ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 7818–7820

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Efficient aerobic oxidative synthesis of 2-aryl quinazolines *via* benzyl C–H bond amination catalyzed by 4-hydroxy-TEMPO†‡

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Received 20th April 2011, Accepted 17th May 2011
DOI: 10.1039/c1cc12308d

A novel and efficient aerobic protocol for the oxidative synthesis of 2-aryl quinazolines *via* benzyl C-H bond amination by a one-pot reaction of arylmethanamines with 2-aminobenzoketones and 2-aminobenzaldehydes has been carried out using the 4-hydroxy-TEMPO radical as the catalyst, without any metals or additives.

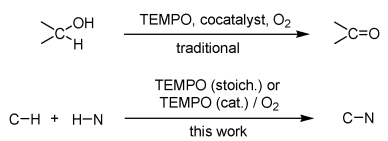
The aminoxyl radical TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl radical) has been proven to be a powerful promoter for the aerobic oxidation of alcohols.[1] However, its application in C–H bond activation/functionalization[2] and the synthesis of heterocycles is rarely reported. Herein, we wish to report a novel and efficient approach for the aerobic oxidative synthesis of 2-aryl quinazolines *via* benzyl C–H bond amination using the 4-hydroxy-TEMPO radical as the catalyst (Scheme 1), by a one-pot reaction of arylmethanamines with 2-aminobenzoketones and 2-aminobenzaldehydes.

Six-membered heterocycles, such as quinazolines, are present in natural products and synthetic pharmaceutical compounds.[3] Substituted quinazolines have been synthesized by a number of methods involving a variety of substrates.[4] Recently, facile approaches for the synthesis of 2-phenyl quinazolines using 2-aminobenzoketones and benzylamines as the starting materials and TBHP (*tert*-butyl hydroperoxide) as the oxidant promoted by iodine or copper nanoparticles have been reported.[5] Although accessible starting materials were used and good yields were obtained, a stoichiometric and non-renewable oxidant is still needed and the reaction scale and substrate applicability are limited. Therefore, a more effective and environmentally friendly process is needed.

Catalytic oxidative reactions using oxygen as the terminal oxidant have received much attention in view of the concepts of green chemistry and atom economy. Recently, we developed an efficient aerobic oxidative process for the synthesis of benzoxazoles, benzimidazoles and benzothiazoles catalyzed by TEMPO.[6] As an extension of this chemistry, we attempted to synthesize 2-aryl quinazolines by a one-pot aerobic reaction of arylmethanamines with 2-aminobenzoketones and 2-aminobenzaldehydes using TEMPO as the catalyst.

The study was initiated by treating a mixture of 2-aminobenzophenone **1a** (1 equiv.) and benzylamine **2a** (1.5 equiv.) in *o*-xylene with a stoichiometric amount of 4-hydroxy-TEMPO **3** as the oxidant[7] at 120 °C in an argon atmosphere. As expected, the desired reaction took place, leading to the formation of the product 2,4-diphenylquinazoline **4aa** in excellent yield (Scheme ESI-1 and Table ESI-1 in ESI‡).[8] 4-Hydroxy-TEMPO **3** was converted to 4-hydroxy-TEMPOH during the reaction. As 4-hydroxy-TEMPOH can be oxidized quantitatively to **3** by oxygen or air, a strategy for the aerobic catalytic oxidative synthesis of 2-aryl quinazolines using **3** as the catalyst was developed.

In order to optimize the reaction conditions, we used various solvents and discovered that nonpolar aromatic solvents gave better results than polar solvents under the same reaction conditions (Table 1, entries 1–6). Such a phenomenon is in accordance with our previous observations.[6] In addition, the reaction temperature significantly affected the reaction, as high temperatures accelerated the rate of hydrogen abstraction between the TEMPO radical and the substrate (Table 1, entries 3 and 5–7). Moreover, the amount of the solvent also affected the reaction rate, as a high reaction concentration could facilitate the oxidative process (Table 1, entry 8). It is noteworthy that using 15–20 mol% of **3** as the catalyst would guarantee excellent yields of **4aa** (Table 1, entries 6, 7 and 9), while the reaction could not proceed in the absence of **3** under the same conditions, indicating that **3** is the key catalyst in the reaction (Table 1, entry 11). In addition, another aminoxyl radical precursor NHPI (*N*-hydroxy-phthalimide) was also tested in the reaction (Table 1, entries 12–14). Recently, NHPI has been widely used for the C–H oxidation of hydrocarbons



Scheme 1 TEMPO-mediated benzyl C–H bond oxidation and C–N bond formation.

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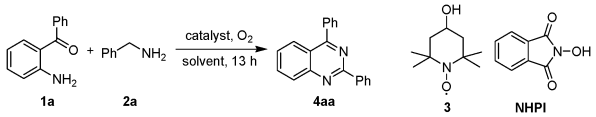
† Dedicated to Professor Zhong-Li Liu on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: General information, experimental details, characterization data for the products. See DOI: 10.1039/c1cc12308d

Table 1 Optimization of the catalytic aerobic oxidative synthesis of 2-aryl quinazoline[a]



Entry	Catalyst (mol%)	Solvent	T/°C	Yield[b] (%)
1	**3** (20)	MeCN	80	0[c]
2	**3** (20)	ethyl acetate	80	0[c]
3	**3** (20)	benzene	80	trace[c]
4	**3** (20)	*t*-butanol	120	0[c]
5	**3** (20)	toluene	100	43
6	**3** (20)	*o*-xylene	120	87
7	**3** (20)	*o*-xylene	140	91
8	**3** (20)	*o*-xylene[d]	140	35
9	**3** (15)	*o*-xylene	140	88
10	**3** (10)	*o*-xylene	140	66[e]
11	—	*o*-xylene	140	0
12	NHPI (10)	MeCN	80	0[c]
13	NHPI (10)	*o*-xylene	140	0[c]
14	NHPI (10)	PhCl	140	0[c]

[a] A mixture of 2-aminobenzophenone **1a** (1 mmol), benzylamine **2a** (3 mmol), catalyst (0.1–0.2 mmol) and solvent (0.3 mL) was stirred for 13 h under O_2 at different temperatures. [b] Isolated yield based on substrate **1**. [c] TLC analysis. [d] 3 mL solvent was used. [e] After 24 h.

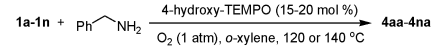
and alcohols by an *in situ* generated PINO (phthalimido-*N*-oxyl) radical under oxygen atmosphere[1a–c,9] and we also reported its application in the aerobic oxidative dehydrogenation of dihydropyridines and pyrazolines.[10] However, NHPI is inefficient in the reaction because it would be deactivated by benzylamine.[11] Therefore, 15–20 mol% of **3** was used in the following reaction.

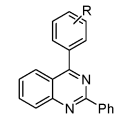
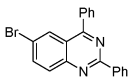
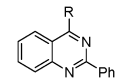
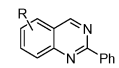
The 4-hydroxy-TEMPO-catalyzed aerobic oxidative process was not only suitable for 2-aminobenzoketones but also for 2-aminobenzaldehydes. 2-Aminobenzoaryl and alkyl ketones (**1a–1i**) gave excellent yields of 4-aryl and 4-alkyl quinazolines (Table 2, entries 1–9), respectively, and 2-aminobenzaldehydes (**1j–1n**) participated in the reaction to give the corresponding 4-H quinazolines in good yields (Table 2, entries 10–15). Notably, the aerobic oxidative reaction could also be easily carried out on a gram scale without difficulty, thereby delivering **4aa** in good yield.

4-Substituted benzylamines (**2a–2h**) with a range of electronic properties also gave the corresponding quinazolines (Table 3). Weak steric effects were observed when *ortho*, *meta* and *para*-substituted benzylamines were used in the reaction (Table 3, entries 2–6). In addition, a heterocyclic methanamine, such as 3-picolylamine (**2i**), could also be used in the reaction, resulting in 2-(3-picolyl)-4-phenyl quinazoline in excellent yields (Table 3, entry 9).

To gain some insight into the mechanism of the above-mentioned process, the intermolecular kinetic isotopic effects (KIE) were measured through a competition process, by subjecting **1j** to a 1 : 1 mixture of **2a** and **2a–d$_7$** (Scheme 2). The relative rate constant of **2a** to **2a–d$_7$** was determined to be 20.3,[12] indicating that the hydrogen atom abstraction from the benzyl C–H bond of the imines **A** by TEMPO is a rate-determining step during the oxidation process. The measured high value of KIE also suggests a possible involvement of the

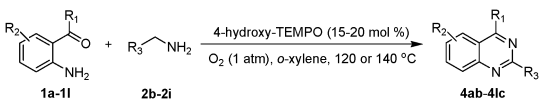
Table 2 The catalytic aerobic reaction of 2-aminobenzoketones and 2-aminobenzaldehydes with benzylamine[a]

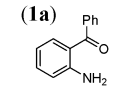
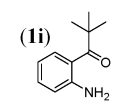
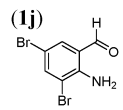
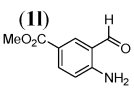


Entry	Product	R	t/h	Yield[b] (%)
1		(**1a**) H	13	91, 80[c] (**4aa**)
2		(**1b**) 2,5-di-Me	24	63 (**4ba**)
3		(**1c**) 4-MeO	15	88 (**4ca**)
4		(**1d**) 4-Br	11	91 (**4da**)
5		(**1e**)	10	91, 88[d] (**4ea**)
6		(**1f**) Et	7	57 (**4fa**)
7		(**1g**) *n*-Bu	9	70 (**4ga**)
8		(**1h**) *i*-Pr	7	60 (**4ha**)
9		(**1i**) *s*-Bu	10	78 (**4ia**)
10[e]		(**1j**) 6,8-di-Br	10	0[f] (**4ja**)
11[e]		(**1j**) 6,8-di-Br	10	80, 73[d] (**4ja**)
12[e]		(**1k**) 6-NO_2	4	65 (**4ka**)
13[e]		(**1l**) 6-CO_2CH_3	6	65 (**4la**)
14[e]		(**1m**) 7-CO_2CH_3	6	60 (**4ma**)
15[e]		(**1n**) H	4	70 (**4na**)

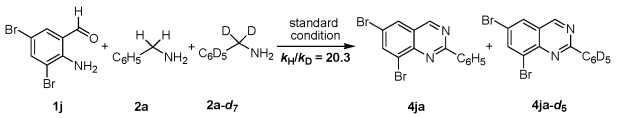
[a] A mixture of 2-aminobenzoketone or 2-aminobenzaldehyde **1** (1 mmol), benzylamine **2a** (3 mmol), 4-hydroxy-TEMPO **3** (0.2 mmol) and *o*-xylene (0.3 mL) was stirred under O_2 at 140 °C. [b] Isolated yield based on substrate **1**. [c] Gram scale. [d] 0.15 mmol of **3** was used. [e] At 120 °C. [f] In the absence of **3**.

Table 3 The catalytic aerobic reaction of 2-aminobenzoketones and 2-aminobenzaldehydes with arylmethanamines[a]

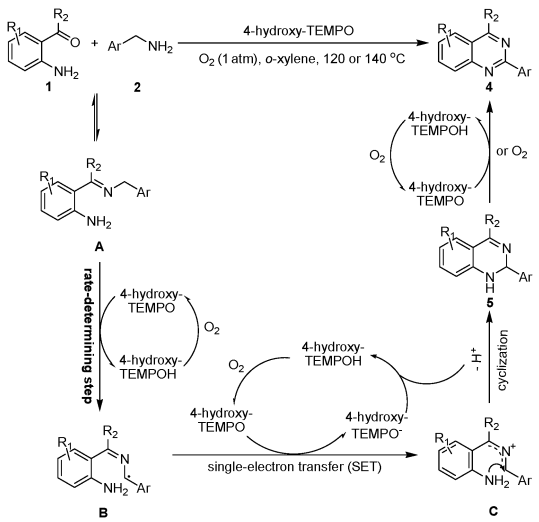


Entry	Substrate **1**	R_3	t/h	Yield[b] (%)
1	 (**1a**)	4-$MeOC_6H_4$ (**2b**)	15	90, 87[c] (**4ab**)
2		4-MeC_6H_4 (**2c**)	10	88 (**4ac**)
3		3-MeC_6H_4 (**2d**)	12	80 (**4ad**)
4		2-MeC_6H_4 (**2e**)	13	70 (**4ae**)
5		4-ClC_6H_4 (**2f**)	13	88 (**4af**)
6		2-ClC_6H_4 (**2g**)	14	77 (**4ag**)
7		4-FC_6H_4 (**2h**)	20	73 (**4ah**)
8		3-pyridinyl (**2i**)	13	82 (**4ai**)
9	 (**1i**)	4-MeC_6H_4 (**2c**)	12	70 (**4ic**)
10		4-ClC_6H_4 (**2f**)	13	65, 57[c] (**4if**)
11[d]	 (**1j**)	4-MeC_6H_4 (**2c**)	8	73, 62[c] (**4jc**)
12[d]		4-FC_6H_4 (**2h**)	15	70, 62[c] (**4jh**)
13[d]	 (**1l**)	4-MeC_6H_4 (**2c**)	10	71, 64[c] (**4lc**)

[a] A mixture of 2-aminobenzoketone or 2-aminobenzaldehyde **1** (1 mmol), arylmethanamine **2** (3 mmol), 4-hydroxy-TEMPO **3** (0.2 mmol) and *o*-xylene (0.3 mL) was stirred under O_2 at 140 °C. [b] Isolated yield based on substrate **1**. [c] 0.15 mmol of **3** was used. [d] At 120 °C.



Scheme 2 The kinetic isotope effect (KIE) experiment.



Scheme 3 A plausible mechanism for the 4-hydroxy-TEMPO-catalyzed aerobic oxidative synthesis of 2-aryl quinazolines.

quantum tunneling effect. Similar KIE was observed for the reaction of ethyl benzene with PINO radical.[13]

Based on the above observations, we propose a plausible mechanistic pathway for the present oxidation. We believe that 4-hydroxy-TEMPO **3** initially abstracts a hydrogen atom from the benzyl C–H bond of compound **A** to produce the α-amino benzyl radical **B** and 4-hydroxy-TEMPOH, which can be reoxidized to **3** by oxygen. The α-amino benzyl radical **B** is further oxidized by **3** *via* single-electron transfer (SET) to produce carbocation intermediate **C**,[14] which is attacked by the amino group *via* intramolecular cyclization and subsequent deprotonation to form the corresponding compound 1,2-dihydroquinazoline **5**.[15] The 4-hydroxy-TEMPO anion traps a proton to form 4-hydroxy-TEMPOH, which can be reoxidized to **3** by oxygen. Next, **5** can be easily aromatized to the target compound quinazolines **4** by **3** or oxygen. A proposed oxidative cycle is shown in Scheme 3.

In conclusion, a novel, efficient and environmentally friendly one-pot approach for the aerobic oxidative synthesis of 2-aryl quinazolines *via* benzyl C–H bond amination, using 2-aminobenzoketones or 2-aminobenzaldehydes and arylmethanamines as the accessible starting materials and catalyzed by 4-hydroxy-TEMPO, was successfully developed. In addition, a mechanistic proposal is made on the basis of the kinetic isotope effects and isolation of the reaction intermediate 1,2-dihydroquinazoline. The extension of this catalytic system for the preparation of other useful heterocycles is under way in our laboratory.

We thank the National Natural Science Foundation of China (20902040) and the Fundamental Research Funds for the Central Universities (lzujbky-2009-74) for financial support.

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14 For the oxidation of the α-amino carboradical to the carbocation by TEMPO *via* SET, see ref. 1*b*.

15 1,2-Dihydroquinazoline **5** was obtained as the reaction intermediate and could be oxidized easily to quinazoline **4** using TEMPO or oxygen as the oxidant. For details, see electronic supplementary information†.

