EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: Visible-light induced benzylic C-H functionalization for the synthesis of 2-arylquinazolines

Authors: Jingchang Zhang, Qibao Wang, Yongen Guo, Lin Ding, Maocai Yan, Yinglin Gu, and Jiajia Shi

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900996

Link to VoR: http://dx.doi.org/10.1002/ejoc.201900996

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201900996

Visible-light induced benzylic C-H functionalization for the synthesis of 2-arylquinazolines

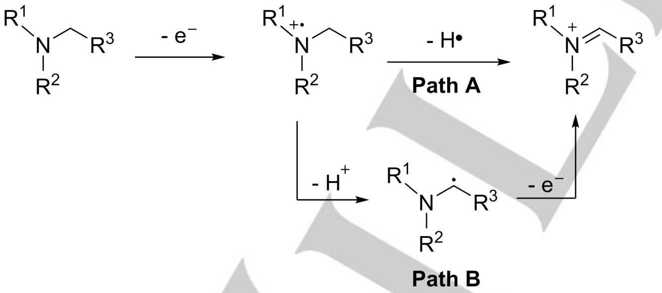
Jingchang Zhang,* Qibao Wang,* Yongen Guo, Lin Ding, Maocai Yan, Yinglin Gu, Jiajia Shi

Abstract: This work reports a mild and efficient approach for the synthesis of substituted quinazolines using 1-(2-aminoaryl)ethan-1-ones in conjunction with arylmethanamines as starting materials via visible light induced benzylic C-H functionalization. The reaction proceeded at room temperature with low catalyst loading and the reaction system was clean from beginning to end. Significantly, this method exhibited good tolerance even to free hydroxyl group and amino group contained in substrates.

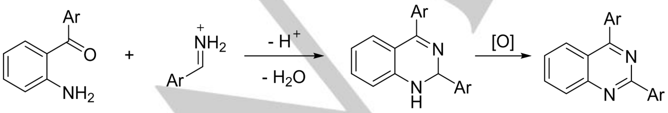
Introduction

The C-H activation catalyzed by photoredox catalysts including organic photoredox catalysts and transition metal complexes has been widely used in the organic synthesis because of its efficiency and mildness[1]. These reactions usually proceeded at room temperature with low catalyst loading. Quinazolines were a kind of six-membered natural products with medicinal value[2] and a lot of methods for the construction of quinazolines have been developed from diffrent substrates such as 2-(aminomethyl)arylamines[3], 2-aminoarylamides[4], etc[5]. Although synthesis of quinazoline derivates using 2-aminobenzoketones or 2-aminobenzaldehydes and arylmethanamines as starting materials have been developed, high temperature was usually needed and substrates tolerance was limited in these methods[6]. These methods all involved a benzylic C-H activation of arylmethanamines.

As we knew, amines were very good electron donors, readily undergoing single-electron oxidation by excited-state photocatalyst to yield an aminium radical cation which had the effect of lowering the bond dissociation energy of the C−H bonds at amine α-positions[7]. A good hydrogen atom acceptor present in the reaction could abstract a hydrogen atom from α-position of amine, converting the aminium radical cation to the iminium ion (**Scheme 1, Path A**). At same time, aminium radical cation had lower pKa value of the protons at α-positions[8] that might be deprotonated to yield an α-amino radical and then converted to iminium ion via a second single-electron oxidation[9] (**Scheme 1 , Path B**). These processes usually proceeded at room temperature under visible light irradiation, and the catalytically generated iminium ions could undergo cycloaddition with 2-aminobenzoketones to yield 1, 2-dihydroquinazolines which were subsequently oxidized to generate corresponding quinazoline products (**Scheme 2**). Herein, we aimed to develop a mild and efficient approach with higher substrates tolerance for the synthesis of 2-arylquinazolines via visible light induced benzylic C-H functionalization at room temperature using 1-(2-aminoaryl)ethan-1-ones in conjunction with arylmethanamines as starting materials.



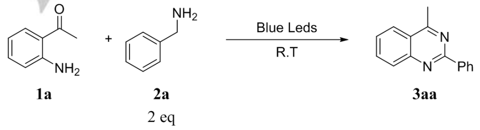
Scheme 1. Pathways of Amine Oxidation to Iminium Ions[1a]



Scheme 2. Cycloaddition between 2-aminobenzoketones and arylmethaniminium ions

Results and Discussion

Table 1. Optimization of the Reaction Conditions^{a}



Entry	Catalyst (mol%)	Oxidant (eq)	Additive (eq)	Solvent (V:V)	Yield(%)^{b}
1	$Ru(bpy)_3Cl_2$(2)	TBPB(4)		DMSO	55
2	$Ir(ppy)_3$(2)	TBPB(4)		DMSO	65
3^{c}	Eosin Y(2)	TBPB(4)		DMSO	30
4	$Ir(ppy)_3$(2)	TBHP(4)		DMSO	20
5	$Ir(ppy)_3$(2)	DTBP(4)		DMSO	10
6	$Ir(ppy)_3$(2)	TBPB(4)	K_2CO_3(3)	DMSO	50
7	$Ir(ppy)_3$(2)	TBPB(4)	Na_2CO_3(3)	DMSO	50
8	$Ir(ppy)_3$(2)	TBPB(4)	Li_2CO_3(3)	DMSO	69
9	$Ir(ppy)_3$(2)	TBPB(4)	Li_2CO_3(3)	MeCN	62
10	$Ir(ppy)_3$(2)	TBPB(4)	Li_2CO_3(3)	$PhCF_3$	50
11	$Ir(ppy)_3$(2)	TBPB(4)	Li_2CO_3(3)	DMSO:MeCN=1:1	67
12	$Ir(ppy)_3$(2)	TBPB(4)	Li_2CO_3(3)	DMSO:$PhCF_3$=1:1	77
13	$Ir(ppy)_3$(2)	TBPB(4)	Li_2CO_3(3)	DMSO:$PhCF_3$=1:4	81
14	**$Ir(ppy)_3$(1)**	**TBPB(4)**	**Li_2CO_3(3)**	**DMSO:$PhCF_3$=1:4**	**81**
15		TBPB(4)	Li_2CO_3(3)	DMSO:$PhCF_3$=1:4	-
16	$Ir(ppy)_3$(1)		Li_2CO_3(3)	DMSO:$PhCF_3$=1:4	-
17^{d}	$Ir(ppy)_3$(1)	TBPB(4)	Li_2CO_3(3)	DMSO:$PhCF_3$=1:4	-

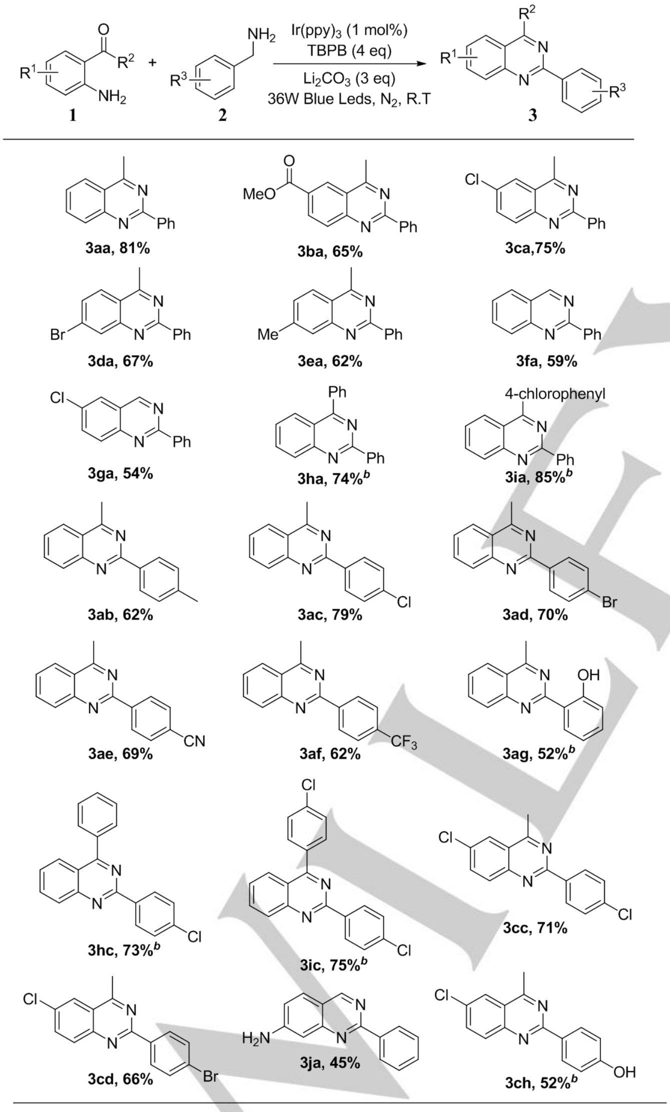
^{a} A mixture of 1-(2-aminophenyl)ethan-1-one **1a** (0.2 mmol), phenylmethanamine **2a** (0.4 mmol), oxidant (0.8 mmol), catalyst (0.004 mmol except where otherwise indicated) and solvent (1 mL) was stirred for12 h under N_2 atmosphere with blue leds irradiation. ^{b} Isolated yield based on substrate **1a**. ^{c} react with green leds irradiation. ^{d} without Blue leds irradiation

School of Pharmacy, Jining Medical University, 669 Xueyuan Road, Rizhao, Shandong, China
Email: zhangjingchang84@outlook.com
http://yxy.jnmc.edu.cn/2017/0530/c160a862/page.htm

Supporting information for this article is given via a link at the end of the document.

We started our research by treating 1-(2-aminophenyl)ethan-1-one (**1a**) with 2 eq phenylmethanamine (**2a**), 2 mol % Ru(bpy)$_3$Cl$_2$ and 4eq tert-butyl peroxybenzoate (TBPB) in DMSO and got the desired product **3aa** in 55% yield (Table 1, Entry 1). With this good result in hand, we sequentially optimized a series of reaction conditions including catalysts, oxidants, additives, and solvents. Compared to Ru(bpy)$_3$Cl$_2$, Ir(ppy)$_3$ was cheaper and obviously improved the yield while Eosin Y decreased the yield (Table 1, Entry 2-3). The oxidative efficiency of TBHP and DTBP were all inferior to TBPB (Table 1, Entry 4-5). Addition of Li$_2$CO$_3$ improved the yield to 69% smoothly while K$_2$CO$_3$ and Na$_2$CO$_3$ all decreased the yield (Table 1, Entry 6-8). Various solvents, such as MeCN, PhCF$_3$ and a series of mixed solvents, were sequentially examined, among which the mixed solvent of DMSO and PhCF$_3$ (1:4, v/v) gave the best result (Table 1, Entry 9-13). Reducing catalyst loading did not decrease the reaction yield (Table 1, Entry 14). Moreover, in the absence of catalyst, oxidant and blue leds irradiation respectively, there was no product observed which indicated catalyst, oxidant and blue leds irradiation were all necessary for the reaction (Table 1, Entry 15-17). After a series of reaction conditions optimization, we finally got the optimal reaction condition: the mixture of 1-(2-aminophenyl)ethan-1-one (**1a**), 2 eq phenylmethanamine (**2a**), 1 mol% Ir(ppy)$_3$, 4 eq TBPB, 3 eq Li$_2$CO$_3$ and solvent (PhCF$_3$:DMSO=4:1, v/v) were stirred for 12 h under N$_2$ atmosphere with blue leds irradiation (Table 1, Entry 14).

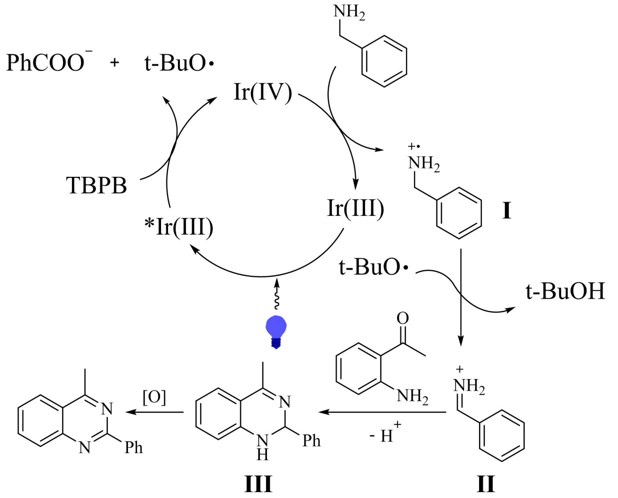
Table 2. Preparation of 2-aryl quinazolines [a]



[a] A mixture of **1** (0.2 mmol), **2** (0.4 mmol), Ir(ppy)$_3$ (0.002 mmol), TBPB (0.8 mmol), Li$_2$CO$_3$ (0.6 mmol) and PhCF$_3$:DMSO=4:1 (v/v, 1 mL) was stirred for 12 h under N$_2$ atmosphere with blue leds irradiation. [b] PhCF$_3$:DMSO=1:1(v/v, 1 ml) was used as solvent

We subsequently investigated the reaction scope of substrates and prepared a series of substituted quinazolines as shown in **Table 2**. For the 1-(2-aminoaryl)ethan-1-ones, it was interesting that the anilino ring bearing whether electron-donating groups or electron-withdrawing groups all decreased the reaction yield at different level. Electron-donating groups had more adverse effects than electron-withdrawing groups on this reaction. 2-aminobenzaldehydes or 2-aminobenzoketones could also participate in the reaction smoothly and give the corresponding products in good to excellent yield. For the 2-aminobenzoketones, the introduction of electron-withdrawing groups to the *para* position of the free phenyl ring could obviously improve the yield (Table 2, **3ha**, **3ia**). The reaction scope of arylmethanamines were also examined. A series of arylmethanamines participated in the reaction smoothly and gave the corresponding products in good to excellent yield. The introduction of whether electron-donating groups or electron-withdrawing groups to phenyl ring of arylmethanamines all decreased the yield at different level, especially the electron-donating groups. It was noteworthy that free hydroxyl group borne on the phenyl ring of arylmethanamines or free amino group borne on the anilino ring of 2-aminobenzaldehydes could also be tolerated perfectly in the reaction which was rarely reported in the related field of transition metal catalyzed C-H functionalization (Table 2, **3ag**, **3ja, 3ch**). We also examined the applicability of alkanamines for this method. Unfortunately, there were no products observed when alkanamines participated in the reaction. The results may due to unstability of alkaniminium ions.

A proposed mechanism was shown in **Scheme 3**. The photocatalyst Ir(ppy)$_3$ absorbed visible light to give the strongly reducing excited-state *Ir(ppy)$_3$ ($E_{1/2}^{IV/*III}$ = −1.73 V vs SCE)[10] which was oxidized by TBPB to generate benzoate anion, tert-butoxy radical and Ir(IV) intermediate ($E_{1/2}^{IV/III}$ = +0.77 V vs SCE). This Ir(IV) intermediate accepted an electron from phenylmethanamine to generate intermediate **I**. tert-Butoxy radical might then abstract a hydrogen atom from the benzylic



Scheme 3. Proposed mechanism

position of intermediate **I** to give intermediate **II**. The intermediate **II** underwent cycloaddition with 1-(2-aminoaryl)ethan-1-ones to give intermediate **III** which was subsequently oxidized to generate corresponding quinazoline product. Abstracting a hydrogen atom from the benzylic position of phenylmethanamine by tert-butoxy radical initially, followed by oxidation by Ir(IV) intermediate to generate intermediate **II** was also plausible.

Conclusion

In conclusion, we successfully developed a mild and efficient approach for synthesis of quinazolines via photo-induced C-H functionalization using 1-(2-aminoaryl)ethan-1-ones in conjunction with arylmethanamines as starting materials and Ir(ppy)$_3$ as photocatalyst. The reaction proceeded at room temperature with low catalyst loading and the reaction system was clean from beginning to end. A series of substituted groups contained in substrates even including free hydroxyl group and amino group were well-suited for this process. A plausible mechanism was proposed based on the reported theories. The application of this new method for the preparation of other useful heterocycles is underway in our laboratory.

Experimental Section

Genaral Procedure: 1-(2-aminoaryl)ethan-1-ones or 2-aminobenzaldehydes or 2-aminobenzoketones (0.2 mmol), Ir(ppy)$_3$ (0.002 mmol, 13 mg) and Li$_2$CO$_3$ (0.6 mmol, 44.3 mg) were added to a Schlenk tube. The tube was degassed and refilled with N$_2$ for three times. Then arylmethanamines (0.4 mmol), TBPB (0.8 mmol, 155.4 mg) and solvent (PhCF$_3$:DMSO=4:1, V/V, 1ml) was added by syringe. The reaction mixture was stirred at room temperature for 12h under the irradiation of a 36 W blue LEDs (distance app. 3.0 cm from the bulb). Then the reaction mixture was extracted with EtOAc (3 × 5 ml)and water. The combined organic extracts were dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc as an eluent) to afford 2-arylquinazolines.

Keywords: photocatalyst • room temperature• quinazolines

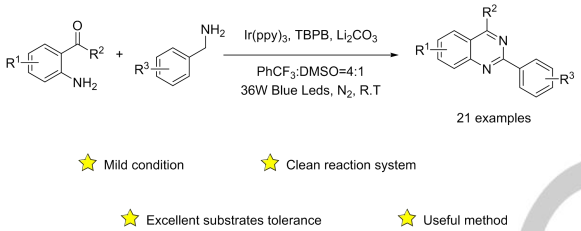
1. For the reviews of photo-induced C-H functionalization, please see: (a) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322-5363. (b) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075-10166. (c) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102-113. (d) K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.* **2016**, *116*, 10035-10074. (e) H. Yi,G. Zhang,H. Wang,Z. Huang,J. Wang,A. K. Singh, A. W. Lei, *Chem. Rev.* **2017**, *117*, 9016-9085. (f) D. Ravelli, S. Protti, M. Fagnoni, *Chem. Rev.* **2016**, *116*, 9850-9913. (g) D. Ravelli, D. Dondi, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2009**, *38*, 1999-2011. (h) M. Fagnoni, D. Dondi, D. Ravelli, A. Albini, *Chem. Rev.* **2007**,*107*, 2725-2756.
2. (a) A. Foster, H. A. Coffrey, M. J. Morin, F. Rastinejad, *Science*. **1999**, *286*, 2507-2510. (b) R. Gundla, R. Kazemi, R. Sanam, R. Muttineni, J. A. R. P. Sarma, R. Dayam, N. Neamati, *J. Med. Chem.* **2008**, *51*, 3367-3377. (c) A. Luth, W. Lowe, *Eur. J. Med. Chem.* **2008**, *43*, 1478-1488.
3. (a) R. Gujjarappa, S. K. Maity, C. K. Hazra, N. Vodnala, S. Dhiman, A. Kumar, U. Beifuss, C. C. Malakar, *European. Journal. Of. Organic. Chemistry.* **2018**, *33*, 4628-4638. (b) H. Yuan,W.J. Yoo, H. Miyamura, S.Kobayashi, *Adv. Synth. Catal*. **2012**, *354*, 2899-2904.
4. (a) S. Sharma, D. Bhattacherjee, P. Das, *Org. Biomol. Chem*. **2018**, *16*, 1337-1342. (b) Z. Zhang, M. Wang, C. Zhang, Z. Zhang, J. Lu, F. Wang, *Chemical Communications*. **2015**, *51*, 9205-9207.
5. (a) K. Ezaki, K. Kobayashi, *Helvetica. Chimica. Acta*. **2014**, *97*, 822-829. (b) M. Vashist, K. Kushwaha, R. Kaushik, S. C. Jain, *RSC. Advances*. **2014**, *4*, 23679-23684.
6. (a) J. T. Zhang, C. M. Yu, S. J. Wang, C. F. Wan, Z. Y. Wang, *Chem. Commun.* **2010**, *46*, 5244-5246. (b) J. T. Zhang, D. P. Zhu, C. M. Yu, C. F. Wan, Z. Y. Wang, *Org. Lett.* **2010**, *12*, 2841-2843. (c) B. Han, C. Wang, R. F. Han, W. Yu, X. Y. Duan, R. Fang, X. L. Yang, *Chem.Commun.* **2011**, *47*, 7818-7820. (d) Y. Z. Yan, Y. H. Zhang, C. T. Feng, Z. G. Zha, Z. Y. Wang, *Angew. Chem. Int. Ed.* **2012**, *51*, 8077-8081.
7. J. P. Dinnocenzo, T. E. Banach, *J. Am. Chem. Soc.* **1989**, *111*, 8646-8653.
8. D. D. M. Wayner, J. J. Dannenberg, D. Griller, *Chem. Phys. Lett.* **1986**, *131*, 189-191.
9. V. D. Parker, M. Tilset, *J. Am. Chem. Soc.* **1991**, *113*, 8778-8781.

10. L. Flamigni, A. Barbieri, C. Sabatini, B. Ventura, F. Barigelletti, *Top. Curr.Chem.***2007**,*281*,143-203.

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION

Visible-light induced synthesis of substituted quinazolines using1-(2-aminoaryl)ethan-1-ones in conjunction with arylmethanamines as starting materials



Photochemistry*

Jingchang Zhang, Qibao Wang,* Yongen Guo, Lin Ding, Maocai Yan, Yinglin Gu, Jiajia Shi*

Page No. – Page No.

Visible-light induced benzylic C-H functionalization for the synthesis of 2-arylquinazolines