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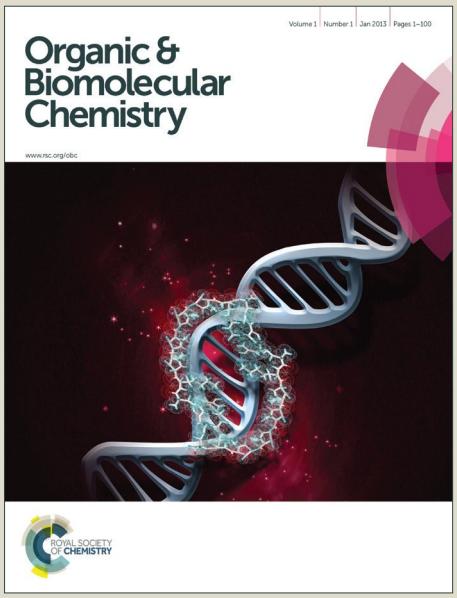

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Synthesis of Quinazolines from 2-aminobenzylamines with Benzylamines and *N*-substituted Benzylamines under Transition Metal - Free Conditions

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Abhishek R. Tiwari and Bhalchandra M. Bhanage*

This work reports the synthesis of quinazolines from 2-aminobenzylamines with *N*-substituted benzylamines in the presence of molecular iodine. The developed methodology works smoothly under transition-metal free, additive free and solvent free condition. The use of O_2 as a green oxidant makes it a greatly economical, green and sustainable protocol. Moreover, no aqueous work up is required thereby enhancing the efficiency. A series of quinazoline derivatives were synthesized successfully in good to excellent yields.

Ever since the introduction of the concept of green chemistry, efforts have been made by chemists to reduce pollutants at their source during the design of a chemical product or process.[1] From the Green and Sustainable Chemistry aspect, an ideal reaction would be the one which incorporates all the starting materials thereby producing minimum waste. Secondly, a reaction should be carried out using green reaction media such as water, glycerol and polythene glycol etc. Nothing could be more ambitious than carrying out a reaction under solvent free conditions. Oxidation reactions are one of the most important reactions in organic synthesis.[2] Molecular Oxygen is the most abundant and green oxidant that could be used in oxidation reactions as it produces only water as a by-product. Over the past decades, the metal-free approach has been of a great interest to researchers.[3] Although, the use of transition metals in catalytic amount is referred to as a greener approach, however, organic reactions which do not involve the use of metals are considered more sustainable as these reactions not only reduce the cost of those processes, but also make processes environmentally benign by avoiding the use of toxic metals.

Quinazolines are important building blocks of many natural products and synthetic pharmaceutical compounds as they are known to have various biological activities.[4] Various synthetic methodologies have been developed for the preparation of quinazolines. The synthetic methodologies are (i) combination of 2-aminobenzaldehydes with benzylamines or ammonia and various carbon sources in the presence of catalyst,[5] (ii) reaction of oximes with benzaldehydes using zinc metal as a suitable catalyst under microwave reaction conditions,[6] (iii) tandem cyclization of 2-halobenzaldehydes, 2-halobenzylamines and 2-halobenzylhalides with amidines; in case of 2-halobenzaldehydes along with catalyst ligand is needed,[7] (iv) intermolecular oxidative cyclization of *N*-arylated amidines with hypervalent iodine-substituted alkynes and benzaldehydes or benzylalcohols[8] and (v) intramolecular oxidative cyclization of *N*-arylated amidines.[9] Even though, these methodologies have made great contributions in the preparation of quinzolines, but they have some limitations as well. Apart from the use of transition metal as a catalyst these protocols are limited by excess or equivalent use of oxidants, toxic solvents, aqueous work up and high temperature for long duration. Alternate protocols for the synthesis of quinazolines from 2-aminobenzylamines with benzaldehydes or benzylalcohols are also known.[10-14] The coupling of 2-aminobenzylamines with benzaldehydes has been carried out in the presence of (i) four equivalents of oxidant NaOCl in MeOH solvent for longer reaction durations,[10] (ii) bi-metallic Pt/Ir alloyed nanoclusters as a catalyst, 5,5',6,6'-tetrahydroxy-3,3,3',3'-tetramethyl-1,1'-spiro-bisindane, (TTSBI) as a co-catalyst and K_2CO_3 as a base in $CDCl_3/H_2O$ solvent for longer reaction duration,[11] (iii) Cu/N-ligand/TEMPO/O_2 catalytic system in CH_3CN solvent,[12] (iv) $[Cp^*IrCl_2]_2$ as a catalyst, four equivalents of styrene in xylene solvent under N_2 and reflux condition for 24 h.[13] The same optimized reaction of last example has been employed for the synthesis of quinazolines from benzylalcohol additionally with KOH as a base. Quinazolines synthesis has also been achieved from 2-aminobenzylamine with benzylalcohols in the presence of MnO_2 as a catalyst and TBHP as an oxidant at 80 °C for 16 h.[14] Another alternative protocols for the synthesis of quinazolines have been reported with imines in the presence of $K_2S_2O_8$ as an oxidant in CH_3CN solvent at 90 °C for 6 h.[15] Despite, the

[a] *Department of Chemistry, Institute of Chemical Technology (ICT), Mumbai, India*
Email ID: bm.bhanage@gmail.com; bm.bhanage@ictmumbai.edu.in;
Fax: +91 2233611020; Tel: +91 2233612601

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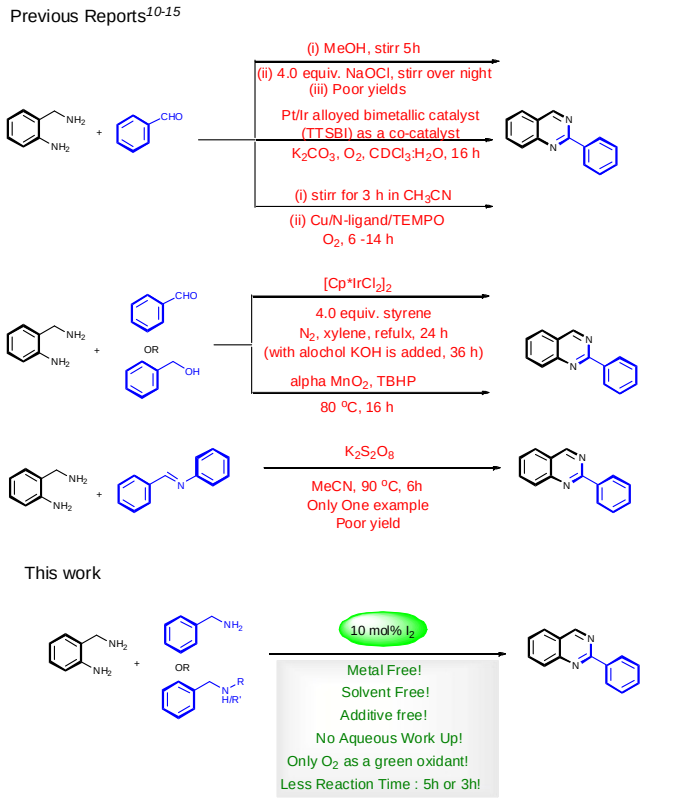
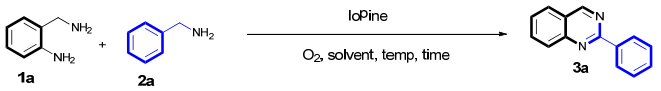


Scheme 1. Synthesis of quinazolines

efficiency of these protocols, they also suffer from some disadvantages such as the use of expensive metal as a catalyst along with co-catalyst or ligand, the need of a base, use toxic oxidant NaOCl. Moreover, since the synthesis of quinazolines forms part of the fine chemical and pharmaceutical industry, it would be of great value if one can avoid the use of transition metal. In addition, these protocols are also limited by the use of toxic solvent under reflux condition for long reaction time.

The investigation was initiated by choosing the 2-amiobenzylamine (**1a**, 1.0 mmol) and benzylamines (**2a**, 2.0 mmol) as starting substrates and the results are summarized in table 1. At first the reaction was performed in PEG-400 at 100 ^{0}C for 12 h in the presence of oxygen. To our delight there was a formation of expected product 2-phenylquinazoline (**3a**) in a significant amount (Table 1, entry 1). Surprisingly, addition of 15 mol% of molecular iodine led to a considerable increase in the yield of **3a** (Table 1, entry 2). However, the desired product **3a** was obtained in poor yield when reaction was performed in the absence of oxygen (Table 1, entry 3). This indicated that oxygen is necessary for this organic transformation. With this in mind, the next reaction was performed under oxygen balloon, as expected the yield of the desired product increased significantly and furnished 68% yield of **3a** (Table 1, entry 4). When the reaction was performed in the presence of PEG-400 and DMSO in a ratio of 1:1, no considerable increase in the yield of the product **3a** was noted (Table 1, entry 5). Surprisingly, a remarkable increase in the yield of **3a** (up to 86%) was found when the reaction was performed in the absence of solvent (Table 1, entry 6). Next, the reaction was performed at different intervals of time and it was found that

Table 1. Optimization of reaction condition



Entry	I_2 (mol%)	Solvent	Temp (^{o}C)	Time (h)	Yield[b] (%)
1	-	PEG-400	100	12	40
2	15	PEG-400	100	12	55
3	15	PEG-400	100	12	32[c]
4	15	PEG-400	100	12	68
5	15	PEG-400: DMSO (1:1)	100	12	69
6	15	-	100	12	86
7	15	-	100	8	86
8	15	-	100	4,5,6	80,84,84
9	15	-	90	5	84
10	15	-	80	5	83
11	15	-	70,130	5,2	71,85
12	10,5	-	80	5	83,63

[a] Reaction condition: 2-aminobenzylamine (**1**, 0.5 mmol), benzylamine (**2**, 2.0 mmol) and solvent (2.0 mL). [b] GC Yield. [c] Reaction was performed in the absence of oxygen.

the minimum time required to complete this reaction is 5 h (Table 1, entries 7 and 8). Decreasing the reaction duration to less than 5 h led to a decrease in the yield of **3a** (Table 1, entry 8). The temperature study revealed that the reaction temperature could be reduced to 80 ^{o}C (Table 1, entries 9-11). A further decrease in the reaction temperature decreases the yield of **3a**. An attempt was also made to check whether the reaction time could be reduced with the application of higher temperature. Interestingly, 85% yield of the desired product **3a** was obtained in just 2 h (Table 1, entry 11). In the next set of experiments, the concentrations of iodine were examined. It was observed that a minimum 10 mol% of iodine is necessary to accomplish this organic transformation successfully (Table 1, entry 12). Thus, the optimized reaction conditions are: 2-aminobenzylamine (**1a**, 0.5 mmol), benzylamine (**2a**, 2.0 mmol), I_2 (10 mol%) at 80 ^{o}C for 5 h under O_2 balloon.

Having established the optimized reaction conditions, we attempted to synthesise various derivatives of quinazolines using different 2-aminobenzylamines (**1**) and benzylamines (**2**). At first, 2-aminobenzylamines (**1**) were made to react with different benzylamines (**2**) and the obtained results are summarized in table 2. The reaction of 2-aminobenzylamine (**1a**) with benzylamines (**2a**) gave the desired product **3a** in 83% yield (Table 2, entry 1). In the next set of experiments, the effect of electron donating substituents such as –Me and –OMe on the benzylamine were explored (Table 2, entries 2-4). The *p*-methylbenzylamine (**2b**) furnished the product **3b** in

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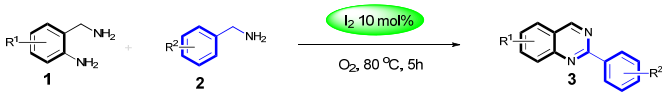
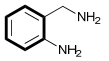
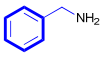
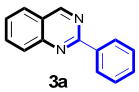
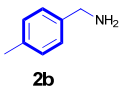
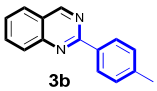
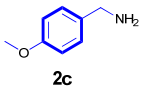
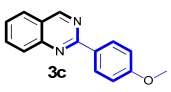
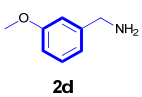
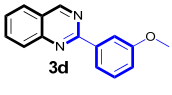
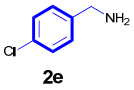
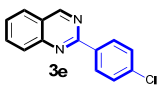
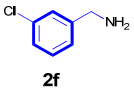
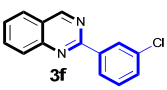
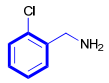
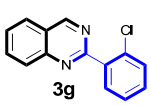
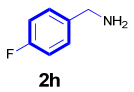
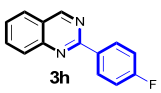
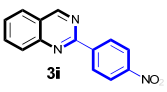
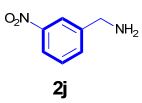
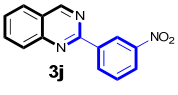
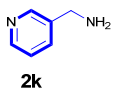
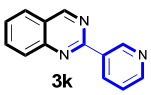
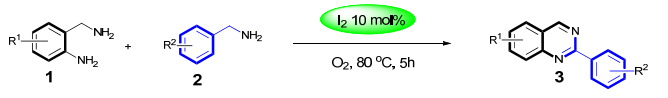
Table 2 Reaction of 2-aminobenzylamines with benzylamines



Entry	1	2	Products (3)	Yield[b] (%)
1	 1a	 2a	 3a	83
2	1a	 2b	 3b	82
3	1a	 2c	 3c	90
4	1a	 2d	 3d	91[c]
5	1a	 2e	 3e	80
6	1a	 2f	 3f	79
7	1a	 2g	 3g	56
8	1a	 2h	 3h	77
9	1a	 2i	 3i	71
10	1a	 2j	 3j	72
11	1a	 2k	 3k	87

[a] Reaction condition: 2-aminobenzylamine (**1**, 0.5 mmol), benzylamines (**2**, 2.0 mmol). [b] Isolated Yield. [c] Reaction was performed at 130 °C for 2 h.

Table 2 (*Contd.*)



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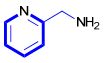
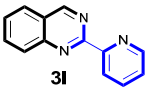
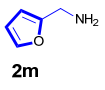
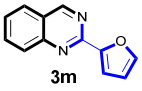
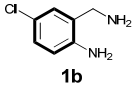
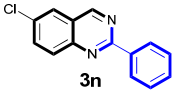
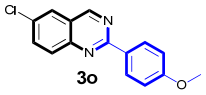
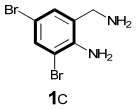
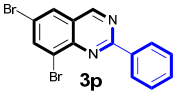
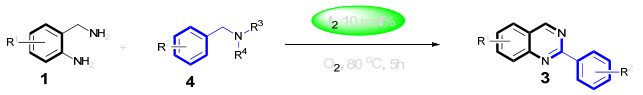
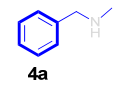
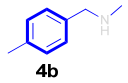
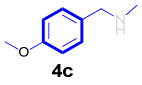
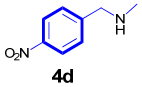
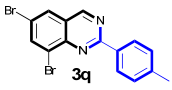
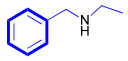
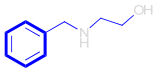
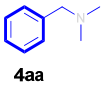
12	1a	 2l	 3l	88[c]
13	1a	 2m	 3m	80
14	 1b	2a	 3n	79
15	1b	2c	 3o	70
16	 1c	2a	 3p	78[c]

[a] Reaction condition: 2-aminobenzylamine (**1**, 0.5 mmol), benzylamines (**2**, 2.0 mmol). [b] Isolated Yield. [c] Reaction was performed at 130 °C for 2 h.

very good yield (Table 2, entry 2). The reaction of 2-aminobenzylamine (**1a**) with *p*-methoxybenzylamine (**2c**) and *m*-methoxybenzylamine (**2d**) produced the desired products (**3c** and **3d**) in excellent yields (Table 2, entries 3 and 4). Next, the halo-substituted benzylamines were explored (Table 2, entries 5-8). The *p*-chlorobenzylamine (**2e**) and *m*-chlorobenzylamine (**2f**) produced the corresponding products (**3e** and **3f**) in very good yields (Table 2, entries 5 and 6). However, relatively lower yield of **3g** was obtained when 2-chlorobenzylamine (**2g**) was employed for this transformation (Table 2, entry 7). The *p*- fluorobenzylamine (**2h**) furnished the product **3h** in 77% yield (Table 2, entry 8). The strong electron withdrawing $-NO_2$ group at different position such as *p*-nitrobenzylamine (**2i**) and *m*-nitrobenzylamine (**2j**), could also be converted into the corresponding products **3i** and **3j** in good yields (Table 2, entries 9 and 10). Further, hetero atom containing benzylamines such as pyridin-3-ylmethanamine (**2k**) pyridin-2-ylmethanamine (**2l**), and furan-2-ylmethanamine (**2m**) were also explored. To our delight they produced the desired products **3k**, **3l** and **3m** in very good yields (Table 2, entries 11-13). Furthermore, the reaction of 2-(aminomethyl)-4-chloroaniline (**1b**) and 2-(aminomethyl)-4,6-dibromoaniline (**1c**) with different benzylamines produced the respective products **3n**-**3p** in very good yields (Table 2, entries 14-16). Moreover, *N*- mono substituted benzylamines (**4**) were employed for this reaction and the results are summarized in

Table 3 Reaction of 2-aminobenzylamines with *N*-mono and *N,N*-disubstituted benzylamines

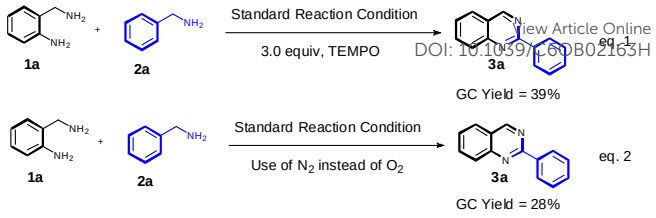


Entry	1	4	Products (3)	Yield[b] (%)
1	1a	 4a	3a	83
2	1a	 4b	3b	85
3	1a	 4c	3c	87
4	1a	 4d	3i	76
5	1c	4b	 3q	81[c]
6	1a	 4e	3a	78
7	1a	 4f	3a	83
8	1a	 4aa	3a	61

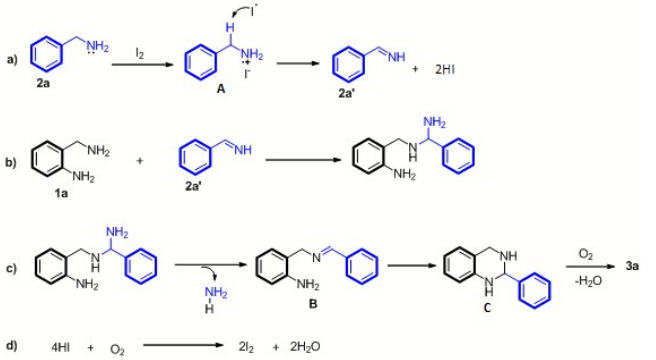
[a] Reaction condition: 2-aminobenzylamie (**1**, 0.5 mmol), *N*-substituted benzylamines (**4**, 2.0 mmol). [b] GC Yield. [c] Isolated Yield.

Table 3. The reaction of 2-aminobenzylamines (**1**) with various electron donating and electron withdrawing *N*-methylbenzylamines (**4**) produced the corresponding products (**3a**-**3i**) in good to very good yields (Table 3, entries 1-4). Next, the reaction of **1b** with **2b** provided 81% of **3q** (Table 2, entry 5). The reaction of **1a** with N-ethylbenzylamine (**4e**) and 2-(benzylamino)ethanol furnished the desired product in 73% yield (Table 3, entries 6-7 (**4f**). Unexpectedly, *N,N*-dimethylbenzylamine could also be converted in the desired product **3a** successfully (Table 3, entry 8).

In order to understand the reaction mechanism of this organic transformation, some control experiments were performed as shown in scheme 2. The addition of radical



Scheme 2. Control experiments



Scheme 3. A plausible reaction mechanism

scavenger 3.0 equiv. of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to the reaction mixture under optimized reaction conditions resulted in lowering the GC yield (39%) of **3a** (Scheme 2, eq. 1). This suggests that there is possibility of a radical intermediate.[17] Very poor GC yield (28%) of the desired product **3a** was obtained when the reaction was performed under nitrogen atmosphere indicating that O_2 plays a key role in the success of this reaction (Scheme 2, eq. 2).

Based on the previous reports,[10-16] we cautiously proposed a plausible reaction mechanism (Scheme 3). The reaction starts with the generation of radical intermediate **A**[17] which then give imine (**2a'**) (Scheme 3, eq. a). Next, 2-aminobenzylamine (**1a**) reacts with **2a'** to give intermediate **B** (Scheme 3, eq. b and c), followed by formation of intermediate **C**. At last, the dehydrogenative aromatizations of **C** into the desired product **3a** take place. The I_2 is regenerated by reacting HI with O_2 (Scheme 3, eq. d). There is a possibility that the intermediate **B** could be obtained directly without radical intermediate similar to autoxidation of benzylamines reported by Nguyen *et. al.*[16a]

Conclusions

In summary, this work reports a green and sustainable method for the synthesis quinazolines from 2-aminobenzylamines with *N*-mono substituted benzylamines, in the presence of catalytic amount of molecular iodine. The developed methodology works smoothly under transition-metal free, additive free and solvent free conditions. The use of O_2 as a green oxidant makes it a greatly economical protocol. Moreover, no aqueous work up is required. A variety of quinazoline derivatives were synthesized successfully in good to excellent yields. This

methodology could be applied in academics and in industries as it is very simple to operate.

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