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Original article

Efficient synthesis of 2-arylquinazolines *via* copper-catalyzed dual oxidative benzylic C–H aminations of methylarenes

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ABSTRACT

A novel copper-catalyzed dual oxidative benzylic C–H aminations of methylarenes with 2-aminobenzoketones in the presence of ammonium acetate was developed. This reaction represents a new avenue for 2-arylquinazolines with good yields. A key intermediate was detected and the kinetics isotope effect (KIE) indicated that C–H bond cleavage was the rate-determining step.

1. Introduction

In recent years, the synthesis of quinazolines and its derivatives has become a hot spot in organic synthetic chemistry due to their broad biological and medicinal activities, such as antibacterial, anticarcinogenic and antihypertensive properties [1–5]. Usually, the traditional synthesis of quinazolines involves reactions of Bischler cyclization, dicarbonyl compounds with diamines and reactions from 2-aminobenzonitriles or anthranilic acids as well as *N*-arylbenzamides [6–9]. Our group have been focusing in the synthesis of quinazolines and a variety of excellent approaches to the quinazolines were developed [10–13]. At the same time, other groups also developed some novel methods to prepare these quinazoline derivatives [14–20]. For example, Li [20] developed a KI-catalyzed synthesis of quinazolines from 2-aminobenzoketones, toluene and ammonium salt. In these syntheses, the key step is to construct C–N bonds of the cyclization. Recently, transition-metal-catalyzed oxidative aminations of sp^3 C–H bond have emerged as important methods for C–N bond formations because of short steps and atom-economical advantages [21–38]. In particular, copper as an inexpensive and lowly toxic metal catalyst, has been employed to catalyze the formation of C–N bond *via* a sp^3 C–H amination [22,39–47]. For instance, copper-catalyzed cascade coupling of 2-halobenzaldehyde with acetamidine hydrochloride (or benzaldehyde) to construct C–N bond was reported [48–52]. Nevertheless, these methods generally suffered from limitations of substrate generality and availability of starting material. Especially, for those substrates bearing electro-withdrawing group, there reaction hardly occurs. Therefore, to develop some novel and efficient method for the synthesis of quinazolines still remains highly desirable.

Herein, we report a novel copper-catalyzed double oxidative C–H aminations of methylarenes with 2-aminobenzoketones and ammonium acetate, constructing one C=N bond and one C–N bond in one step.

2. Experimental

Unless otherwise indicated, all commercial reagents and solvent were used without additional purification. ^{1}H NMR spectra were recorded with a Bruker AVIII-400 spectrometer. Chemical shifts (in ppm) were referenced to tetramethylsilane ($\delta = 0$) in $CDCl_3$ as internal standard. ^{13}C spectra were obtained by the same NMR spectrometer and were calibrated with $CDCl_3$ ($\delta = 77.00$). HRMS (ESI) were recorded on a Waters^{TM} Q-TOF Premier Mass Spectrometer.

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2.1. Preparation of substrates

Substrates **1a**, **1f**, **1m** and **1n** are commercially available. Other substrates (**1b**–**1e**, **1g**–**1l** and **1o**) were prepared using our previous literature procedure [10].

2.2. Experimental Procedure for preparation of 3

Substrate **1** (0.2 mmol), NH_4OAc (31.2 mg, 0.4 mmol), $CuCl_2{\cdot}2H_2O$ (6.8 mg, 20 mol%), TBHP (90 μL, 70% aq, 0.6 mmol), were added to a tube, followed by addition of solvent **2** (2 mL). The mixture was stirred at assigned temperature and monitored by TLC. The solution was cooled to r.t., diluted with ethyl acetate (5 mL), washed with saturated aqueous sodium hydrogen sulfite. The aqueous layers was extracted with EtOAc (3× 10 mL), the combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by column chromatography on silica gel (petroleum ether:ethyl acetate = 20:1) to afford the desired product **3**.

Characterization data of compounds **3** were given in Supporting information.

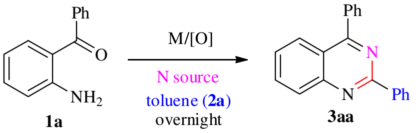
3. Results and discussion

We began our studies with the reaction of (2-amino-phenyl)-phenyl-methanone (**1a**, 1 equiv.), NH_4OAc (2 equiv.), *tert*-butyl hydroperoxide (TBHP, 70% in water, 2 equiv.) as an oxidant, 20 mol% $Cu(OAc)_2$ as catalyst and 2 mL toluene (**2a**) as the solvent and reagent. When heated under air at 80 °C overnight, 2,4-diphenyl quinazoline (**3aa**) was obtained in 43% yield (Table 1, entry 1). When we replaced $Cu(OAc)_2$ with other transition metal acetates, the reaction yield was reduced (Table 1, entries 2–4). Among various copper salts examined (Table 1, entries 5–9), copper chloride dehydrate gave the best yield of 86% (Table 1, entry 6). Next, we optimized the oxidant such as di-*tert*-butyl peroxide (DTBP), cumene hydroperoxide (CHP), H_2O_2 (30% in water) and O_2 (Table 1, entries 10–13). Also, the nitrogen sources (Table 1, entries 14–16) and the reaction temperature (Table 1, entries 17–19) were optimized, but no better yield was obtained. In addition, we increased the loading of TBHP to 3 equiv. since **1a** was not used out, giving **3aa** in 88% yield (Table 1, entry 20). Finally, the optimal conditions were described in entry 20.

Subsequently, we investigated the substrate scope of this reaction under the optimized reaction conditions and obtained the product (**3aa**–**3oa**, Fig. 1). Firstly, when R^1 is an aromatic substituent, the reaction of substrates **1a**–**1d** can be carried out to give the corresponding products **3aa**–**3da** with good yields. Substrates with electro-withdrawing group (4-F and 4-Br) gave higher yields than substrates with electro-donating group (4-Me) on the phenyl ring. When R^1 is a 2-naphthyl substituent, the corresponding product **3ea** was generated with an 88% yield. To our delight, substrate **1f**–**1l** with aliphatic substituents also gave the corresponding products **3fa**–**3la** in good yields. When R^1 is an aliphatic alkyl group, the alkyl with the tertiary carbon favoured the reaction, as shown in **3la**. Notably, it was found that R^1 benzylic C–H can be oxidized into C=O bond to give **3ga′**. On the other hand, R^2 substituent had a little influence on the reaction. When R^2 alternated from electron-donation group (5-Me) to electro-withdrawing group (5-Cl and 5-NO_2), the yields was reduced to some extent, as shown in **3ma**, **3na** and **3oa**.

Then we tried to use different methylarenes **2** as the solvent and regent to extend generality of this reaction (Table 2). Both methylarenes bearing electro-donating group (**2b**–**2e**) and weaker electro-withdrawing group (**2f** and **2g**) could generate the desired products **3ab**–**3ag** with good to excellent yields. The position of the methyl group on the phenyl ring of **2** affected the reaction yields slightly (Table 2, entries 1–3). However, when a strong electro-withdrawing-group was induced into *ortho*-position (**2h**), no

Table 1
Optimization of reaction conditions.[a]



Entry	Catalyst	Oxidant	N sources	Temp (°C)	Yield (%)[b]
1	$Cu(OAc)_2$	TBHP	NH_4OAc	80	43
2	$Co(OAc)_2{\cdot}4H_2O$	TBHP	NH_4OAc	80	42
3	$Ni(OAc)_2{\cdot}4H_2O$	TBHP	NH_4OAc	80	38
4	$Pd(OAc)_2$	TBHP	NH_4OAc	80	24
5	$CuBr_2$	TBHP	NH_4OAc	80	46
6	$CuCl_2{\cdot}2H_2O$	TBHP	NH_4OAc	80	86
7	$Cu(OH)_2$	TBHP	NH_4OAc	80	62
8	$CuSO_4{\cdot}5H_2O$	TBHP	NH_4OAc	80	67
9	$CuCO_3$	TBHP	NH_4OAc	80	51
10	$CuCl_2{\cdot}2H_2O$	DTBP	NH_4OAc	80	<10
11	$CuCl_2{\cdot}2H_2O$	CHP	NH_4OAc	80	43
12	$CuCl_2{\cdot}2H_2O$	H_2O_2	NH_4OAc	80	n.d.
13	$CuCl_2{\cdot}2H_2O$	O_2	NH_4OAc	80	n.d.
14	$CuCl_2{\cdot}2H_2O$	TBHP	NH4Cl	80	50
15	$CuCl_2{\cdot}2H_2O$	TBHP	$(NH_4)_2SO_4$	80	45
16	$CuCl_2{\cdot}2H_2O$	TBHP	$NH_3{\cdot}H_2O$[c]	80	65
17	$CuCl_2{\cdot}2H_2O$	TBHP	NH_4OAc	90	78
18	$CuCl_2{\cdot}2H_2O$	TBHP	NH_4OAc	100	70
19	$CuCl_2{\cdot}2H_2O$	TBHP	NH_4OAc	110	65
20	$CuCl_2{\cdot}2H_2O$	TBHP	NH_4OAc	80	88[d]

[a] Reaction conditions: **1a** (0.2 mmol), N source (0.4 mmol), catalyst (0.04 mmol), oxidant (0.4 mmol), **2a** (2 mL), overnight.
[b] Isolated yield, n.d. = not detected.
[c] 25% in water.
[d] 0.6 mmol TBHP was used.