Iodine: Selectively Promote the Synthesis of Mono Substituted Quinazolin-4(3*H*)-ones and 2,3-Dihydroquinazolin-4(1*H*)-ones in One-Pot

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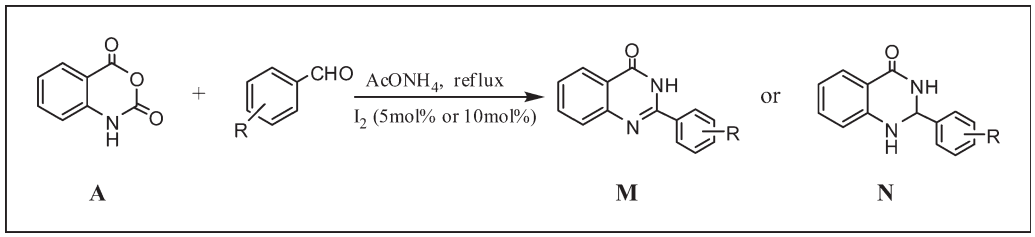
Received September 6, 2009
DOI 10.1002/jhet.414
Published online 13 July 2010 in Wiley Online Library (wileyonlinelibrary.com).



A general and versatile one-pot three-component procedure for the selective synthesis of mono substituted quinazolin-4(3*H*)-ones and 2,3-dihydroquinazolin-4(1*H*)-ones were described. The selectivity could be controlled by the ratio of iodine concentration.

J. Heterocyclic Chem., **47**, 1035 (2010).

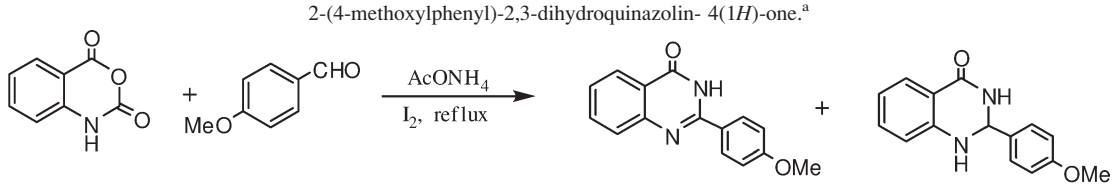
INTRODUCTION

2,3-Dihydroquinazolin-4(1*H*)-ones are an important class of heterocycles with a broad spectrum of biological and pharmaceutical activities, such as antitumor, analgesic, anticancer, and diuretic [1–3]. Traditional procedure for the synthesis of these compounds involves the condensation of anthranilamides, as well as the reductive cyclization of *o*-nitrobenzamide or *o*-azidobenzamide with aldehydes or ketones in the presence of Brφnsted or Lewis acid catalyst [4–12]. On the other hand, quinazolin-4(3*H*)-ones, the oxidized products of 2,3-dihydroquinazolin-4(1*H*)-ones [13], were important precursors for the synthesis of natural and pharmacological compounds including febrifugine and isofebrifugine [14]. It can also be obtained by the cyclization of anthranilamides with aldehyde and other similar methods [15]. With the one-pot multicomponent reactions (MCRs) emerged as a powerful tool to routinely find out novel biologically active compounds [16], recently, various approaches to 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones, promoted by Brφnsted or Lewis acid, or by supported acid with the help of special instrument, were explored independently in a one-pot three-component protocol starting from isatoic anhydride **A**, primary amine, and aldehyde [17–23]. However, there is a paucity of efficient synthetic route to implement the selectivity of two such compounds, an extra-oxidize step was always required to complete the fusion of the quinazolin-4(3*H*)-ones. Although Chen reported quinazolin-4(3*H*)-ones could be obtained by employing DMSO as solvent instead of EtOH, which was utilized to prepare 2,3-dihydroquinazolin-4(1*H*)-ones in the same protocol [23], novel flexible strategies for selective synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones without toxicity, unavailable or expensive agent should benefit both synthetic and medicinal chemistry in terms of Green Chemistry.

As an oxidant, iodine is widely used for the oxidation of alcohols, aldehydes, sulfides, and amines; for the oxidation to aromatics; for the introduction of protecting groups; for the deprotection, and so on [24]. Meanwhile, iodine has a wide range of application as a mild Lewis acid catalyst in organic synthesis, such as the Michael addition, the mannich reaction, the hantzsch reaction and many other transformations [25,26]. However, a literature survey suggested that few studies have been performed on applying both the oxidizing and catalyzing abilities of iodine simultaneously to organic functional group conversions. As a cheap, less toxic, easily accessible, and eco-benign reagent, iodine would be more practical for organic synthesis if the selectivity could be controlled quantificationally via modulating the ratio in as much as the oxidizing ability require more iodine to fulfill. Herein, we would like to disclose a versatile procedure for the fabrication of mono substituted quinazolin-4(3*H*)-ones and 2,3-dihydroquinazolin-4(1*H*)-ones selectively in the presence of different ratio of iodine.

Table 1

The optimization of reaction conditions to synthesis 2-(4-methoxylphenyl)quinazolin-4(3*H*)-one and 2-(4-methoxylphenyl)-2,3-dihydroquinazolin- 4(1*H*)-one.[a]



A **M1** **N1**

Entry	I_2 (mol %)	Solvent	A/$AcONH_4$	*t* (min)	Yield (%)[b]	M1/N1[c]
1	20	EtOH	1:1.2	25	86	100/0
2	20	H_2O	1:1.2	15	77	100/0
3	20	EtOH	1:1.1	40	81	100/0
4	20	EtOH	1:1.3	30	85	100/0
5	20	EtOH	1:1.5	30	85	100/0
6	25	EtOH	1:1.2	25	86	100/0
7	20	EtOH	1:1.2	25	85[d]	100/0
8	15	EtOH	1:1.2	60	91	97/3
9	10	EtOH	1:1.2	120	90	48/52
10	5	EtOH	1:1.2	70	89	1/99
11	0	EtOH	1:1.2	24h	23	0/100

[a] Reaction conditions: 4-methoxylbenzaldehyde(5 mmol), was added to the solution containing **A**(5mmol), iodine, and $AcONH_4$ at room temperature, which was then increased to refluxing temperature.
[b] Isolated yield of **M**1 and **N**1 mixture.
[c] Determined by LC-MS.
[d] N_2 was used.

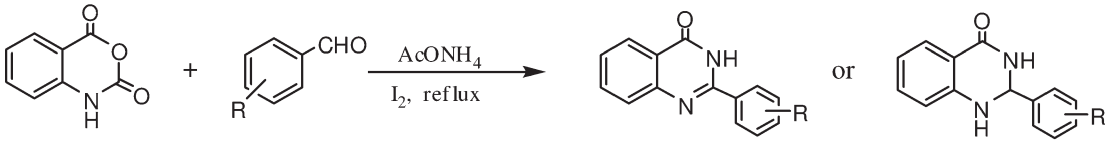
RESULTS AND DISCUSSION

Following our continued interest in the iodine-catalyzed MCRs [26a–d], 20 mol % of iodine was initially selected to catalyze the model reaction of isatoic anhydride, 1.2 equiv. of ammonium acetate, and 4-methoxybenzaldehyde in refluxing ethanol, aimed at obtaining the compound **N**1. After 40 min stirring, the white flocs were totally precipitated from the reaction solution, the final pure product yielded in 63% after work up, unexpectedly melted at 241°C, which is the melt point of compound **M**1 exactly. Subsequent ^{1}H NMR and LC-MS analysis certified that the white floc was just **M**1. Therefore, the optimization of the reaction conditions was carried out. First, the addition order of reactants was considered. As the enamine could be formed *in situ* and thus influence the yield of desired product, the aldehyde was added at last to the stirring solution at room temperature, which was increased to refluxing temperature as soon as possible, to our delight, the yields of product **M**1 could be up to 86%. With these conditions in hand, the solvent, ratio of **A** and $AcONH_4$, and the iodine concentration were screened subsequently. The results in Table 1 showed that refluxing the **A**, 4-methoxylbenzaldehyde and $AcONH_4$ rationed at 1:1:1.2 in the presence of 20 mol % of iodine about 25 min would provide the best result. Increasing the iodine amounts was ineffective for improvement of final yields. Interestingly, product **N**1 was detected and increased with the iodine concentration decreased from 20 mol % (Table 1, Entries 6–9), the pure product **N**1 could not be obtained until the amount of iodine reduced to 5 mol %, which was the right concentration to catalyze this three-compound reaction to give product **N**1, more iodine may present the oxidizing ability, resulting in mixed products of **M**1 and **N**1 (Table 1, Entries 8 and 9). As all the reactions were exposed in air, the O_2 may play the role of oxidant in the preparation of **M**1, so we employed the N_2 as an inert gas to perform the reaction (Table 1, Entry 7), and found that only the oxidated product **M**1 was detected in the reaction mixture by LC-Ms, which indicate that the catalytic iodine (20 mol %) played the roles of both catalyst and oxidant. Preliminary results unprecedentedly implied that we can selectively construct the structure of **M**1 and **N**1 promoted by 20 and 5 mol % of iodine, respectively.

In a comprehensive study, a sampling of the aldehydes was employed to explore the scope of this one-pot three-component reaction under optimal conditions (Table 2). Generally, all of the aldehydes participated smoothly and afforded the desired products in good to excellent yields, except for the 4-nitrobenzaldehyde yielded in 77% of **M** and 56% of **N** (Table 2, Entry 9 and 15). According to LC-MS monitoring of reaction mixtures, the benzylaldehyde and aromatic aldehydes bearing 4-Cl, 2-Cl, 4-Br demand more iodine to furnish the pure product **M** (Table 2, Entry 2, 4, 5, 8). The reaction time was slightly extended in the cases of producing pure product **N**.

Table 2

The preparation of 2-substituted-quinazolin-4(3*H*)-ones and 2-substituted-2,3-dihydroquinazolin- 4(1*H*)-ones.[a]



A **M** **N**

Entry	R	I_2 (mol %)	*t* (min)	Yield (%)[b]	M/N[c]
1	4-OMe	20	25	86	100/0
2	4-Cl	20	40	90	98/2
		25	25	91	100/0
3	4-OH	20	150	81	100/0
4	H	20	90	87	1/99
		25	65	89	84/16
		30	45	83	100/0
5	2-Cl	20	60	94	3/97
		30	45	93	99/1
6	4-$N(Me)_2$	20	15	92	100/0
7	3-Cl	20	20	81	100/0
8	4-Br	20	60	89	2/98
		30	30	87	99/1
9	4-NO_2	20	90	77	100
10	4-OMe	5	70	89	1/99
11	H	5	100	82	1/99
12	4-Cl	5	55	95	0/100
13	4-$N(Me)_2$	5	120	91	0/100
14	4-Br	5	90	91	0/100
15	4-NO_2	5	600	56	0/100

[a] Reaction conditions: 1 equiv. of aldehyde(5 mmol) was added to the solution containing **A**(5 mmol), iodine, and 1.2 equiv. of $AcONH_4$(5 mmol) at room temperature, which was then increased the to refluxing temperature.
[b] Isolated yield
[c] Determined by LC-MS

Besides, benzylaldehyde and 3-chlorobenzaldehyde provide somewhat lower yields and probable reason for this may be the lack of electron-influence.

Encouraged by these successes, we evaluated orthoester and *p*-toluidine for the MCR performance to furnish 3-substituted quinazolin-4(3*H*)-ones **E** and 2,3-dihydroquinazolin-4(1*H*)-ones **F** under the same conditions. Fortunately, the desired product 3-*p*-tolylquinazolin-4(3*H*)-one was favourably generated in 78% yield (Table 3, Entry 1). Thereafter, 5 mol % of iodine was tested aiming at constructing the structure 3-*p*-tolylquinazolin-2,3-dihydroquinazolin-4(1*H*)-one **F** (Fig. 1), whereas the same product 3-*p*-tolylquinazolin-4(3*H*)-one was obtained again in a 99% LC yield (Table 3, Entry 2). After carefully literature search, it was found that all of the methods reported [9,10,21] starting from orthoester were apt to form quinazolin-4(3*H*)-ones, for this may be the potential hydrogen-acquiring ability of —OEt dissociated from orthoester. Further attempt to optimize the conditions suggested that increasing the amount of amine up to 1.5 equiv. and replace the EtOH with H_2O could improve the yield up to 89% and shorten the reaction time. As the pure product should be crystallized from EtOH, we chose EtOH as the solvent to exam other representative aromatic amine. As shown in Table 3, all of the substrates were compatible and the aromatic amine possessing electron-withdrawn group would lead to longer reaction time and slightly lower yield (Table 3, Entry 3).

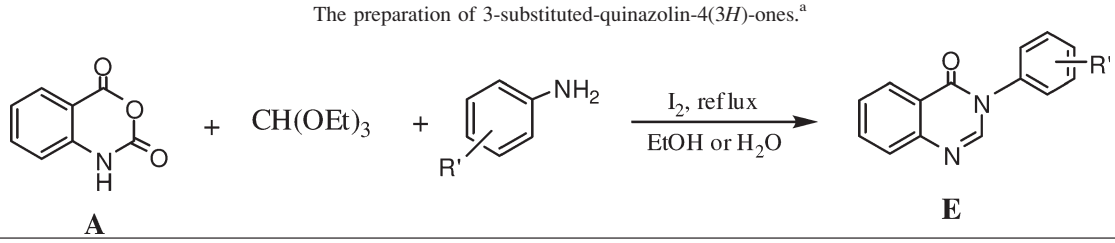
In conclusion, we have developed a novel and versatile method for the first time to selectively synthesize 2-substituted-quinazolin-4(3*H*)-ones and 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones from isatoic anhydride, primary amine and various aldehydes in one-pot MCR protocol via modulating the iodine concentration, and also prepared 3-substituted-quinazolin-4(3*H*)-ones under the same conditions in the presence of 5 mol % of iodine. All of the reactions provided good to excellent yields of products that could be crystallized from the reaction solution. The operational simplicity, conditional generality, electively controllability made this method attractive to extensive application in organic chemistry.

EXPERIMENTAL

The isatoic anhydride and iodine were obtained from commercial suppliers and used without further purification. All of the products are known and their physical data, mass data, and ^1H

Table 3

The preparation of 3-substituted-quinazolin-4(3*H*)-ones.[a]



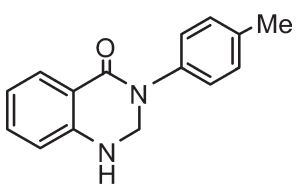
A **E**

Entry	R′	Solvent	I_2 (mol %)	*t* (min)	Yield (%)[b]
1	4-Me	EtOH	20	25	78
		EtOH	5	30	75
		EtOH	5	60	74[c]
		EtOH	5	25	88[d]
		H_2O	5	15	89
2	4-OMe	EtOH	5	25	93
3	4-Cl	EtOH	5	200	81
4	H	EtOH	5	55	84

[a] Reaction conditions: 1 equiv. of othoester(5 mmol) was added to the solution containing **A**(5 mmol), iodine, and aromatic amine at room temperature, which was then increased the to refluxing temperature.
[b] Isolated yield.
[c] 1 equiv. of *p*-toluidine was added.
[d] 1.5 equiv. of *p*-toluidine was added.

NMR were essentially identical with those of authentic samples. Mass spectra were taken on an Agilent LC-MS 1100 series instrument in the electrospray ionization (positive ESI) mode. ^{1}H NMR spectra were recorded at 300 MHz in DMSO-*d*6, and chemical shifts were reported in ppm from internal TMS (δ).

The typical procedure for the preparation of 2-substituted-quinazolin-4(3*H*)-ones M. 4-methoxylbenzaldehyde (0.68 g, 5 mmol), was added to the stirring solution containing **A**(0.815 g, 5 mmol), iodine(0.253 g, 1 mmol), and $AcONH_4$(0.462 g, 6 mmol) at room temperature in EtOH, then refluxing the mixture, after 25 min the white solid precipitated and EtOH was added till the solid dissolved again. The mixture was cooled to room temperature and the white flocs were crystallized slowly. After simple filtration and dryness, the product **M**1 was yielded in 86% (1.09 g, white flocs, m.p. 241°C). 2-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (Table 2, Entry 1): ^{1}H NMR(300 MHz, DMSO-*d*6) δ 3.81 (s, 3H), 7.04–7.07 (d, 2H), 7.42–7.47 (m, 1H), 7.65–7.68 (d, 1H), 7.76–7.78 (m, 1H), 8.08–8.11 (d, 1H), 8.14–8.17 (d, 2H), 12.53 (br s, NH); MS (ES^+) *m*/*z* 253(M + H); 2-(4-Chlorophenyl)quinazolin-4(3*H*)-one (Table 2, Entry 2): ^{1}H NMR(300 MHz, DMSO-*d*6) δ 7.52–7.57 (m, 1H), 7.62–7.65 (m, 2H), 7.74–7.76 (d, 1H), 7.83–7.88 (m, 1H), 8.15–8.22 (m, 3H), 12.83 (br s, NH); MS (ES^+) *m*/*z* 257(M + H).



F

Figure 1. The expected structure 3-*p*-tolylquinazolin-2,3-dihydroquinazolin-4(1*H*)-one **F**.

The 2-substituted-2,3-dihydroquinazolin-4(1*H*)-ones **N** were synthesized by a similar procedure except that 5 mol % of iodine(0.063 g, 0.25 mmol) was used. The products **N** were white flake. 2-(4-Methoxyphenyl)-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, Entry 12): ^{1}H NMR(300 MHz, DMSO-*d*6) δ 3.73 (s, 3H), 5.68 (s, 1H), 6.66–6.74 (m, 2H), 6.92 (d, 2H), 6.94 (s, NH), 7.23 (m, 1H), 7.39–7.41 (d, 2H), 7.58–7.60 (d, 1H), 8.21 (s, NH); MS (ES^+) *m*/*z* 255(M + H); 2-(4-Chlorophenyl)-2,3-dihydroquinazolin-4(1*H*)-one (Table 2, Entry 12): ^{1}H NMR(300 MHz, DMSO-*d*6) δ 5.78 (s, 1H), 6.69–6.77 (m, 2H), 7.16 (s, NH), 7.22–7.28 (m, 1H), 7.44–7.53 (m, 4H), 7.60–7.63 (m, 1H), 8.36 (s, NH); MS (ES^+) *m*/*z* 259(M + H).

The typical procedure for the preparation of 3-substituted-quinazolin-4(3*H*)-ones E. Orthoester (5 mmol) was injected slowly into the stirring solution of **A**(0.815 g, 5 mmol), iodine(0.063 g, 0.25 mmol) and *p*-toluidine (0.8 g, 7.5 mmol) in EtOH at room temperature, increasing the temperature and refluxing the mixture 25 min followed by adding hot ethanol to further dissolve the solid formed, the product **E** was precipitated from the homogeneous solution slowly with the temperature decreased. Simple filtration and dryness would afford the pure 3-*p*-tolylquinazolin-4(3*H*)-one (1.04 g, 88%, white solid, m.p. 146–148°C) (Table 3, Entry 1): ^{1}H NMR(300 MHz, DMSO-*d*6) δ 2.40 (s, 3H), 7.35–7.44 (m, 4H), 7.57–7.62 (m, 1H), 7.73–7.76 (d, 1H), 7.85–7.91 (m, 1H), 8.19–8.21 (d, 1H), 8.32 (s, 1H); MS (ES^+) *m*/*z* 237(M + H); 3-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (Table 3, Entry 2): ^{1}H NMR(300MHz, DMSO-*d*6) δ 3.83 (s, 3H), 7.09–7.12 (m, 2H), 7.45–7.48 (m, 2H), 7.57–7.62 (m, 1H), 7.73–7.75 (m, 1H), 7.85–7.91 (m, 1H), 8.18–8.21 (m, 1H), 8.31 (s, 1H); MS (ES^+) *m*/*z* 253(M + H).

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