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A Simple and Efficient Approach to the Synthesis of 2-Phenylquinazolines via sp^3 C−H Functionalization

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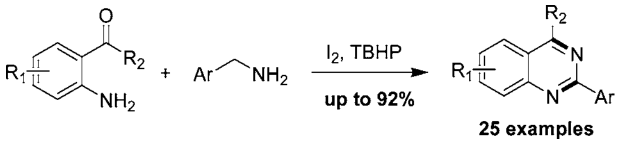
ABSTRACT



A facile and novel approach to the synthesis of 2-phenylquinazolines was developed via a tandem reaction following sp^3 C−H functionalization. Twenty-five examples of 2-phenylquinazolines were obtained from easily available 2-aminobenzophenones and benzylic amines with good to excellent yields.

Transition-metal-catalyzed C−H functionalization and subsequent formation of C−N bonds have attracted worldwide interest in recent years.[1] Although many excellent results have been achieved, various transition-metal catalysts are always essential to the C−H functionalization, such as catalysts of Ru, Rh, Ir, Pt, Pd, Mg, etc. (Scheme 1).[1c] There are only a few examples on C−H functionalization under transition-metal-free conditions.[2] In addition, the application of C−H functionalization in tandem reactions has been scarce until now.

On the other hand, quinazoline derivatives have drawn much attention for their various biological and medicinal activities, and they can be used as anticonvulsant, antibacterial, antidiabetic, anticarcinogen, and other biological or medicinal agents.[3] Although there are a number of well-established methods to prepare quinazolines,[3a,4] they mainly depend on the availability of the indispensable 2-aminobenzoic acid or 2-nitrobenzoic acid derivatives or 2-aminobenzonitrile or 2-nitrobenzonitrile derivatives or 2-halophenyl precursors. The availability of these special starting materials restricts the application of these methods.

Scheme 1. Methods for C−H Functionalization

$$\mathrm{C{-}H} + \mathrm{H{-}Z} \xrightarrow{\textit{cat.}\ \mathrm{M}} \mathrm{C{-}Z}$$

Z = C, O, N
M = Ru, Rh, Pd, Ag, Cu, Co, Mg, Fe

Recently, we reported an efficient nonmetal catalytic oxidation system by using molecular iodine.[5] Herein, based

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(1) For selected reviews, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439–2463. (d) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061–5074. (e) Li, C.-J. *Acc. Chem. Res.* **2008**, *42*, 335–344.

(2) (a) Tu, W. Y.; Liu, L.; Floreancig, P. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 4184–4187. (b) Fan, R. H.; Li, W. X.; Pu, D. M.; Zhang, L. *Org. Lett.* **2009**, *11*, 1425–1428. (c) Bajracharya, G. B.; Daugulis, O. *Org. Lett.* **2008**, *10*, 4625–4628. (d) Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242–4243.

(3) For selected reviews, see: (a) Witt, A.; Bergman, J. *Curr. Org. Lett.* **2003**, *7*, 659–677. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166–187. (c) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223–246.

(4) For selected examples, see: (a) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153–10202. (b) Liu, X. W.; Fu, H.; Jiang, Y. Y.; Zhao, Y. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 348–351. (c) Li, J. R.; Chen, X.; Shi, D. X.; Ma, S. L.; Li, Q.; Zhang, Q.; Tang, J. H. *Org. Lett.* **2009**, *11*, 1193–1196.

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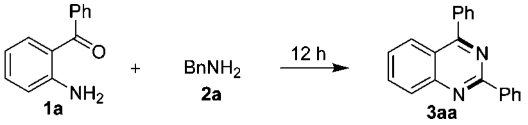
on this result, we developed a simple and efficient approach to the synthesis of 2-phenylquinazolines with this catalytic oxidation system. Various 2-phenylquinazolines were prepared from 2-aminobenzophenones and benzylic amines via a tandem reaction following sp^3 C−H functionalization under metal-free conditions.

Table 1. Optimization of the Reaction Conditions for the Construction of Quinazoline[a]



entry	I_2 (mol %)	$BnNH_2$ (equiv)	TBHP (equiv)	temp (°C)	yield[b] (%)
1[c]	5	2	2	80	42
2	5	2	2	80	49
3		2	2	80	0
4	5	2	*d*	80	5
5[e]	5	2	2	80	42
6[f]	5	2	2	80	0
7[g]	5	2	2	80	0
8[h]	5	2	2	80	0
9	5	2	2	90	83
10	5	2	2	100	84
11	5	1.5	2	90	72
12	5	2.5	2	90	87
13	5	3	2	90	86
14	5	2.5	1.5	90	78
15	5	2.5	2.5	90	89
16	10	2.5	2	90	94
17	20	2.5	2	90	87

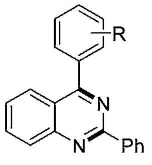
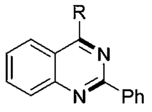
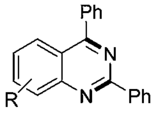
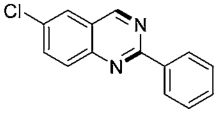
[a] Reaction conditions: **1a** (0.2 mmol) and **2a** were heated with I_2 and TBHP for 12 h. [b] Yield was determined by GC−MS based on peak areas. [c] 5 mol % of pyridine was added. [e] 30% of aqueous H_2O_2 was used as oxidant. 0.2 mL of solvent was added. [d] Solvent: MeCN. [f] Solvent: water. [g] Solvent: *t*-BuOH. [h] Solvent: dioxane.

Initially, when 2-aminobenzophenone (**1a**) was treated with 2 equiv of benzylic amine (**2a**), 5 mol % of iodine and pyridine, and 2 equiv of aqueous *tert*-butyl hydroperoxide (TBHP) at 80 °C for 12 h, 42% of **3aa** was obtained (Table 1, entry 1). In the absence of pyridine, the reaction can give a higher yield (Table 1, entry 2). Without iodine, no product was observed (Table 1, entry 3). Then other environmental benign oxidants, such as *t*-BuOO*t*-Bu, aqueous H_2O_2, and oxygen, were also examined, but only aqueous H_2O_2 can generate a trace amount of the product (Table 1, entry 4). No better result was observed when various solvents were introduced to the reaction (Table 1, entries 5−8). Raising the reaction temperature to 90 °C can increase the reaction yield to 83%. Further raising the reaction temperature cannot enhance the reaction yield obviously (Table 1, entries 9 and 10). After the ratios of iodine, benzylic amine, and TBHP were optimized, the reaction yield was finally improved to 94% (Table 1, entries 11−17). Therefore, the optimal reaction conditions were obtained; that is, the mixture of 2-aminobenzophenone (**1a**) and 2 equiv of benzylic amine (**2a**) was heated at 90 °C for 12 h with 10 mol % of iodine as catalyst and 2 equiv of TBHP as oxidant (Table 1, entry 16).

Subsequently, we investigated the scope of the reaction substrates under the optimized conditions, as shown in Table 2. Compound **3aa** without any substitution on the phenyl rings was obtained with an isolated yield of 91% (Table 2, entry 1). The introduction of electron-withdrawing group to the *para* position of the free phenyl ring of 2-aminobenzoketone affected the reaction slightly. For instance, **3ba** and **3ca** could give similar yields to **3aa** (Table 2, entries 2 and 3). When this phenyl ring bore an electron-donating group at the *para* position, such as a methyl group, there was a negative effect on the reaction and the corresponding reaction yield was decreased to 78% (Table 2, entry 4). When the *ortho* position of the phenyl ring was occupied with a methyl group, the reaction yield was decreased further to 73% (Table 2, entry 5). This implied steric effect had an adverse influence on the reaction, as was verified with the failure when 2,4,6-trimethyl substitution on the phenyl ring was employed as a

Table 2. Reaction of Different 2-Aminobenzoketones with Benzylic Amine[a]

$$\mathbf{1a\text{-}1r} + \underset{\mathbf{2a}}{BnNH_2} \xrightarrow[12\ h]{90\ °C} \underset{\mathbf{3aa\text{-}3ra}}{\text{product}}$$

entry		R	product	yield (%)[b]
1		H	**3aa**	91
2		4-F	**3ba**	92
3		4-Br	**3ca**	89
4		4-Me	**3da**	78
5		2,5-di-Me	**3ea**	73
6		2,4,6-tri-Me	**3fa**	0[c]
7		Me	**3ga**	-[d]
8		*n*-Bu	**3ha**	86
9		hexadecyl	**3ia**	83
10		isopropyl	**3ja**	87
11		*t*-Bu	**3ka**	90
12		cyclopropyl	**3la**	88
13		cyclopentyl	**3ma**	85
14		4-chlorostyryl	**3na**	31
15		6-Cl	**3oa**	84
16		6-Br	**3pa**	80
17		6,7-di-OMe	**3qa**	51
18			**3ra**	43

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.5 mmol), I_2 (10 mol %), and TBHP (0.4 mmol) were heated at 90 °C for 12 h. [b] Isolated yields. [c] The starting material was recovered. [d] The starting material was converted to a complex mixture.

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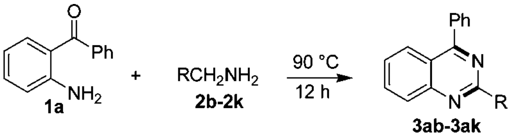
(5) (a) Zhang, J. T.; Wang, Z. T.; Wang, Y.; Wan, C. F.; Zheng, X. Q.; Wang, Z. Y. *Green Chem.* **2009**, *11*, 1973–1978. (b) Wan, C. F.; Wan, C. F.; Zhang, J. T.; Wang, S. J.; Fan, J. M.; Wang, Z. Y. *Org. Lett.* **2010**,DOI: 10.1021/ol100688c.

reaction substrate (Table 2, entry 6). This phenyl ring of 2-aminobenzoketone was then replaced with different aliphatic alkyl groups. Although **3ga** was not obtained, other alkyl substitutions, including straight chains with different lengths, branched chains, and cycloalkyl, provided the desired products with good yield (Table 2, entries 7−13). It was noteworthy that an unsaturated carbon−carbon bond can also survive the reaction (Table 2, entry 14). Different substituents on the anilino ring of 2-aminobenzoketone were also examined. The chloro or bromo group had little influence on the result (Table 2, entries 15 and 16), while the electron-donating group disfavored the reaction obviously (Table 2, entry 17). Finally, when 2-amino-5-chlorobenzaldehyde was employed as a substrate, the reaction also provided the desired product with a yield of 43% (Table 2, entry 18).

The generality of benzylic amines was also examined, as shown in Table 3. Generally, different benzylic amines could give the corresponding products with good to excellent yields. When a methyl group was moved from the *para* position to the *ortho* position of benzylic amine, the yield was reduced from 90% to 81% (Table 3, entries 1−3), which indicated that steric hindrance disfavored this reaction. When electron-donating groups were introduced to the phenyl ring of benzylic amine, the yield decreased further (Table 3, entries 4 and 5). However, when electron-withdrawing groups, such as bromo-, fluoro-, and trifluoromethyl-, were introduced to the phenyl ring of benzylic amine, good results were obtained (Table 3, entries 6−8). Moreover, naphthalen-1-ylmethanamine was also a suitable substrate for this reaction, providing the desired product with a yield of 63% (Table 3, entry 9).

Table 3. Reaction of 2-Aminobenzophenone with Different Benzylic Amines[a]

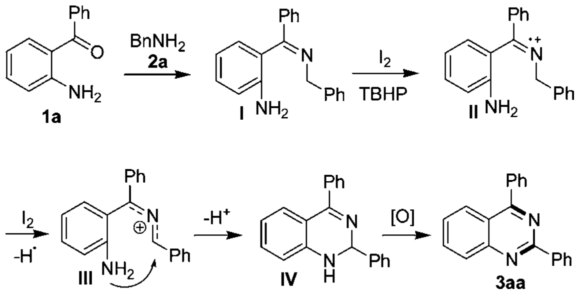


entry	R	product	yield[b] (%)
1	*p*-tolyl	**3ab**	90
2	*m*-tolyl	**3ac**	88
3	*o*-tolyl	**3ad**	81
4	4-methoxyphenyl	**3ae**	78
5	benzo[*d*][1,3]dioxol-5-yl	**3af**	71
6	4-chlorophenyl	**3ag**	88
7	4-fluorophenyl	**3ah**	82
8	4-(trifluoromethyl)phenyl	**3ai**	91
9	naphthalen-1-yl	**3aj**	63

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.5 mmol), I_2 (10 mol %), and TBHP (0.4 mmol) were heated at 90 °C for 12 h. [b] Isolated yields.

A tentative mechanism was proposed in Scheme 2. First, intermediate **I** can be generated from 2-aminobenzophenone (**1a**) and benzylic amine (**2a**). Subsequently, **I** is oxidized to intermediate **III** via sp^3 C−H functionalization under the reaction conditions.[6] Then intermediate **III** is converted to the quinazoline product after intramolecular cyclization and further oxidization in tandem process (Scheme 2).[7]

Scheme 2. Tentative Reaction Mechanism



In conclusion, a facile and efficient approach to the synthesis of 2-phenylquinazolines was developed via a tandem reaction following sp^3 C−H functionalization. Various 2-phenylquinazolines were obtained from easily available 2-aminobenzophenones and benzylic amines. This new method can avoid the use of hazard reagents or any kind of metal. A detailed investigation of the mechanism and the application of this reaction are currently in progress in our laboratory.

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Supporting Information Available: Experimental details and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org

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(6) This may undergo a similar procedure to that proposed by C. J. Li.: (a) Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 11810–11811. (b) Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673.

(7) Intermediate **I** was prepared according to the literature and could be converted to the desired product completely under the reaction conditions.