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# Potassium Iodide-Catalyzed Three-Component Synthesis of 2-Arylquinazolines *via* Amination of Benzylic C–H Bonds of Methylarenes

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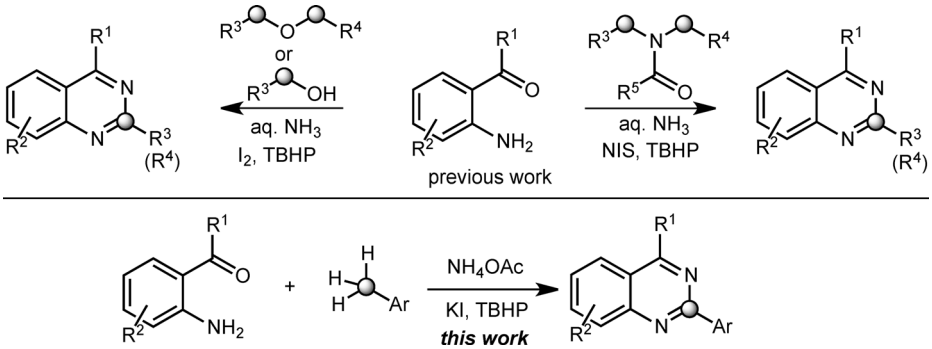
**Abstract:** A novel potassium iodide-catalyzed three-component synthesis of quinazolines *via* benzylic C–H bonds amination was developed. Commonly used ammonia salt and the $sp^3$ carbon in commercially available methylarenes were used as nitrogen and $C_1$ sources, respectively. Mechanistic studies indicated that an aryl aldehyde is involved as a key intermediate in the reaction.

**Keywords:** amination; C–H activation; multicomponent reactions; potassium iodide; quinazolines

In recent years, C–H bond activation has experienced significant progress, and the methods, especially those based on $sp^3$ C–H bond activation, have attracted much attention for the construction of complex molecules.[1] In this context, direct functionalization of the relatively active benzylic $sp^3$ C–H bonds has been investigated extensively. To date, methodologies for direct conversion of benzylic C–H bonds into C–C,[2] C–O,[3] C–N,[4] C–F,[5] C–S[6] and C–Si bonds[7] have been developed that exhibit synthetic efficiency and atom economy compared with traditional strategies. In addition, intramolecular annulation *via* benzylic C–H bonds activation is an efficient way to prepare heterocyclic compounds, which mainly depends on the use of complex prefunctionalized toluene derivatives bearing an *ortho*-functional group.[8] The benzylic C–H bond activation of toluenes is particularly important since it can produce industrially important chemicals. Moreover, if toluene derivatives could participate in intermolecular annulations, the processes would represent high levels of brevity and diversity by allowing two readily accessible and flexible building blocks to be combined in the construction of highly substituted heterocyclic compounds. Despite these advances, however, the introduction of toluene derivatives to construct heterocycles *via* C–H bonds activation has been little explored.[9] Besides, the limited examples were restricted to transition metal-assisted approaches, which are not the best choices because of metal contamination. Therefore, the development of metal-free intermolecular annulations is highly desirable. Very recently, we have reported a direct approach for the synthesis of quinazolinones from 2-aminobenzamides and methylarenes under metal-free conditions.[10] Although pioneering work has been done in the one- and two-component reactions mentioned above, the examples of methylarenes applied in multicomponent processes for the synthesis of heterocycles are very few.

Quinazoline derivatives have attracted significant attention due to their various biological and pharmacological activities.[11] Because of the wide demand for substituted quinazolines, many synthetic strategies have been developed.[12] Recent methods toward 2-substituted quinazolines starting from a variety of substrates, such as 2-aminobenzylamines,[13] 2-aminobenzyl alcohols,[14] 2-halobenzyl halides,[15] 2-bromobenzylamines,[16] 2-aminophenyl ketones,[17] 2-carbonylaryl halides[18] and amidines,[19] were reported. Among these starting substrates, the one-pot reaction of 2-aminophenyl ketones with aldehydes and a nitrogen source under mild conditions is more attractive due to its flexible, step efficient and environmentally friendly nature.[20] Furthermore, Wang presented a highly efficient and practical procedure for the synthesis of quinazolines from 2-aminophenyl ketones, ammonia, and commonly used solvents, such as *N*-alkylamides, ethers, or alcohols *via* amination of $sp^3$ C–H bonds adjacent to nitrogen or oxygen atoms (Scheme 1).[21] From these examples, we can conclude that the key to the success of this reaction is to choose appropriate nitrogen and $C_1$ sources as the additional nitrogen and carbon atom of the quinazolines,



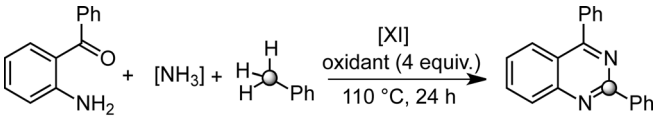

**Scheme 1.** Three-component synthesis of quinazolines from 2-aminophenyl ketones, nitrogen and $C_1$ sources.

respectively. Inspired by previous results, and in the continuation of our research on quinazolines,[22] we herein report a mild KI-catalyzed three-component synthesis of quinazolines from 2-aminophenyl ketones, ammonium acetate and methylarenes (Scheme 1).

Initially, 2-aminobenzophenone (**1a**), toluene (**2a**) and the common inorganic ammonium salt $NH_4Cl$ as a nitrogen source were selected as the model substrates to optimize the reaction conditions (Table 1). When 70% aqueous TBHP was used as oxidant, the expected product **3aa** was obtained under $I_2$ catalytic conditions. albeit in a low 11% yield (entry 1). Encouraged by this result, we investigated the applicability of different nitrogen sources (entries 2–7). Previous reports revealed that $NH_4OAc$ usually gave a better yield in three-component reactions for quinazoline preparation,[20a–c] and a similar result was obtained in current optimization (entry 3). A control experiment confirmed that no product was observed in the absence of catalyst (entry 8). Among the examination of various oxidants, TBPB and a decane solution of TBHP were also efficient, but did not enhance the yield (entries 9–14). Next, other iodine-based catalysts usually employed in C–H bond activation were tested,[23] and KI was the most effective one affording a superior result (15–18). It was noteworthy that a higher catalyst loading improved the yield to 66%, even after decreasing the reaction temperature (entry 19). It was reported that adding the phase-transfer catalyst 18-crown-6 into KI catalytic system could improve the yield significantly,[24] however, it had little influence on the current reaction (entry 20). Moreover, a higher reaction concentration could facilitate the annulation reaction (entry 21). Finally, by adding the TBHP in two portions of 2 equiv., the yield was improved to 84% (entry 22). After optimization, the reaction conditions were: $NH_4OAc$ as nitrogen source, 30 mol% KI as catalyst and 2 equiv. × 2 of TBHP as oxidant at 90 °C for 24 h.

Then, various methylarenes were employed for annulations with 2-aminobenzophenone (**1a**) to give the corresponding 2-arylquinazolines (Table 2). Xylenes were examined, and the steric hindrance had little influence on the reactivity (**3ab**–**ad**). When *para*-me-

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

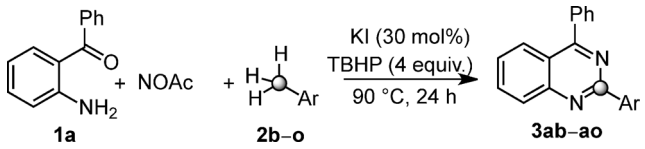



**1a** **2a** **3aa**

| Entry | XI (mol%) | Oxidant[b] | $[NH_3]$ | Yield[c] [%] |
|---|---|---|---|---|
| 1 | $I_2$ (20) | TBHP | $NH_4Cl$ | 11 |
| 2 | $I_2$ (20) | TBHP | aq. $NH_3$ | trace |
| 3 | $I_2$ (20) | TBHP | $NH_4OAc$ | 54 |
| 4 | $I_2$ (20) | TBHP | $NH_4HCO_3$ | trace |
| 5 | $I_2$ (20) | TBHP | $NH_4Br$ | 23 |
| 6 | $I_2$ (20) | TBHP | $NH_4HCO_2$ | 13 |
| 7 | $I_2$ (20) | TBHP | urea | 38 |
| 8 | – | TBHP | $NH_4OAc$ | nd. |
| 9 | $I_2$ (20) | TBHP[d] | $NH_4OAc$ | 50 |
| 10 | $I_2$ (20) | DTBP | $NH_4OAc$ | trace |
| 11 | $I_2$ (20) | TBPB | $NH_4OAc$ | 47 |
| 12 | $I_2$ (20) | BPO | $NH_4OAc$ | trace |
| 13 | $I_2$ (20) | $K_2S_2O_8$ | $NH_4OAc$ | 10 |
| 14 | $I_2$ (20) | $H_2O_2$ | $NH_4OAc$ | trace |
| 15 | NIS (20) | TBHP | $NH_4OAc$ | 36 |
| 16 | TBAI (20) | TBHP | $NH_4OAc$ | 20 |
| 17 | KI (20) | TBHP | $NH_4OAc$ | 57 |
| 18 | PhI (20) | TBHP | $NH_4OAc$ | 20 |
| 19[e] | KI (30) | TBHP | $NH_4OAc$ | 66 |
| 20[e,f] | KI (30) | TBHP | $NH_4OAc$ | 63 |
| 21[e,g] | KI (30) | TBHP | $NH_4OAc$ | 78 |
| 22[e,g] | KI (30) | TBHP[h] | $NH_4OAc$ | 84 |

[a] *Reaction conditions:* **1a** (0.3 mmol), $[NH_3]$ (0.9 mmol), **2a** (2 mL), XI (20–30 mol%), oxidant (1.2 mmol), 110 °C, 24 h.
[b] TBHP = 70% *t*-BuOOH in water, DTBP = $(t\text{-BuO})_2$, TBPB = PhCOOO-*t*-Bu, BPO = $(PhCOO)_2$, $H_2O_2$ = 30% in water.
[c] Isolated yield, nd. = not detected.
[d] TBHP: 5.5 M in decane.
[e] At 90 °C.
[f] 30 mol% 18-crown-6 were added as additive.
[g] 1.5 mL **2a** were used.
[h] 2 equiv. × 2, the second portion was added after 4 h.

**Table 2.** Substrate scope of methylarenes.[a]

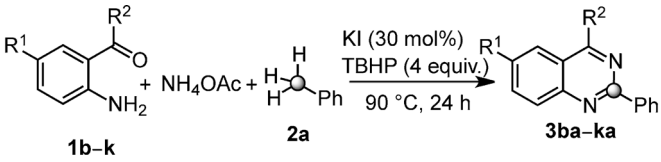



1a 2b–o 3ab–ao

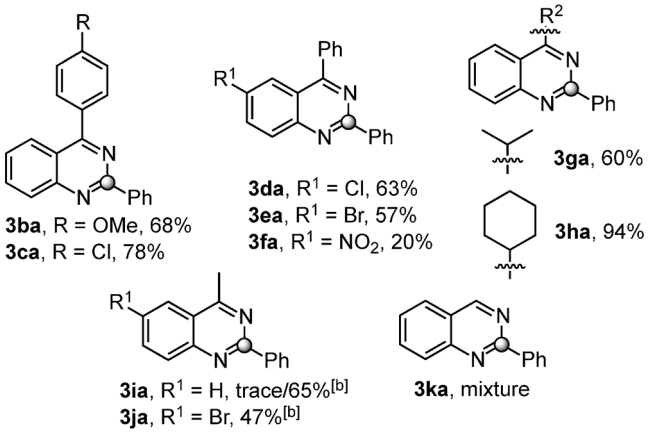
| Entry | Ar | Product | Yield[b] [%] |
|---|---|---|---|
| 1 | 2-Me-$C_6H_4$ (**2b**) | **3ab** | 62 |
| 2 | 3-Me-$C_6H_4$ (**2c**) | **3ac** | 71 |
| 3 | 4-Me-$C_6H_4$ (**2d**) | **3ad** | 65 |
| 4 | 4-*t*Bu-$C_6H_4$ (**2e**) | **3ae** | 75 |
| 5 | 4-MeO-$C_6H_4$ (**2f**) | **3af** | 44 |
| 6 | 4-F-$C_6H_4$ (**2g**) | **3ag** | 59 |
| 7 | 4-Cl-$C_6H_4$ (**2h**) | **3ah** | 83 |
| 8 | 4-Br-$C_6H_4$ (**2i**) | **3ai** | 70 |
| 9 | 4-$CF_3$-$C_6H_4$ (**2j**) | **3aj** | 64 |
| 10 | 4-$NO_2$-$C_6H_4$ (**2k**) | **3ak** | 31 |
| 11 | 3,5-di-Me-$C_6H_3$ (**2l**) | **3al** | 78 |
| 12 | 3-Br-5-Me-$C_6H_3$ (**2m**) | **3am** | 71 |
| 13 | 2-naphthyl (**2n**) | **3an** | 43 |
| 14 | 2-thienyl (**2o**) | **3ao** | 35 |

[a] *Reaction conditions:* **1a** (0.3 mmol), $NH_4OAc$ (0.9 mmol), **2** (1.5 mL), KI (0.09 mmol), 70% aqueous TBHP (0.6 mmol × 2, the second portion was added after 4 h), 90 °C, 24 h.
[b] Isolated yield.

**Table 3.** Substrate scope of 2-aminophenyl ketones.[a]




1b–k 2a 3ba–ka

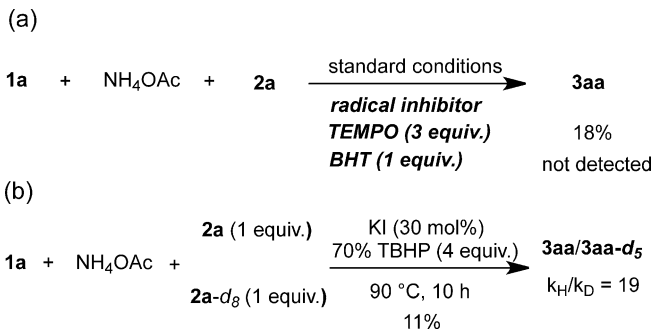



[a] *Reaction conditions:* **1** (0.3 mmol), $NH_4OAc$ (0.9 mmol), **2a** (1.5 mL), KI (0.09 mmol), 70% aqueous TBHP (0.6 mmol × 2, the second portion was added after 4 h), 90 °C, 24 h.
[b] **1** (0.3 mmol), $NH_4OAc$ (0.9 mmol), **2a** (1.5 mL), $FeCl_3$ (0.03 mmol), 70% aqueous TBHP (1.2 mmol), DMSO (0.5 mL), 100 °C, 24 h, $N_2$. Yields are for the isolated products.

thoxytoluene was applied, the yield decreased due in part to the instability of the ether bond in this reaction system (**3af**). Notably, halogen groups were compatible with the reaction conditions, which allow for further functionalization of the products (**3ag**–**ai**). Toluene substrates bearing strong electron-withdrawing substituents, such as $CF_3$ and $NO_2$, also gave the desired products, while the latter showed a lower efficiency (**3aj**–**ak**). Interestingly, polysubstituted toluene derivatives provided the target products in good yields (**3al**–**am**). In addition, methyl-substituted naphthalene and heteroarene were also applicable (**3an**–**ao**).

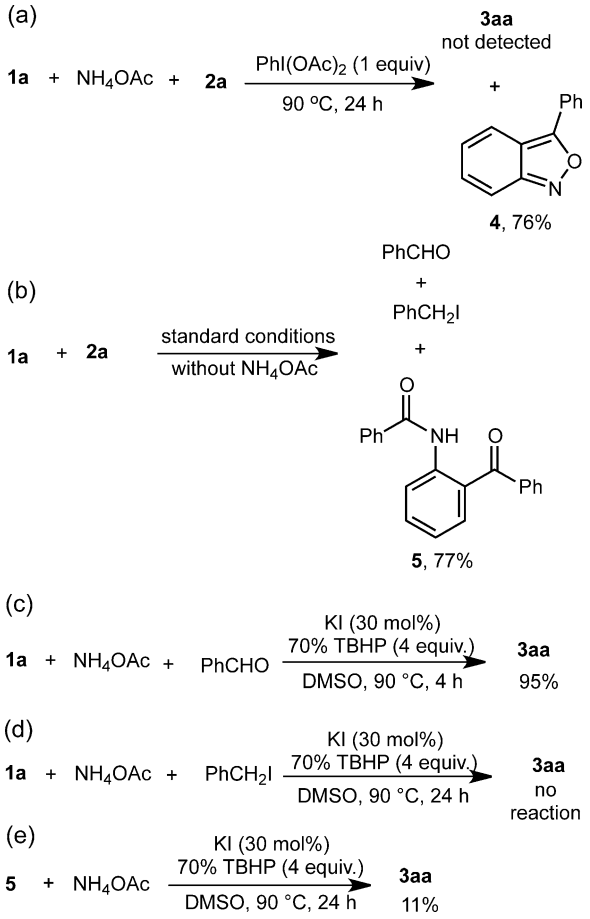
We next investigated the scope of 2-aminophenyl ketones under the optimized reaction conditions (Table 3). Both electron-donating and withdrawing substituents in the free phenyl ring of 2-aminobenzophenone were well tolerated, and gave good yields (**3ba**–**ca**). Substrates with a Cl or Br group in the aniline ring gave moderate yields, while the $NO_2$ group disfavored the reaction obviously (**3da**–**fa**). In contrast, when 4-position substituents were changed from phenyl rings to alkyl groups, such as branched and cycloalkyl groups, they were also suitable for the present transformation (**3ga**–**ha**). The challenging substrate 2-aminophenylethanone (**1i**)[17d] was also tested, and indeed, the target product was obtained in trace amounts. To our delight, we found that 10 mol% $FeCl_3$ could catalyze the annulations of 2-aminophenylethanone derivatives (**1i**–**j**) after optimization (see the Supporting Information). However, when 2-aminobenzaldehyde (**1k**) was used, no product was observed either under iodine or iron catalytic conditions.

Several control experiments have been performed to gain an insight into the reaction mechanism. Firstly, adding a radical inhibitor TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxyl) or BHT (2,6-di-*tert*-butyl-4-methylphenol) to the reaction system decreased the yield (Scheme 2a). The results suggested that the reaction probably proceeded *via* a radical pathway. Secondly, a large intermolecular kinetic isotope effect




**Scheme 2.** Investigation of the reaction mechanism.

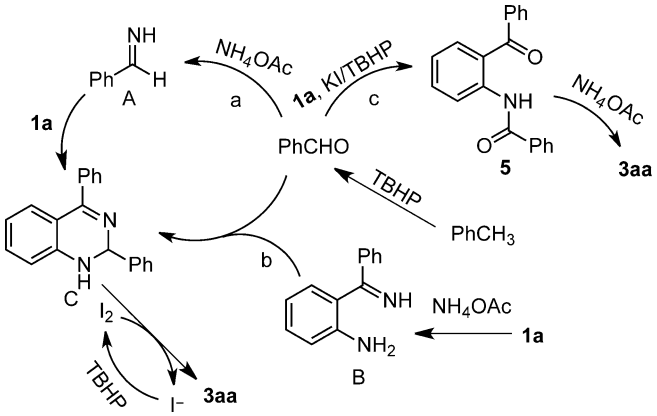
  




**Scheme 3.** Investigation of the catalytically active species and the reaction intermediate.

(KIE, $k_H/k_D = 19$) was observed in the competitive annulations involving toluene and toluene-$d_8$ (Scheme 2b, see the Supporting Information),[25] thus indicating that benzyl C–H bond cleavage was the rate-determining step.

To ascertain the catalytically active species, stoichiometric amounts of $PhI(OAc)_2$ were employed. No desired product was observed except for an unexpected by-product **4**, indicating that a hypervalent iodine reagent might not be involved in the transformation (Scheme 3a). Then, analysis of the reaction mixture between **1a** and **2a** in the absence of $NH_4OAc$ divulged the formation of benzaldehyde, benzyl iodide and a coupling compound **5** (Scheme 3b, see the Supporting Information). To find out the reaction intermediate, these three compounds were examined under similar reaction conditions. The reaction of benzaldehyde with **1a** and $NH_4OAc$ generated **3aa** in high yield within 4 h, while benzyl iodide was unreactive (Scheme 3c, d). We then explored the coupling of **5** and $NH_4OAc$, **3aa** was also obtained in a low yield (Scheme 3e). These results strongly suggested that benzaldehyde and **5** were most likely reaction intermediates that played roles in different reaction pathways.




**Scheme 4.** Possible mechanism.

Based on the above evidence and previous research, a possible mechanism is proposed as shown in Scheme 4. Initially, benzaldehyde is formed from toluene *via* radical oxidation in the presence of TBHP.[2b,f,26] The carbonyl in benzaldehyde or 2-aminobenzophenone (**1a**) reacts with $NH_4OAc$ to give aldimine (**A**) or ketimine (**B**), respectively, which after cyclization generates dihydroquinazoline **C** (paths a and b).[20a] Subsequently, **C** is converted to the quinazoline product **3aa** *via* iodine-promoted oxidative aromatization. Alternatively, a minor pathway may occur according to control experiments (path c). Based on a very recent report,[27] intermediate **5** could be formed *via* amidation under the KI/TBHP catalytic system, and subsequent condensation with $NH_4OAc$ would afford **3aa**.

In conclusion, we have developed a novel, three-component approach for the synthesis of 2-arylquinazolines under metal-free conditions. $NH_4OAc$ as cheap nitrogen source and $sp^3$ carbon in commercially available methylarene as $C_1$ source were introduced as the additional nitrogen and carbon atoms of the quinazolines, respectively. The investigation of mechanism indicated that aryl aldehyde as a key intermediate was involved in the reaction. Further applications of the methodology in the synthesis of other N-heterocycles are currently under study in our laboratory.

## Experimental Section

### General Procedures for the Synthesis of Products

**Synthesis of Products 3aa–ao, 3ba–ha:** To a solution of 2-aminophenyl ketone **1** (0.3 mmol) in 1.5 mL methylarene **2** (for **2k**, 1.9 g were added; for **2n**, 2.0 g were added) were added $NH_4OAc$ (70 mg, 0.9 mmol) and KI (15 mg, 0.09 mmol), followed by 70% aqueous TBHP (82 μL, 0.6 mmol). The reaction mixture was stirred in a Schlenk

tube at 90 °C. After 4 h, the remaining 70% aqueous TBHP (82 μL, 0.6 mmol) was added, and then, the reaction mixture was stirred at 90 °C for another 20 h. After the reaction had finished, the reaction mixture was cooled to room temperature and then directly purified by flash column chromatography on silica gel (petroleum ether:ethyl acetate = 50:1–30:1) to afford the desired product **3**.

**Synthesis of Products 3ia–ja:** To a solution of 2-aminophenyl ketone **1** (0.3 mmol) in 1.5 mL toluene and 0.5 mL DMSO were added $NH_4OAc$ (70 mg, 0.9 mmol) and $FeCl_3$ (5 mg, 0.03 mmol), followed by 70% aqueous TBHP (164 μL, 1.2 mmol). Then the Schlenk tube was charged with $N_2$, and the reaction mixture was stirred at 100 °C for 24 h. After the reaction had finished, the reaction mixture was cooled to room temperature and diluted with ethyl acetate, then washed with brine. The aqueous layers were extracted with ethyl acetate (3 × 5 mL), the combined organic layers were dried over $Na_2SO_4$ and evaporated under vacuum. The residue was then purified by flash column chromatography on silica gel (petroleum ether:ethyl acetate = 50:1–30:1) to afford the desired product **3**.

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Potassium Iodide-Catalyzed Three-Component Synthesis of 2-Arylquinazolines *via* Amination of Benzylic C–H Bonds of Methylarenes

*Adv. Synth. Catal.* **2014**, *356*, 1 – 7

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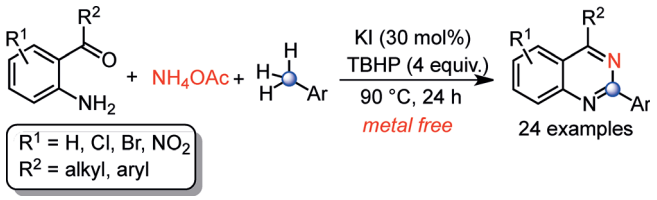


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