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Molecular Iodine-Catalysed Benzylic sp³ C–H Bond Amination for the Synthesis of 2-Arylquinazolines from 2-Aminobenzaldehydes, 2-Aminobenzophenones and 2-Aminobenzyl Alcohols

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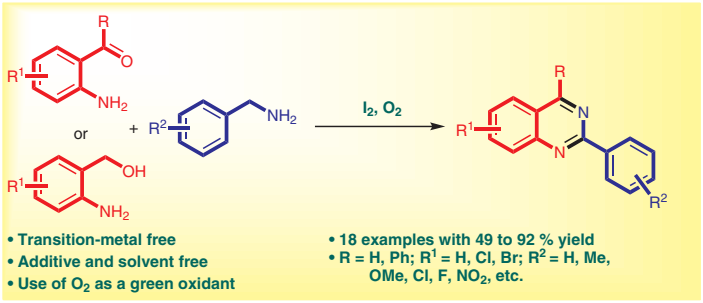

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Abstract Molecular iodine catalysed benzylic sp³ C–H bond amination has been developed for the synthesis of quinazolines from 2-aminobenzaldehydes and 2-aminobenzophenones with benzylamines. The use of oxygen as a green oxidant combined with the transition-metal-, additive- and solvent-free conditions makes the methodology economical and greener. The lack of aqueous work up also enhances the efficiency of this protocol. A series of 2-arylquinazolines was synthesised in good to excellent yields by using the developed protocol. 2-Aminobenzyl alcohols could also be employed to prepare the corresponding quinazoline derivatives.

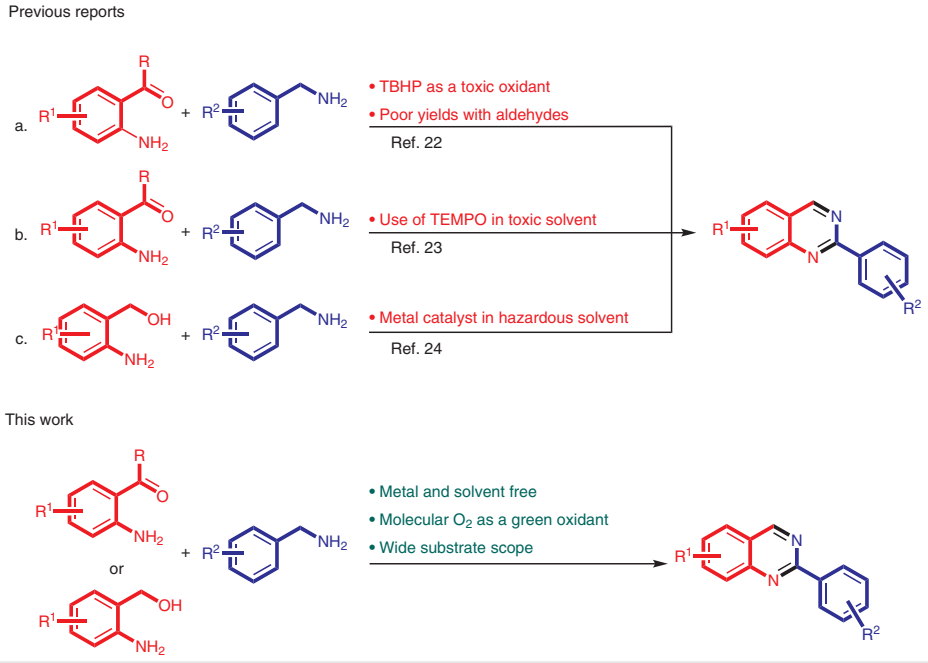
Key words transition-metal free, benzylic sp³ amination, 2-arylquinazoline, molecular iodine, oxygen

The direct functionalisation of an sp³ C–H bond into a C–N bond has emerged as a powerful strategy in organic synthesis because it improves the overall efficiency of the desired transformations. It not only avoids the additional prefunctionalisation of starting material but also provides greener and more economical strategies than conventional cross-coupling reactions.[1] Benzylic sp³ C–H/N–H coupling reactions have been extensively studied in the presence of transition metals such as cobalt,[2] copper,[3] iridium,[4] ruthenium,[5] rhenium[6] and palladium.[7] Alternatively, transition-metal-free protocols for the functionalisation of benzylic sp³ C–H bonds have also been well documented in recent years.[8] Various heterocycles have been synthesised through intra- or intermolecular pathways via functionalisation of benzylic sp³ C–H/N–H coupling.[9]

Molecular iodine is an established catalyst in organic synthesis.[10] Being mildly Lewis acidic in nature, it acts as an efficient and versatile reagent for reactions such as iodination, Michael additions, oxidation reactions, protection–deprotection of functional groups, Prins related reactions and functionalisation of alcohols.[11]

Quinazolines and their derivatives show a wide range of biological properties including antimicrobial, anticancer, cytotoxic, analgesic, anti-inflammatory, antidiabetic, antidepressant, anti-Parkinsonian, phosphodiesterase inhibitory, antitubercular, antimalarial and antihypertensive activities.[12] A number of synthetic methods have been documented for the preparation of quinazoline derivatives, including coupling of 2-aminobenzylamines,[13] 2-aminobenzyl alcohols,[14] 2-halobenzyl alcohols,[15] 2-halobenzylamine,[16] 2-halobenzyl tosylates,[17] 2-halobenzyl bromides,[18] 2-nitrobenzaldehyde oxime[19] and 2-nitrophenones[20] with different aryl precursors. In addition, the synthesis of 2-arylquinazolines from carbonyl compounds, which generally proceeds through condensation with arylamines followed by cyclisation, has been well documented.[21] In 2010, Wang et al. reported the oxidative cyclisation of 2-aminobenzophenones with benzylamines in the presence of molecular iodine as catalyst and *tert*-butyl hydroperoxide oxidant (Scheme 1).[22] Subsequently, Han et al. reported a protocol using 2-aminobenzaldehydes and 2-aminobenzophenones with benzylamine in the presence of 4-hydroxy-TEMPO/O_2 in *o*-xylene at elevated temperatures and extended reaction periods.[23] Recently, Gopalaiah and co-workers reported the synthesis of 2-arylquinazolines by using an iron-catalysed cascade reaction of 2-aminobenzyl alcohols with benzylamines.[24] Nevertheless, there continues to be the need to develop new protocols for the synthesis of 2-arylquinazolines from 2-aminobenzaldehydes and 2-aminobenzophenones with benzylamines, which can overcome the limitations of previous reports.

In a continuation to our research in the area of green and sustainable chemistry,[25] we report herein a highly efficient, green and sustainable protocol for the synthesis of

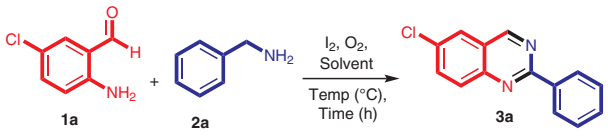


Scheme 1 Synthesis of 2-arylquinazolines

quinazolines from 2-aminobenzaldehydes and 2-aminobenzophenones with aryl amines in the presence of molecular iodine. Notably, the reaction works very well for both 2-aminobenzaldehydes and 2-aminobenzophenones under solvent-free conditions in short reaction times. Moreover, 2-aminobenzyl alcohols could also be converted into their corresponding quinazolines.

Our preliminary studies focused on the synthesis of 2-arylquinazolines from 2-aminobenzaldehydes and benzylamines in the presence of molecular iodine as a catalyst in dimethyl sulfoxide (DMSO). On reacting 2-amino-5-chlorobenzaldehyde (**1a**) with benzylamine (**2a**) at 80 °C for 24 h under an oxygen balloon, the desired product 6-chloro-2-phenylquinazoline (**3a**) was obtained in 84% yield (Table 1, entry 1). Next, the reaction was performed at different intervals of time and it was found that the reaction time could be reduced to 12 h from 24 h (entries 2 and 3); although considerable decrease in the yield of **3a** was observed when the reaction was performed for less time (entry 3). This may be due to the fact that the reaction proceeds through initial imine formation. In the next set of experiments, the reaction was carried out at different reaction temperatures (entries 4–6). No significant increase in the yield of the desired product **3a** was noted when reaction was performed at 90 °C (entry 4) and performing reaction at 70 °C led to decrease in the yield of desired product **3a** (entry 5). Interestingly, the desired product **3a** was obtained in a very good yield when the reaction was carried out at 130 °C for just 3 h; however, a decrease in the yield was noted when the reaction was performed at 120 °C (entry 6). When the reaction was attempted without solvent, there was no substantive decrease in yield of **3a** (entry 7). Different concentrations of molecular iodine were tested (entries 8–10) and it was found that 10 mol% of molecular

Table 1 Optimization of Reaction Conditions[a]



1a **2a** **3a**

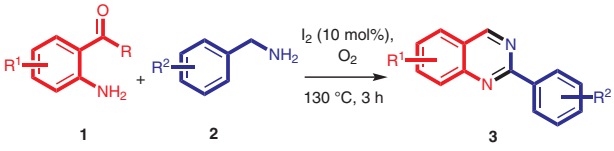
Entry	I_2 (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	20	DMSO	80	24	84
2	20	DMSO	80	12	83
3	20	DMSO	80	6, 8	71, 74
4	20	DMSO	90	12	84
5	20	DMSO	70	12	76
6	20	DMSO	130, 120	3	84, 77
7	20	–	130	3	82
8	15	–	130	3	82
9	10	–	130	3	82
10	5	–	130	3	64
11[c]	10	–	130	3	41

[a] Reaction conditions: 2-amino-5-chlorobenzaldehydes (**1a**, 0.5 mmol), benzylamines (**2a**, 1.5 mmol).
[b] GC yield.
[c] Without oxygen.

iodine was necessary for this reaction (entry 9). Further decreasing the concentration of molecular iodine to 5 mol% led to a decrease in yield of **3a** (entry 10). We also observed that the absence of oxygen reduced the yield of product (entry 11). Thus, the optimised reaction conditions were selected as 2-amino-5-chlorobenzaldehydes (**1a**, 0.5 mmol), benzylamine (**2a**, 1.5 mmol) and I_2 (10 mol%) under an O_2 atmosphere at 130 °C for 3 h. With 2-aminobenzophenones, the optimised reaction parameters found to be 2-aminobenzophenone (**1d**, 0.5 mmol), benzylamine (**2a**, 1.5 mmol) and I_2 (10 mol%) under O_2 atmosphere at 130 °C for 8 h. (see the Supporting Information for the optimization of the experimental conditions for the reaction of **1d** with **2a**).

With the optimised reaction conditions in hand, a range of 2-aminobenzaldehydes and benzylamines were investigated as starting reactants for the synthesis of 2-arylquinazolines; the corresponding results are shown in Table 2. The reaction of **1a** with **2a** provided 82% isolated yield of the desired product **3a** (entry 1) under the optimised reaction conditions. The effect of electron-donating and -withdrawing groups on benzylamine was examined and it was observed that substituents that increase electron density on the benzene ring of benzylamines favour the reaction, presumably because this favours formation of the intermediate imine. The reaction of **1a** with *p*-methoxybenzylamine (**2b**) and *p*-fluorobenzylamine (**2c**) proceeded smoothly and furnished products **3b** and **3c** with 88% and 79% yields, respectively (entries 2 and 3). Reaction of 2-aminobenzaldehyde (**1b**) with benzylamine (**2a**) was found to give 2-phenylquinazoline **3d** in 86% yield (entry 4). Studying the scope of the reaction with 2-aminobenzaldehyde (**1b**) and substituted benzylamines for the synthesis of 2-arylquinazolines revealed that the corresponding desired products **3e** and **3f** were obtained in excellent yield with benzylamines having electron-donating substituents at the *para*-position (entries 5 and 6). The reaction of **1b** with benzylamines having electron-withdrawing groups at the *para*-position produced the corresponding products **3g** and **3h** in good yields (entries 7 and 8). Benzylamines with -OMe, $-NO_2$ and -Cl substituents at the *meta*-position had little effect on the product yield (entries 9–11). Heteroaromatic benzylamines such as pyridin-3-ylmethanamine (**2i**), furan-2-ylmethanamine (**2j**) and thiophen-2-ylmethanamine (**2k**) were also examined and products **3l**, **3m** and **3n** were formed in 86%, 76% and 80% yields, respectively (entries 12–14). Reaction of 2-amino-3,5-dibromobenzaldehyde (**1c**) with **2a** and **2c** led to the desired arylquinazolines **3o** and **3p** in 75% and 68% yields, respectively (entries 15 and 16).

Table 2 Synthesis of 2-Aryl quinazolines from 2-Aminobenzaldehydes and 2-Aminobenzophenones[a]



1 2 3

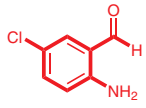
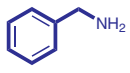
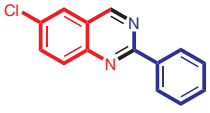
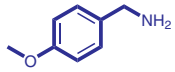
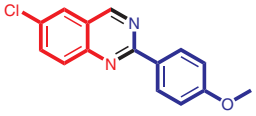
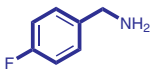
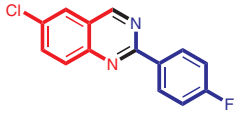
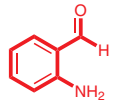
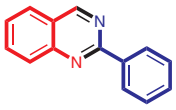
Entry	1	2	Product (3)	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	82
2	**1a**	 **2b**	 **3b**	88
3	**1a**	 **2c**	 **3c**	79
4	 **1b**	**2a**	 **3d**	86

Table 2 (continued)

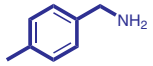
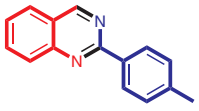
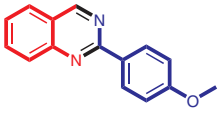
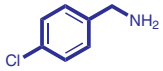
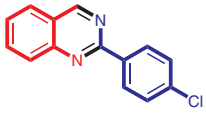
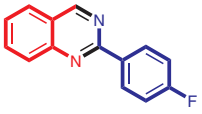
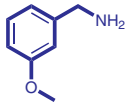
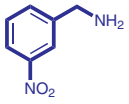
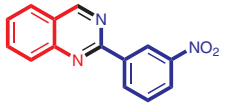
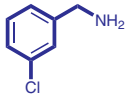
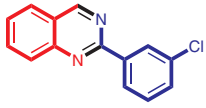
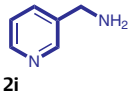
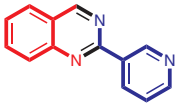
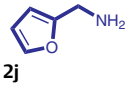
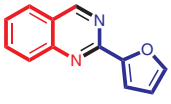
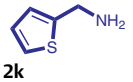
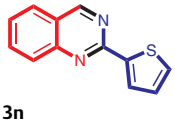
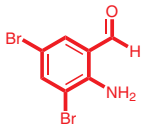
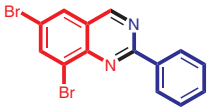
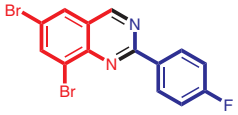
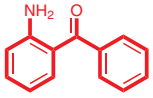
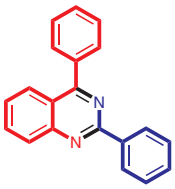
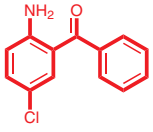
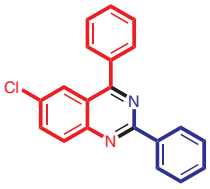
Entry	1	2	Product (3)	Yield (%)[b]
5	1b	 2d	 3e	84
6	1b	2b	 3f	92
7	1b	 2e	 3g	78
8	1b	2c	 3h	73
9	1b	 2f	 3i	82
10	1b	 2g	 3j	69
11	1b	 2h	 3k	74
12	1b	 2i	 3l	86
13	1b	 2j	 3m	76
14	1b	 2k	 3n	80

Table 2 (continued)

Entry	1	2	Product (3)	Yield (%)[b]
15	 **1c**	**2a**	 **3o**	75
16	**1c**	**2c**	 **3p**	68
17[c]	 **1d**	**2a**	 **3q**	88
18[c]	 **1e**	**2a**	 **3r**	81

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol).
[b] GC yield.
[c] Reaction performed for 8 h.

The reaction of 2-aminobenzophenone (**1d**) and 2-amino-5-chlorobenzophenone (**1e**) with **2a** led to products **3q** and **3r**, in 88% and 81% yields, respectively (Table 2, entries 17 and 18). After screening aromatic amines successfully, aliphatic and unsaturated amines such as hexylamine, allylamine hydrochloride and cinnamylamine were also examined under the established protocol. Unfortunately, none of these amines could be converted into the desired products.

Having established an efficient synthesis of 2-arylquinazolines from 2-aminobenzaldehydes and 2-aminobenzophenones, the synthesis of 2-arylquinazoline from 2-aminobenzyl alcohol **4** was then attempted. Gratifyingly, we succeed in synthesising 2-arylquinazoline directly from 2-aminobenzyl alcohol (**4**) and benzylamine (**2a**). A broad range of readily available benzylamines were screened for the synthesis of 2-arylquinazolines from 2-aminobenzyl alcohol (**4**), as summarised in Table 3. Although good tolerance for benzylamines substituted with electron-donating as well as -withdrawing groups was observed, the yields with these substrates were moderate. The reaction of 2-aminobenzyl alcohol with benzylamines having *meta*- and *para*-substituents delivered the corresponding 2-arylquinazoline products in moderate yields (entries 1–5). Furthermore, thiophen-2-ylmethanamine (**2k**) also provided product **3n′** in 55% yield (entry 6).

In summary, we have reported an efficient and simple method for the synthesis of 2-arylquinazolines from 2-aminobenaldehydes or 2-aminobenzophenones with benzylamines in very good to excellent yields.[26] The protocol uses molecular iodine in catalytic amounts and delivers benzylic sp^3 C–H bond functionalisation/amination. Furthermore, 2-aminobenzyl alcohol could also be converted into the corresponding products in moderate to good yields.

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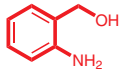
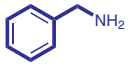
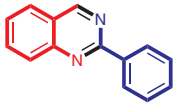
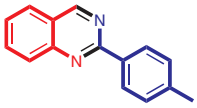
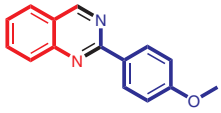
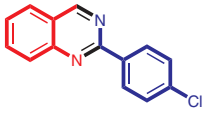
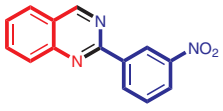
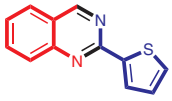
Table 3 Synthesis of 2-Arylquinazolines from 2-Aminobenzyl alcohol[a]

4 2 3

Entry	4	2	Product (3)	Yield (%)[b]
1	 4	 2a	 3d′	62
2	4	2d	 3e′	64
3	4	2b	 3f′	68
4	4	2e	 3g′	58
5	4	2g	 3j′	49
6	4	2k	 3n′	55

[a] Reaction conditions: **4** (0.5 mmol), **2** (1.5 mmol).
[b] GC yield.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609200.

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(26) **General experimental procedure for the synthesis of 2-arylquinazolines** (**3**): An oven-dried 25 mL round-bottom flask was charged with 2-aminobenzaldehyde/2-aminobenzophenone (**1**, 0.5 mmol) or 2-aminobenzyl alcohol (**4a**, 0.5 mmol) with benzylamine (**2**, 1.5 mmol) and molecular iodine (10 mol%). The mixture was then stirred at 130 °C for 3–15 h under an oxygen atmosphere, and the progress of the reaction was monitored by TLC. Upon completion, the mixture was cooled to room temperature and the crude product was purified by column chromatography.
6-Chloro-2-(4-methoxyphenyl)quinazoline (3b)
Yellow solid (88%); mp 168–170 °C; ^{1}H NMR (400 MHz, CDC_3): δ = 9.32 (s, 1 H), 8.54–8.52 (m, 2 H), 7.95 (d, *J* = 9.0 Hz, 1 H), 7.85 (d, *J* = 2.1 Hz, 1 H), 7.77 (dd, *J* = 9.0, 2.3 Hz, 1 H), 7.02 (d, *J* =8.4 Hz, 2 H), 3.88 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 162.0, 161.1, 159.4, 149.3, 135.0, 132.2, 130.2, 130.1, 125.8, 123.7, 114.0, 55.4; GCMS (EI, 70 eV): *m*/*z* (%) = 270 (100), 255 (24), 227 (14), 192 (10).
2,4-Diphenylquinazoline (3q)
White solid (88%); mp 117–119 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 8.1 Hz, 2 H), 8.15 (d, *J* = 8.4 Hz, 1 H), 8.11 (d, *J* = 8.4 Hz, 1 H), 7.89–7.85 (m, 3 H), 7.60–7.58 (m, 3 H), 7.54–7.47 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 160.2, 152.0, 138.2, 137.7, 133.5, 130.5, 130.2, 129.9, 129.2, 128.7, 128.5, 127.0, 121.7; GCMS (EI, 70 eV): *m*/*z* (%) = 282 (65), 281 (100), 203 (8), 178 (8), 151 (6), 141 (7), 77 (8)