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I_2-Catalyzed three-component protocol for the synthesis of quinazolines

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ABSTRACT

An efficient and one-pot three-component strategy for synthesizing highly functionalized quinazoline derivatives is presented. A mixture of 2-aminobenzophenone, aromatic aldehyde and ammonium acetate in the presence of I_2-catalyst provides desired products in excellent yields even at moderate temperature (40 °C) without the involvement of any chromatographic purification. Oxidizing and Lewis acidic properties of molecular I_2 have been utilized here. Detailed mechanism has been established based on an isolated intermediate and its single crystal X-ray crystallographic structure.

The development of a new synthetic methodology that provides an alternative to difficult synthetic protocol to an easier and greener strategy for the production of known complex as well as entirely new organic entity is a key topic of modern synthetic organic chemistry.[1] The creation of carbon-heteroatom (C–X where X=N, O, S etc.) bond is the central theme in heterocyclic chemistry.[2] One relatively modern approach for making organic synthesis more eco-friendly is the multicomponent strategy.[3] The beauty of the multicomponent synthesis has manifold: several transformations in a single manipulation, simple reaction design, high selectivity, convergent and atom-efficient nature and substantial minimization of waste, labour, time and cost.[4] Furthermore, solvent-free multicomponent reactions have greater interest in wide areas of organic chemistry due to the incorporation of eco-friendly green chemistry principles.[5]

Quinazoline is an important class of binuclear heterocyclic scaffold which is the building block for several naturally occurring alkaloids,[6] microorganisms[7] and in several life saving drugs such as gefitinib (Iressa)[10] and erlotinib (Tarceva).[8] Some modified quinazoline derivatives have shown to have remarkable anticancer,[9] antitubercular,[10] antibacterial[11] and antiviral activities.[12] A few of them are also known to act as selective inhibitors of the tyrosine-kinase activity of the epidermal growth factor receptor (EGFR)[13] and as RNA binding reagents. As the moiety is ubiquitous in modern drugs, the new methods and techniques for synthesizing are well sought.[14–19] Unfortunately, in most of these synthetic methods there involves the usage of hazardous, volatile solvents[14], toxic and expensive metal catalysts[15], cumbersome chromatographic separation procedures, high heating[16c] and multistep reaction process.[17] Zhang et.al.[18] have reported quinazoline synthesis with 2-aminobenzophenones and benzylic amines *via* SP^3 C-H activation where I_2 served as catalyst in presence of extra additive oxidant at a relatively high temperature (90 °C) and relatively longer reaction time (12 h). A catalyst and solvent-free microwave assisted improved reaction methodology is recently developed by Prajapati and co-workers for synthesizing dihydroquinazoline derivatives.[19] Though the method is novel and exemplary, it lacks selectivity towards quinazoline derivatives. We are intend to develop a superior, greener and general protocol to fabricate this biologically significant substituted quinazolines using molecular iodine as the catalyst.[20] Here, we report the development of one-pot three-component reaction for functionalized quinazoline derivatives via reactions with substituted *o*-aminoarylketone, substituted benzaldehyde and ammonium acetate catalyzed by I_2. This three-component reaction leads to an excellent yield in lesser time when carried out in neat or with ethanol even at moderate temperature. It was found that I_2 is the suitable catalyst counterpart in these reactions due to its Lewis acidity and oxidizing properties.

Initially, we have started following the normal procedure of multicomponent synthesis; 1 mmol of 2-aminobenzophenone (**1a**), 1 mmol of *o*-pyridinecarboxaldehyde (**2a**), 2.5 mmol of ammonium acetate (**3**) and 0.5 mmol of I_2 were taken in one-pot under solvent free condition and stirred at room temperature (~25 °C) for 8 h which yielded the quinazoline **4a** product

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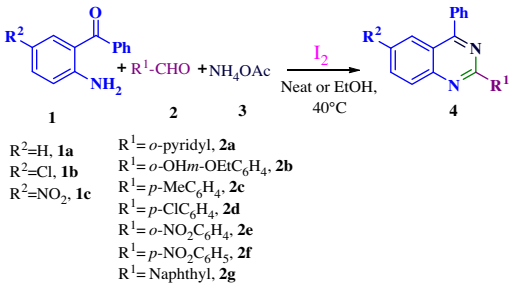


Scheme 1. Synthesis of quinazoline derivatives.

(82%).[21] Interestingly, when the reaction was performed at a slightly elevated temperature (40 °C) within 2.5 h complete conversion of starting material to desired product (>90% yield) was observed (Scheme 1).

For optimization of the reaction conditions like temperature, catalyst loading etc., several sets of reaction were performed varying one or more reaction parameters and the results are presented in Table 1.

From Table 1, it is evident that 5 mol % of molecular iodine in either neat or in ethanol solvent at moderate temperature (40 °C) provides an impressive yield of more than 95% pure isolated product. Similar observations in terms of yield, reaction time and temperature were obtained in ethanol and in solvent-free condition. As seen from the entry 6 and 7 of Table 1, in the absence of I_2, no reaction takes place, either in neat or with ethanol.

The generality of this reaction protocol has been examined by performing several reactions varying the starting materials and the results are presented in Table 2.

The effect of substituent on 2-aminobenzophenone and aldehyde derivatives on the yield and reaction time has also been studied (Table 2, entries 1–12, 18 and 13–17). In the presence of an electron withdrawing group at 5th position of 2-aminobenzophenone, the required reaction time was found to be more than that of electron donating groups (Table 2, entry 11–15). **+ I** or electron withdrawing effect at para position of aldehyde group (Table 2, entries 3, 4, 9, 12, 15) was found to be more pronounced than that of

Table 1
Optimization of the reaction conditions[a]

Entry	**3**	I_2 (mol %)	Temp (°C)	Solvent	Time (h)	Yield[b] (%)
1	NH_4OAc	5	25	Ethanol	8	82
2	NH_4OAc	5	40	Ethanol	2.5	95
3	NH_4OAc	5	40	Neat	2.5	96
4	NH_4OAc	10	40	Neat	2.5	96
5	NH_4OAc	15	40	Neat	2.5	95
6	NH_4OAc	0	40	Ethanol	12	—[c]
7	NH_4OAc	0	40	Neat	12	Trace

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol) and ammonium acetate (2.5 mmol) were heated and stirred with a catalytic amount of I_2 in ethanol or solvent-free condition.
[b] Isolated pure yield.
[c] No reaction.

Table 2
Synthesis of substituted quinazoline derivatives

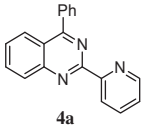
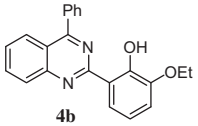
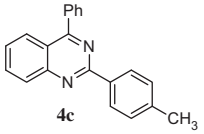
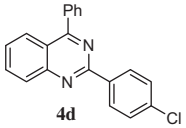
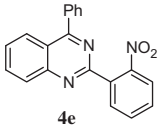
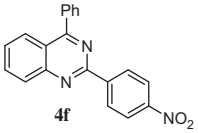
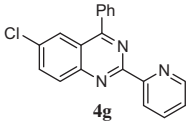
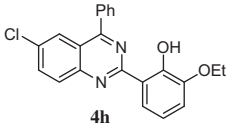
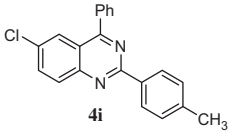
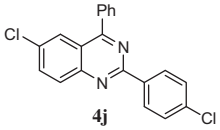
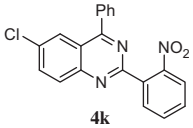
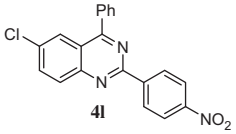
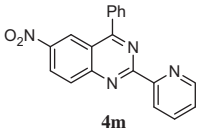
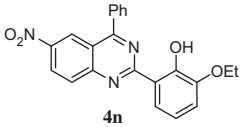
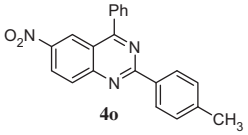
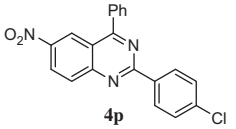
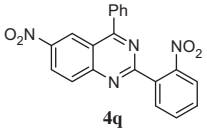
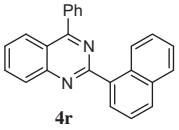
Entry	2-Aminobenzophenone	Aldehyde	Quinazoline	Time (h)	Yield (%)
1	**1a**	**2a**	 **4a**	2.5	95
2	**1a**	**2b**	 **4b**	2.5	96
3	**1a**	**2c**	 **4c**	0.5	96
4	**1a**	**2d**	 **4d**	2.5	95
5	**1a**	**2e**	 **4e**	2.5	92

Table 2 (*continued*)

Entry	2-Aminobenzophenone	Aldehyde	Quinazoline	Time (h)	Yield (%)
6	**1a**	**2f**	 **4f**	0.5	94
7	**1b**	**2a**	 **4g**	2.5	95
8	**1b**	**2b**	 **4h**	2.5	95
9	**1b**	**2c**	 **4i**	0.5	97
0	**1b**	**2d**	 **4j**	2.5	95
11	**1b**	**2e**	 **4k**	2.5	93
12	**1b**	**2f**	 **4l**	0.5	95
13	**1c**	**2a**	 **4m**	3.5	92
14	**1c**	**2b**	 **4n**	3.5	91
15	**1c**	**2c**	 **4o**	1.0	93
16	**1c**	**2d**	 **4p**	3.5	92
17	**1c**	**2e**	 **4q**	3.5	90
18	**1a**	**2g**	 **4r**	2.5	92

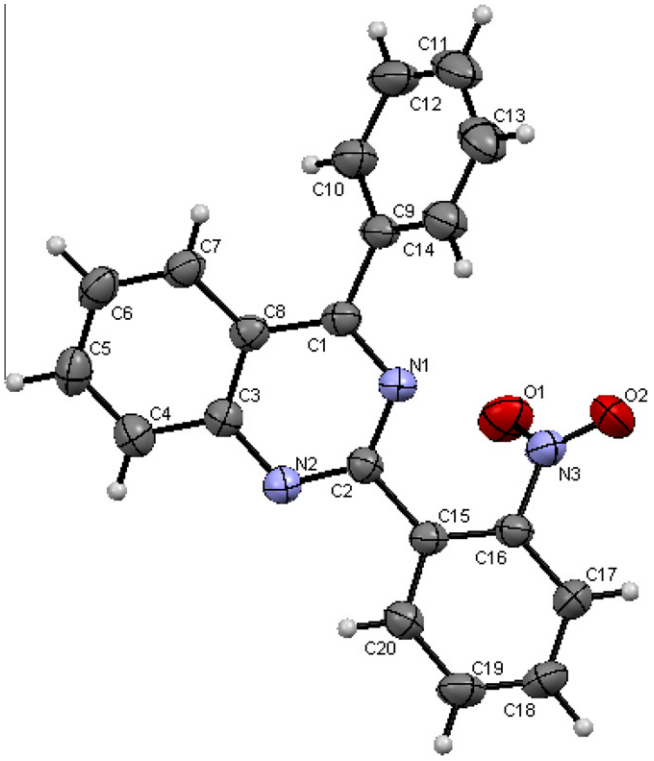
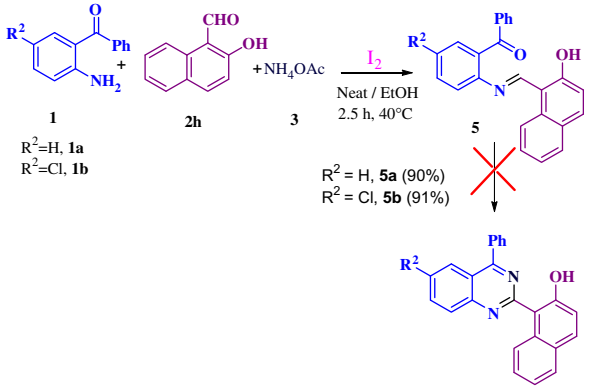


Figure 1. Ortep diagram of 2-(2-Nitro-phenyl)-4-phenyl-quinazoline (**4e**) (50% ellipsoid probability).



Scheme 2. Synthesis of quinazoline intermediate.

at ortho-position (Table 2, entries 5, 11, 17). The sensitivity of air towards product formation was found to be negligible because of the oxidizing properties of catalyst I_2 in contrast to reported procedures[16c,19,22] where the presence of aerial oxygen was found to be must for aromatization.

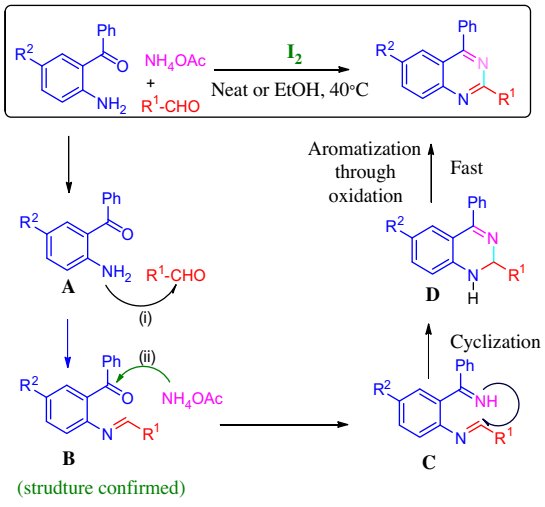
It is important to note that in none of the reactions, column purification was necessary. A few simple steps like evaporation of solvent from the reaction mixture (if ethanol was used), washing several times with water, followed by ethanol provided the desired products in pure form. The yields were more than 90% as can be seen in Table 2.

The confirmations of products were primarily done by the detail analysis of ^{1}H, ^{13}C NMR, FT-IR and ESI-MS (vide Supplementary data). In a fortunate case like **4e**, where suitable single crystal could be obtained, the structure was additionally confirmed by the single crystal X-ray diffraction data (Fig. 1).[23] Interestingly, it was found that while naphthyl derivative (entry 18, Table 2) could be obtained as expected, the presence of *o*-hydroxy group in naphthaldehyde moiety (Scheme 2) did not allow the reaction to proceed further to get the desired final product. Instead, the reaction provides an aldimine intermediate which helped us to formulate a mechanism for these useful three-component one-pot reaction. Scheme 2 reveals that the presence of hydroxy group on 2-hydroxynaphthaldehyde prevents the second step of the reaction (i.e., cyclization). Analysis of single crystal X-ray structure of **5a** (Fig. 2) provides the clue for this interesting fact. It was found that the *o*-hydroxy group attached to naphthyl moiety is H-bonded to the imine group.

This H-bonding interaction which provides stability to the intermediate (**5a**), along with unfavourable orientation of naphthyl moiety prevents the cyclization process, thereby terminating the progress of the reaction (step 2 of Scheme 2). This three-component reaction (Scheme 2) strongly suggests that the reaction proceeds through the intermediate **5a**. It clearly indicates that the first step of these multicomponent reactions is the condensation of aldehyde with the 2-aminobenzophenone substrate, unlikely the attack of ammonium acetate as presumed in literatures.[16a,19] Prajapati and co-wokers[19] have identified one of the intermediates, **D** (in Scheme 3) as major product, which is formed from **C** on cyclization. According to their proposed mechanism[16,19] **C** can be formed in two ways in which the preferred first step was assumed to be the attack of NH_4OAc to the keto group of benzophenone moiety.

With the synthesis and structural identification of **5a**, we have unambiguously established that the condensation of aldehyde with amine forming the **B** intermediate (in Scheme 3) is the first step. Based on our investigation, we have proposed a mechanism which is depicted in Scheme 3. The product **5a** also indicates that the formation of aldimine (**B**) is kinetically more favourable than that of ketimine (**C**).

In conclusion, a new synthetic protocol has been described for the synthesis of quinazoline derivatives. Molecular iodine is used as the catalyst and oxidant for the three-component synthesis of a highly substituted quinazoline. This procedure is found to be much superior in terms of simplicity, high yield and non involvement of chromatographic separation technique compared to previously reported methods. The mechanistic aspects have been investigated and a modified mechanism is proposed. The first step of the reaction is found to be the condensation of aldehyde with aminobenzophenone moiety forming the aldimine.



Scheme 3. Proposed mechanism for quinazoline synthesis.

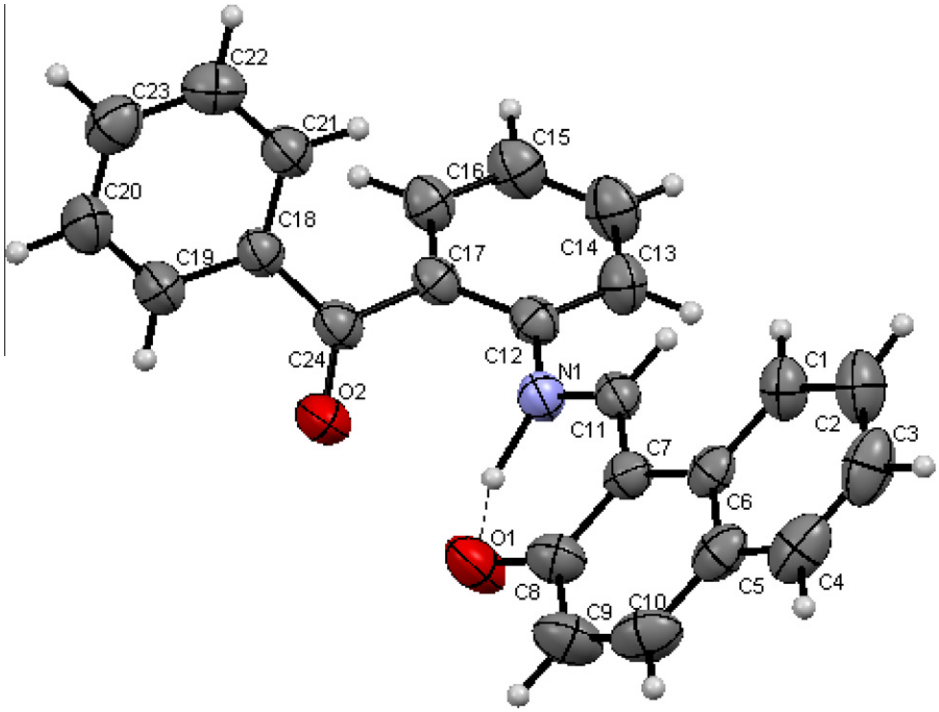


Figure 2. Ortep diagram of the intermediate product, **5a** (50% ellipsoid probability).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.016.

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21. General procedure for the synthesis of quinazoline derivatives: 2-aminobenzophenone (**1**, 1 mmol), an aromatic aldehyde (**2**, 1 mmol), ammonium acetate (**3**, 2.5 mmol) and iodine (0.05 mmol) were taken in a round bottom flask and heated in an oil bath at 40 °C for stipulated period of time (Table 2). After completion of the reaction, crude reaction mixture was washed with water (3 × 10 mL) followed by ethanol (3 × 10 mL) and dried in high vacuum to afford pure product. All the products were confirmed by ^{1}H, ^{13}C NMR, IR and MS (see Supplementary data).
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23. CCDC No. 876278 for compound **4e** and CCDC No. 884436 for compound **5a**.