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A convenient access to 2,4-disubstituted quinazolines *via* one-pot three-component reaction under mild conditions†

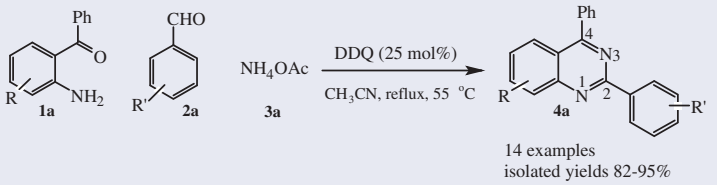
D. Subhas Bose* and Nukala Ramesh

Organic and Biomolecular Chemistry Division, Department of Energy and Environmental Engineering, Fine Chemicals Lab, CSIR-Indian Institute of Chemical Technology, Hyderabad, India

ABSTRACT

A new and practical method has been developed for the synthesis of 2,4-disubstituted quinolines via one-pot three-component reaction of *o*-amino arylketones, aldehydes and ammonium acetate in high yields by using DDQ in CH_3CN under mild conditions. Neutral conditions, atom economy, easy work-up procedures and compatible with different functional groups are the salient features of this protocol.

GRAPHICAL ABSTRACT



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KEYWORDS
o-Aminobenzophenone; aromatic aldehydes; ammonium acetate; DDQ; one-pot; multicomponent reaction

Introduction

Over the past decade, the importance of heterocycles in biological systems has stimulated interest in designing of new drug scaffolds via iterative manipulation of functional groups around the basic skeletal systems. Among the nitrogen heterocycles, quinazoline ring system, in particular, constitute a privileged structural motif widely found in a variety of pharmacologically significant compounds, bioactive natural products,[1] microorganisms[2] functional materials,[3] and in particular life saving drugs such as erlotinib (Tarceva),[4] gefitinib (Iressa)[5] and linagliptin (Tradjenta)[6] (Figure 1). Some of the modified quinazoline derivatives possess potent antiviral,[7] antibacterial,[8] anticancer[9] and antitubercular activities.[5] In addition, quinazoline derivatives have also known to act as selective inhibitors of the tyrosine-kinase activity of the epidermal growth factor (EGF) receptor,[10] ligands for γ-aminobutyric acid (GABA),[11] benzodiazepine receptors[12] in the central nervous system (CNS), CCR4 antagonists[13] or as DNA binders.[14]

CONTACT D. Subhas Bose boseiict@gmail.com Organic and Biomolecular Chemistry Division, Department of Energy and Environmental Engineering, Fine Chemicals Lab, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India.

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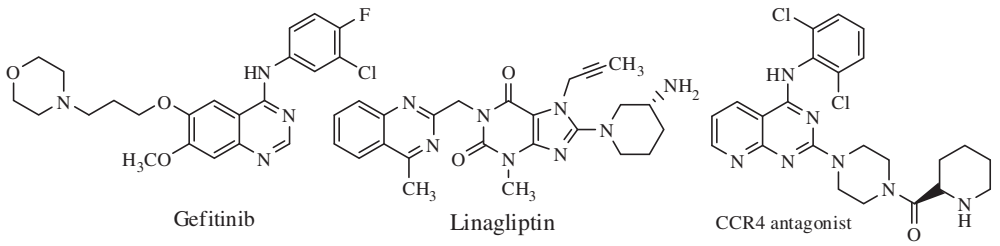
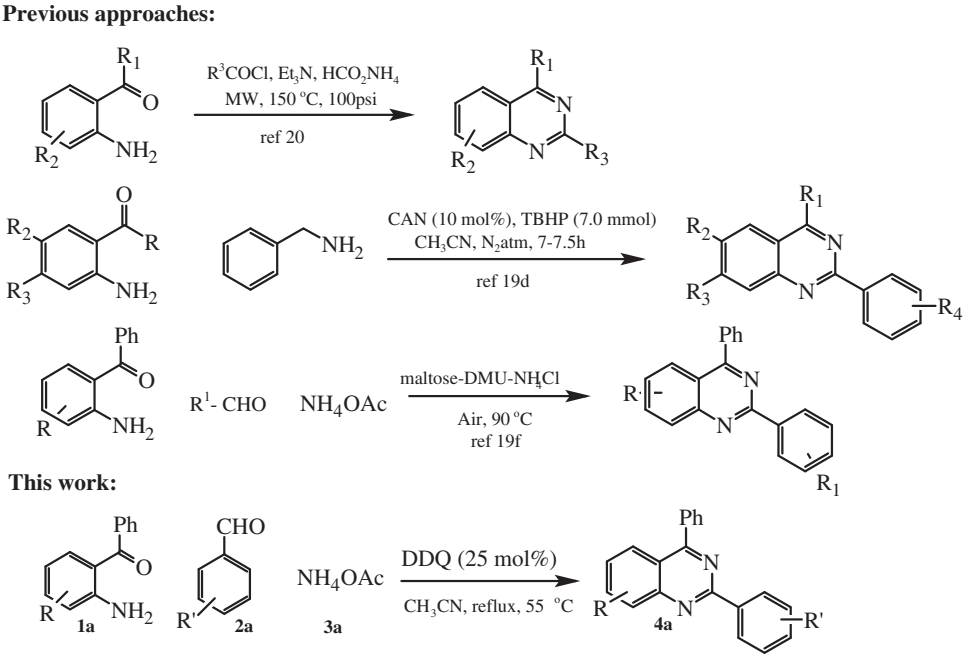


Figure 1. Structures of some pharmacologically important quinazolines.

Results and discussion

In view of the considerable interest of this class of heterocyclic compounds, an effort has been drawn to develop new and efficient synthetic methods to substituted quinazolines in both synthetic organic and medicinal chemistry. *o*-nitrobenzoic acids, anthranilic acids, *o*-halophenyl precursors, *o*-aminobenzonitriles as well as *N*-arylbenzamides are the most commonly used starting materials among those protocols.[15] These methods, however, suffer from limitations such as less availability of these starting materials. The Bischler cyclization is a venerable reaction, it is one of the most simple, and straightforward methods used to produce quinazolines. Classically, the process involves cyclization of an amide derived from 2-aminophenone in the presence of ammonia at high temperature,[16] Niementowski quinazoline reaction,[17] and the reaction of diamines with dicarbonyl compounds.[15] Moreover, synthesis of 2,4-disubstituted quinazolines have been investigated starting from substituted anthranilic acids or *o*-fluorobenzoyl derivatives.[18] However, all of these approaches suffer from one or the other drawbacks such as availability of starting materials, toxic and expensive metal catalysts, harsh reaction conditions, hazardous, volatile solvents, tedious work-up procedures, multistep sequence, which has limited the applicability of these methods in high throughput synthesis[19] Taddei et al[20] have reported 2,4-disubstituted quinazolines synthesis starting from anilides under microwave conditions heating at 100 °C for 3-6 min at 150 psi, which has limited substrate scope with few examples. Wang et al have reported[21] quinazoline synthesis from (i) *o*-aminocarbonyl compounds and benzyl amines using CuO nanoparticles supported on kaolin (ii) I_2/TBHP catalytic system at 90 °C for 12 h.[22] Prajapati and coworkers reported a quinazoline synthesis using urea/NH_4OAc as nitrogen source under microwave conditions.[23] Evenhough this method is novel and it lacks selectivity toward quinazoline derivatives. Therefore, a new alternative protocol needs to be explored having significant practical value for the synthesis of 2,4-disubstituted quinazolines. In order to overcome these limitations, herein, we report a new, practical route for the synthesis of substituted quinazolines via one-pot three-component reaction of *o*-amino arylketones, aldehydes and ammonium acetate in high yields by using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in CH_3CN under mild conditions in the absence of ligands or additives (Scheme 1). Recently, DDQ has emerged as a powerful oxidizing agent to accomplish various organic transformations[24] including the cleavage of linker molecules from solid supports, the introduction of unsaturation, deprotection of functional groups, and potential applications for the formation of carbon–carbon and carbon–heteroatom bonds.

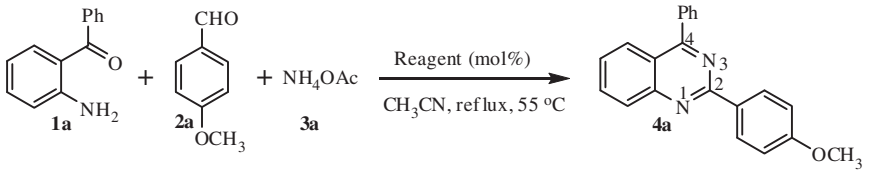


Scheme 1. Various reported strategies for the synthesis of 2,4-disubstituted quinazolines.

We embarked upon our study by examining the conditions for the one-pot three component condensation reaction was performed by the treatment of *o*-amino benzophenone (**1a**), aldehyde (**2a**) with ammonium acetate in the presence of a catalytic amount of DDQ (25 mol%) leads to the formation of 2-(4-methoxyphenyl)−4-phenylquinazoline (**4a**). We first examined the reaction in different solvents including EDC, CH_3CN, THF, CH_3NO_2, H_2O and solvent-free conditions under mild refluxing conditions. It is remarkable to note that the reaction proceeds efficiently in high yields at 55 °C in CH_3CN with low catalyst concentration (25 mol%) in 95% yield after stirring for 5 h (Table 1, entry 8). The role of DDQ catalyst was confirmed when the model reaction between *o*-aminobenzophenone (**1a**), *p*-methoxybenzaldehyde (**2a**), ammonium acetate (**3a**) was carried out in the absence of catalyst; no product was obtained under solvent-free conditions even with a long reaction time. As seen from the entries 5 and 6 of Table 1, among the N source, NH_4Cl was found to be the suitable for this reaction. To our knowledge, DDQ catalyst has not yet been exploited for the synthesis of substituted quinazolines.

To demonstrate the versatility of this protocol, we next investigated the scope of this reaction under the optimized conditions and the results are presented in Table 2. Similarly, a variety of substituted aldehydes possessing electron-donating and electron-withdrawing functional groups, aliphatic aldehydes reacted with *o*-aminoaryl ketones to afford the corresponding 2,4-disubstituted quinazolines **4a–4n** in 65–95% yield without any side products. In order to improve the yields, we have carried out reactions using different quantities of reagents. The optimum results were obtained with a 1:1:0.25 ratio of *o*-aminoaryl ketone, aldehyde, and DDQ respectively. Higher amounts of catalyst did not improve the result to a greater extent (Table 1, entry 14).

Table 1. Optimization of the reaction conditions.[a]



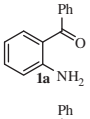
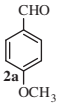
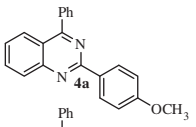
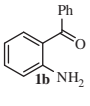
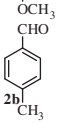
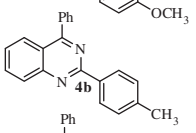
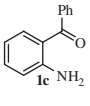
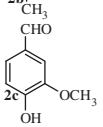
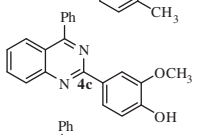
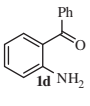
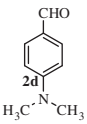
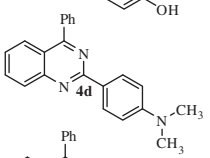
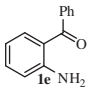
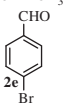
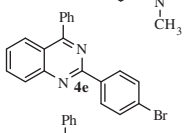
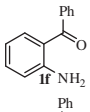
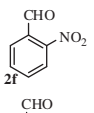
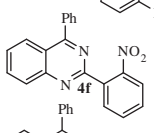
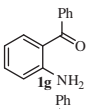
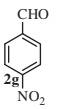
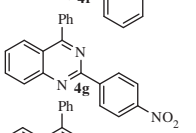
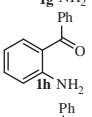
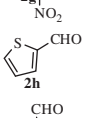
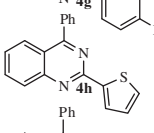
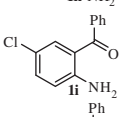
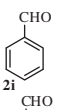
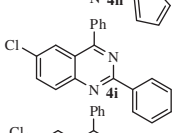
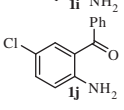
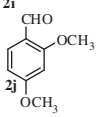
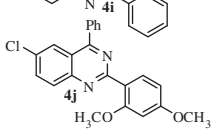
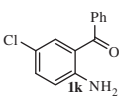
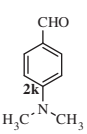
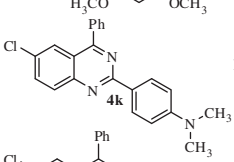
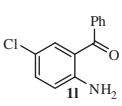
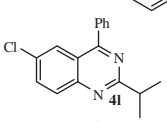
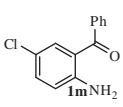
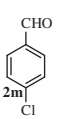
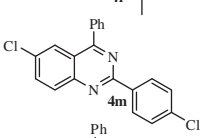
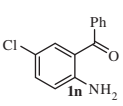
Entry	Reagent (mol %)	N source	Solvent	Time (h)	Yield (%)[b]
1	BQ (25)	NH_4Cl	$ClCH_2CH_2Cl$	8	—[c]
2	BQ (50)	NH_4OAc	CH_3CN	12	Trace
3	Chloranil (25)	NH_4Cl	$ClCH_2CH_2Cl$	8	15
4	Chloranil (50)	NH_4OAc	CH_3CN	12	25
5	DDQ (10)	NH_4Cl	$ClCH_2CH_2Cl$	10	20
6	DDQ (10)	NH_4OAc	CH_3CN	5	45
7	DDQ (25)	NH_4OAC	$ClCH_2CH_2Cl$	5	89
8	DDQ (25)	NH_4OAc	CH_3CN	5	95[d]
9	DDQ (25)	NH_4OAc	CH_3NO_2	5	90
10	DDQ (25)	NH_4OAc	THF	5	74
11	DDQ (25)	aq NH_3	CH_3CN	10	42
12	DDQ (25)	NH_4OAc	H_2O	10	37
13	DDQ (25)	NH_4OAc	solvent-free	20	41
14	DDQ (50)	NH_4OAc	CH_3CN	5	93
15	—	NH_4OAc	solvent-free	>24	no reaction[e]

[a]Reaction conditions: *o*-aminoarylketone (**1a**, 10 mmol), aldehyde (**2a**, 10 mmol), N source (2.5mmol), BQ = 1,4-benzoquinone, Chloranil (tetrachloro 1,4-benzoquinone, DDQ (25 mol %). [b]Isolated and unoptimized yields. [c]No reaction. [d]Optimum reaction conditions. [e]Recovered sarting materials.

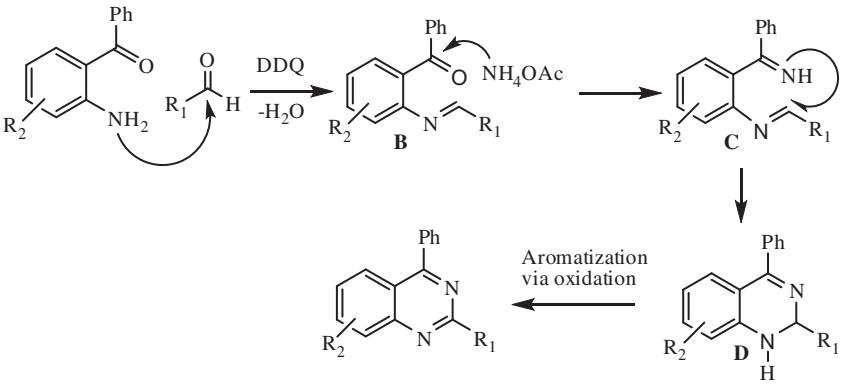
Interestingly, when aldehyde with an electron-donating group, such as 2-hydroxybenzaldehyde, was used as substrate, the corresponding product failed to generate, even after prolonged reaction time. This may be due to the hydrogen bonding interaction to the aldimine group which provides stability via chelation to the intermediate (**B**) in Scheme 2, and orientation of phenyl ring prevents cyclization process. In addition, an analogous quinine oxidants 1,4-benzoquinone (BQ), and chloranil was studied for this three component reaction. The results indicate that the reaction was relatively sluggish, and the yields were very poor. Obviously, these reagents are not efficient as DDQ for this condensation reaction (Table 1, entries 1–4). After the reaction was complete as monitored by TLC, the product was isolated by simple filtration. In the absence of catalyst, the reaction did not yield any product even after longer reaction times (>24 h, Table 1, entry 15). All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy and also by comparison with authentic samples. In general, the reaction is very clean, involves a simple work-up procedure[19,20] and free from side reactions such as self-condensation of carbonyl compounds which normally take place under basic conditions. Unlike previous reports, the current protocol does not require high temperatures, use of strong acids or bases or the use of toxic solvents to produce quinazoline derivatives.

Based on our observations and the literature precedents, a proposed mechanistic pathway for the quinazoline synthesis is illustrated in Scheme 2. First, the aniline

Table 2. DDQ-catalyzed synthesisof 2,4-disubstituted quinazolines under mild conditions.[a]

Entry	*o*-Aminobenzophenone (**1**)	Aldehyde (**2**)	Time (h)	Quinazoline (**4**)	m.p. °C(lit)	Yield (%)[b]
1.			5		157-159(159-162)[19d]	95
2.			5		165-168(167-170)[19d]	91
3.			8		173-175	93
4.			8		133-136	82
5.			5		141-143(140-145)[19d]	85
6.			8		157-160(159-161)[19d]	89
7.			5		193-195(195)[25]	91
8.			5		144-146(146-147)[19f]	93
9.			8		184-186(185)[19b]	87
10.			5		114-116	92
11.			8		158-160(159-161)[26]	86
12.			10		89-90	65
13.			8		187-190(185-187)[19d]	88
14.			8		127-130(128)[19d]	82

[a]Reaction conditions: o-aminoarylketone (1a, 10 mmol), aldehyde (2a, 10 mmol), N source (2.5 mmol), BQ = 1,4-benzoquinone, Chloranil (tetrachloro 1,4-benzoquinone, DDQ (25 mol %). [b]Isolated and unoptimized yields. [c]No reaction. [d]Optimum reaction conditions. [e]Recovered sarting materials.



Scheme 2. A Plausible reaction mechanism for the synthesis of quinazolines.

reacted with a carbonyl species of aldehyde, yielding an Schiff's base intermediate (**B**), which underwent cyclization (**C**) followed by DDQ mediated aromatization via oxidation to obtain the quinazoline. Here, the rate-limiting step is the formation of the aldimine intermediate (**B**) is kinetically more favorable than the ketimine (**C**).

In summary, we have developed a DDQ-catalyzed one-pot, three-component synthesis of a highly substituted quinazolines starting from readily available *o*-aminoarylketones, aldehydes and nitrogen source NH_4OAc in high yields. This method offers a high degree of flexibility to the functional groups that can be incorporated on various positions of the quinazolne moiety, which in turn generates scaffolds for hit discovery. It is a valuable addition to the existing protocols available for the synthesis of substituted quinazolines.

Experimental

Reagents and chemicals were obtained from commercial sources and used as received without further purification. Melting points were determined in open capillaries with a precision digital melting point Veego VMP-DS apparatus and are uncorrected. IR spectra were recorded on a thermo Nicolet Nexus 670 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance 300 (300.132 MHz for ^{1}H, 75.473 for ^{13}C) or Varian FT-200MHz (Gemini) spectrometer in $CDCl_3$. The chemicals shifts (δ) and coupling constants (J) quoted in Hz are reported in parts per million (ppm) relative to tetramethylsilane (TMS; $\delta = 0.00$ ppm) (for ^{1}H) as an internal standard. The resonances of residual proton and those of carbons in deuterated solvents $CDCl_3$ ($\delta_H = 7.26$ ppm, $\delta_c = 77.0$ ppm), DMSO-d_6 ($\delta_H = 2.50$ ppm, $\delta_c = 39.52$ ppm) were used as internal standards. Elemental analyses were performed on a Elementar Vario EL microanalyzer. Low-resolution mass spectra (ESI-MS) and HRMS were recorded on Quattro LC, Micromass, and Q STAR XL, Applied Biosystems respectively. Column chromatography was performed using silica gel (Acme's 60–120 mesh). Solvents for chromatography (*n*-hexane, acetonitrile, cyclohexane, EtOAc) were distilled prior to use. For analytical TLC, Merck pre-coated silica gel 60 F-254 plates were used; the plates were visualized using UV light (254 nm) or iodine vapor or by dipping the plates in

phosphomolybdic acid ceric(IV)sulphate-sulphuric acid (PMA) solution and heating the plates at 100 °C.

2-(4-Methoxyphenyl)-4-phenylquinazoline (4a) (typical procedure)

A solution of *o*-aminobenzophenone (**1a**, 10 mmol), *p*-methoxybenzaldehyde (**2a**, 10 mmol), and ammonium acetate (**3**, 25 mmol) in CH_3CN (5 mL) was heated under reflux in the presence of DDQ (0.25 mmol) for 5 h until starting material could no longer be detected by TLC (Petroleum ether:EtOAc, 9:1). After completion of the reaction, the reaction mixture was extracted with ethyl acetate (30 mL) and washed with water (15 mL), saturated brine solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the pure product **4a** as a brown solid (2.97 g, 95%). *Rf* (Petroleum ether/EtOAc 9:1 v/v): 0.85. mp 157–159 °C (lit.[17i] mp 159–162 °C); IR (KBr): 3062, 2924, 2852, 1604, 1536, 1451, 1249, 1219, 1021, 772, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ: 3.89 (s, 3H, OCH_3), 7.05 (d, $J = 8.5$, Hz, 2H), 7.55 (t, $J = 7.5$ Hz, 1H), 7.59–7.62 (m, 3H), 7.83–7.91 (m, 3H), 8.12 (t, $J = 8.0$ Hz, 2H), 8.66 (d, $J = 8.5$, Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$) δ: 55.3, 113.8, 121.3, 126.5, 126.9, 128.4, 128.8, 129.8, 130.1, 130.2, 130.8, 133.4, 137.7, 152.0, 159.9, 161.7, 168.0 ppm; $[ESI]^+$: $[M+H]^+$ HRMS Calcd: For C_{21} H_{16} N_2 O 313.1336, Found: 313.1339. $C_{21}H_{16}N_2O$.; Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75, H, 5.16; N, 8.97. Found: C, 80.57; H, 5.22; N, 9.05.

Supplemental data associated with this article (Full experimental details and characteristics for all new compounds and copies of ^1H NMR, ^{13}C NMR, and Mass spectral data) can be accessed on the publisher's website.

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