.87 (m, 1H), 8.19 (d, $J = 7.9$ Hz, 1H) ppm; ^{13}C

NMR (75.47 MHz, DMSO-d_6): $\delta = 21.2$, 121.3, 122.9, 127.0, 127.7, 127.9, 129.7, 131.1, 131.5, 135.2, 135.4, 135.5, 138.2, 147.6, 154.8, 161.9 ppm; IR (KBr): $\bar{\nu} = 1{,}659$ [(C=O)] cm^{-1}; MS (70 eV): *m/z* = 392 (60), 391 (M^+ 100), 390 (70), 160 (15), 120 (20), 91 (27), 64 (30).

2-(3-Nitrophenyl)-3-(4-methylphenyl)quinazoline-4(3H)-one (**4p**, $C_{21}H_{14}ClN_3O_3$)

White solid; m.p.: 252–254 °C; ^{1}H NMR (300.13 MHz, DMSO-d_6): $\delta = 2.23$ (s, 3H), 7.13 (d, $J = 8.1$ Hz, 2H), 7.28 (d, $J = 8.1$ Hz, 2H), 7.56–7.49 (m, 1H), 7.66–7.63 (m, 1H), 7.75–7.72 (m, 1H), 7.86–7.79 (m, 2H), 8.15–8.12 (m, 1H), 8.31 (d, $J = 3$ Hz, 1H) ppm; ^{13}C NMR (75.47 MHz, DMSO-d_6): $\delta = 21.2$, 118.5, 124.3, 124.4, 127.6, 129.7, 129.8, 130.3, 133.4, 135.1, 135.2, 135.7, 137.3, 138.5, 147.3, 150.0, 154.5, 159.8, 170.8; IR (KBr): $\bar{\nu} = 1{,}663$ [(C=O)] cm^{-1}; MS (70 eV): *m/z* = 393 (10), 391 (M^+ 30), 366 (20), 256 (25), 192 (25),160 (50), 128 (50), 96 (25), 64 (100).

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