RSC Advances

This article can be cited before page numbers have been issued, to do this please use: T. Yamaguchi, K. Sakairi, E. Yamaguchi, N. Tada and A. Itoh, *RSC Adv.*, 2016, DOI: 10.1039/C6RA04073J.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

View Article Online
DOI: 10.1039/C6RA04073J

Journal Name

COMMUNICATION

Magnesium iodide-catalyzed synthesis of 2-substituted quinazolines using molecular oxygen and visible light

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

T. Yamaguchi, K. Sakairi, E. Yamaguchi, N. Tada, A. Itoh

A novel and efficient approach for the synthesis of quinazolines by aerobic photooxidation with an iodine reagent at room temperature is reported. This method uses harmless visible light from compact fluorescent lamps and molecular oxygen as a sole oxidant without the need for a transition-metal catalyst or harsh reaction conditions.

Nitrogen-containing heterocycles are a common and important structural motif both biologically and industrially.[1] Of these heterocycles, quinazolines have been particularly studied for biological activity and have been reported to exhibit sedative, anticonvulsant, antitussive, hypotensive, and antidiabetic properties.[2] Consequently, they have been used as sympatholytic drugs for the treatment of high blood pressure (Prazosin), non-small cell lung cancer, and pancreatic cancer (Erlotinib), as well as other conditions (Figure 1).[3]

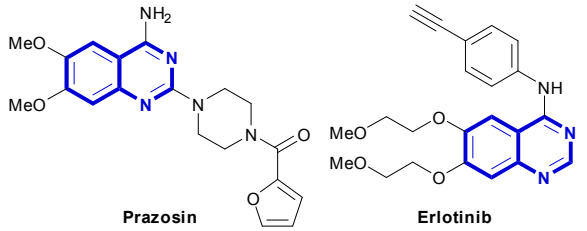
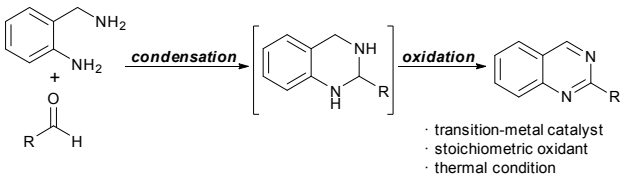


Figure 1 Drugs containing quinazoline moieties.

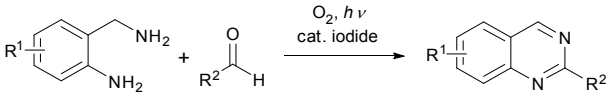
Consequently, many approaches for the efficient synthesis of quinazoline structures have been explored.[4] One such strategy is the condensation of 2-aminobenzylamines and aldehydes followed by the oxidation of the intermediate (Scheme 1). However, these reactions require transition-metal catalysts, such as those based on Cu[5] or Ir,[6] or stoichiometric amounts or a large excess of oxidants, such as NaOCl,[7] DDQ,[8] or MnO_2.[9] Moreover, harsh reaction conditions are required. Thus, the development of more efficient and environmentally benign reactions is necessary to realize sustainable, green methods for quinazoline synthesis.



Scheme 1 Synthesis of quinazolines with 2-aminobenzylamines and aldehydes.

Recently, the use of molecular oxygen instead of other oxidants has received increasing attention because it is cheap and represents high atom economy. Thus, novel reactions using molecular oxygen in the presence of transition-metal catalysts or organocatalysts have been developed.[10]

Our group has previously reported a catalytic cross-dehydrogenative coupling reaction between tertiary amines and nucleophiles using molecular oxygen and I_2 under visible-light irradiation.[11] This C–C bond forming reaction proceeded by oxidation of the amines into iminium ions, followed by addition of the nucleophiles without the need for transition-metal catalysts or thermal conditions. Therefore, we envisioned that a novel synthesis of quinazolines could be achieved by aerobic photooxidation in the presence of catalytic iodide (Scheme 2). Here we report an efficient synthetic approach for quinazolines under mild reaction conditions.



Scheme 2 Synthesis of quinazolines by aerobic photooxidation.

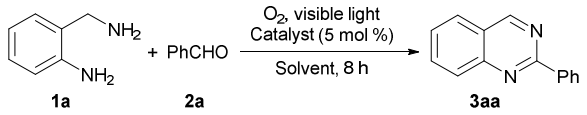
Table 1 shows the results of the optimization of the reaction conditions. As a result of solvent screening, 2-phenylquinazoline (**3aa**) is obtained in moderate yield by employing ethyl acetate as the solvent (entries 1–4). We then

Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu 501-1196, Japan.
E-mail: itoha@gifu-pu.ac.jp; Fax: +81-58-230-8108; Tel: +81-58-230-8108
† Electronic Supplementary Information (ESI) available: Experimental procedures, and characterization data. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C6RA04073J

investigated the effect of the catalyst. This aerobic photooxidation proceeds with various iodide catalysts, and the yield increases to 88% when magnesium iodide is used (entries 5–8). The quantity of benzaldehyde required can be reduced to 1.0 eq. without decreasing the yield (entry 9). Magnesium iodide is essential for this oxidation system because the desired product is not formed without catalyst (entry 10).

Table 1 Optimization of the reaction conditions



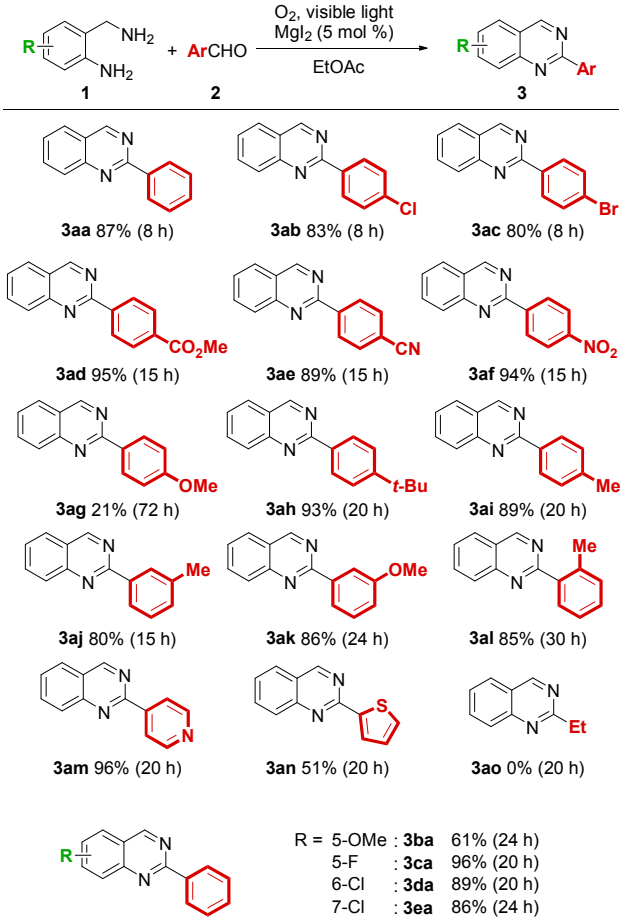
1a 2a 3aa

Entry	Catalyst	Solvent	Yield [%][a]
1	I_2	Hexane	0
2	I_2	EtOAc	43
3	I_2	$CHCl_3$	3
4	I_2	DMF	5
5	HI	EtOAc	70
6	NaI	EtOAc	26
7	MgI_2	EtOAc	88
8	Carbon tetraiodide	EtOAc	22
9[b]	MgI_2	EtOAc	89
10[b]	-	EtOAc	0

Reaction conditions; **1a** (0.3 mmol), **2a** (0.45 mmol), and catalyst (5 mol%) in solvent (5 mL) under O_2 atmosphere was stirred and irradiated with a fluorescent lamp at rt. [a] ^{1}H NMR yield. [b] **2a** (0.3 mmol) was used.

With the optimal reaction conditions established, we investigated the reaction of **1** with various substituted benzaldehydes (Table 2). The corresponding quinazolines are obtained in excellent yields when an electron-deficient benzaldehyde is employed (**3aa–3af**). In contrast, the yield dramatically decreases in the presence of an electron-donating group such as methoxy at the 4-position of the benzene ring (**3ag**). Reaction with 4-tert-butylbenzaldehyde or 4-methylbenzaldehyde generates the product in good yield (**3ah–3ai**). To confirm the effect of steric hindrance, *meta*- and *ortho*-substituted benzaldehydes were employed in this method. It was found that *o*- and *m*-tolualdehyde aldehydes could be applied successfully. Moreover, 3-methoxybenzaldehyde is converted to the corresponding quinazoline in 86% yield (**3aj–3al**). This suggests that the electron density at the C2 position is a critical factor in this oxidation system. Other aldehydes such as 4-pyridinecarboxaldehyde and 2-thiophenecarboxaldehyde are oxidized to **3am** and **3an**, respectively. Unfortunately, no product is formed when an alkylaldehyde is used as the substrate (**3ao**). Furthermore, 4-, 5-, or 6-substituted 2-aminobenzylamines react with **2a**, and the corresponding quinazolines are obtained in good to excellent yields (**3ba–3ea**).

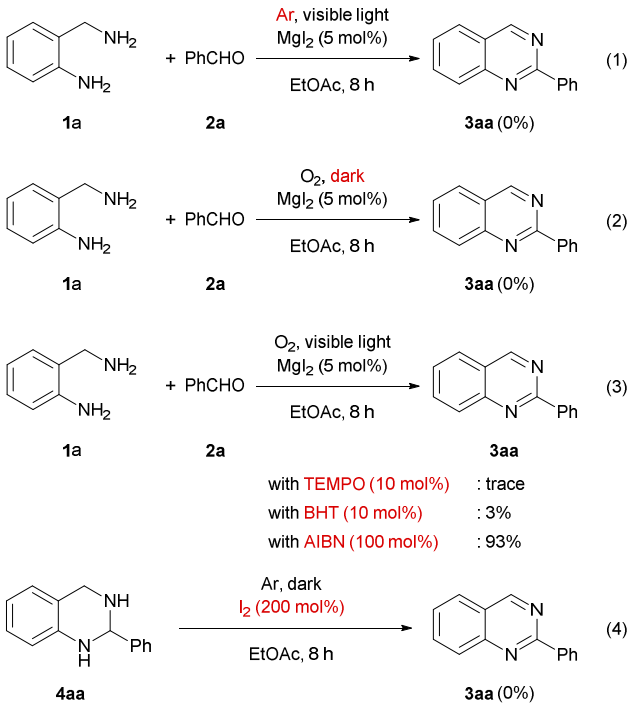
Table 2 Scope of aldehydes and 2-aminobenzylamines[a]



Reaction conditions; **1** (0.3 mmol), **2** (0.3 mmol), and MgI_2 (5 mol%) in EtOAc (5 mL) under O_2 atmosphere was stirred and irradiated with a fluorescent lamp at rt. [a] Isolated yield.

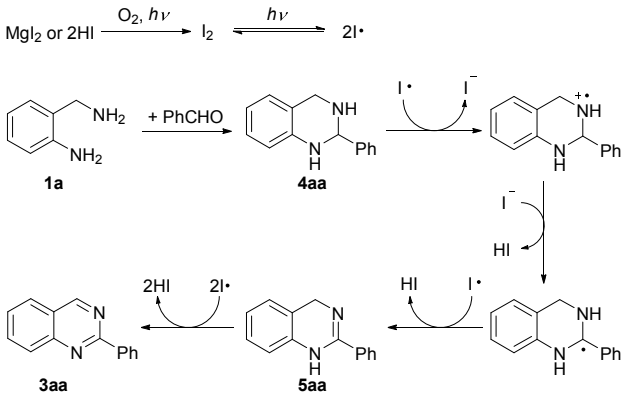
We then conducted several control experiments to investigate the reaction mechanism. The desired product was not formed in the absence of molecular oxygen and visible light irradiation (Scheme 3, equation 1 and 2). 2,2,6,6-Tetramethylpiperidine-1-oxyl and 2,6-di-tert-butyl-p-cresol, which are known to be radical scavengers, inhibit the generation of **3aa**. On the other hand, 2,2'-azobis(isobutyronitrile), which is used to the free radical generator, does not affect the reaction (Scheme 3, equation 3). Thus, this oxidation system probably proceeds *via* a radical process. Next, we investigated whether **4aa** is oxidized by iodine or another active species. When iodine (200 mol%) is employed as the oxidant in the dark under an argon atmosphere, the target product is not detected and dihydroquinazoline is formed in low yield. This result indicates that oxidation by iodine is not the major pathway in this reaction.

View Article Online
DOI: 10.1039/C6RA04073J



Scheme 3 Control experiments.

Scheme 4 shows a plausible mechanism for this reaction, which is postulated by considering all the above results. Initially, magnesium iodide is converted to iodine under irradiation by visible light in an O_2 atmosphere, which is followed by homolysis of the iodine. 2-Phenyl-1,2,3,4-tetrahydroquinazoline (**4aa**), which is formed by condensation of 2-aminobenzylamine (**1a**) with benzaldehyde (**2a**), is converted to a benzyl radical species by single-electron transfer. The oxidation occurs again, and 2-phenyldihydroquinazoline is obtained. Subsequently, the desired product (**3aa**) is formed via oxidation of **5aa** in the same manner. HI is reoxidized to I_2 under aerobic photooxidative conditions; thus the catalytic cycle is completed.



Scheme 4 Plausible reaction mechanism.

Conclusions

In conclusion, we have developed an efficient synthesis of quinazolines under aerobic photooxidative conditions. This novel reaction is interesting as it uses catalytic magnesium iodide, molecular oxygen as the terminal oxidant, and visible light from a general-purpose fluorescent lamp. Further application and mechanistic study of this reaction are now in progress in our laboratory.

Notes and references

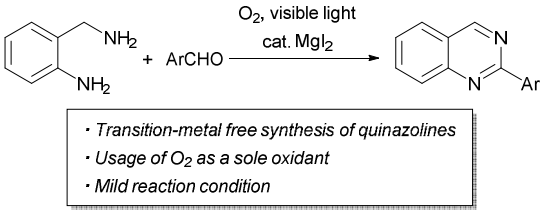
1 (*a*) R. Dua, S. Shrivastava, S. K. Sonwane and S. K. Srivastava, *Advan. Biol. Res*., 2011, **5**, 120; (*b*) A. K. Lawrence and K. Gademann, *Synthesis*, 2008, 331.
2 T. P. Selvam and P. V. Kumar, *Research in Pharmacy*, 2011, **1**, 1.
3 (*a*) R. Gundla, R. Kazemi, R. Sanam, R. Muttineni, J. A. R. P. Sarma, R. Dayam and N. Neamati, *J. Med. Chem*., 2008, **51**, 3367; (*b*) J. F. Mendes da Silva, M. Walters, S. Al-Damluji and C. R. Ganellin, *Bioorg. Med. Chem*., 2008, **16**, 7254.
4 (*a*) A. E. Wendlandt and S. S. Stahl, *J. Am. Chem. Soc*., 2014, **136**, 506; (*b*) Z. Chen, J. Chen, M. Liu, J. Ding, W. Gao, X. Huang and H. Wu, *J. Org. Chem*., 2013, **78**, 11342; (*c*) T. Vlaar, R. C. Cioc, P. Mampuys, B. U. W. Maes, R. V. A. Orru and E. Ruijter, *Angew. Chem., Int. Ed*., 2012, **51**, 13058; (*d*) S. Rachakonda, P. S. Pratap and M. V. B. Rao, *Synthesis*, 2012, **44**, 2065; (*e*) Y. Yan and Z. Wang, *Chem. Commun*., 2011, **47**, 9513; (*f*) B. Han, C. Wang, R.-F. Han, W. Yu, X.-Y. Duan, R. Fang and X.-L. Yang, *Chem. Commun*., 2011, **47**, 7818; (*g*) K. Karnakar, J. Shankar, S. Narayana Murthy, K. Ramesh and Y. V. D. Nageswar, *Synlett*, 2011, **8**, 1089; (*h*) J. Zhang, C. Yu, S. Wang, C. Wan and Z. Wang, *Chem. Coommun*., 2010, **46**, 5244; (*i*) J. Zhang, D. Zhu, C. Yu, C. Wan and Z. Wang, *Org. Lett*., 2010, **12**, 2841; (*j*) F. Portela-Cubillo, J. S. Scott and J. C. Walton, *J. Org. Chem*., 2009, **74**, 4934; (*k*) F. Portela-Cubillo, J. S. Scott and J. C. Walton, *Chem. Commun*., 2008, 2935; (*l*) S. Ferrini, F. Ponticelli and M. Taddei, *Org. Lett*., 2007, **9**, 69.
5 B. Han, X.-L. Yang, C. Wang, Y.-W. Bai, T.-C. Pan, X. Chen and W. Yu, *J. Org. Chem*., 2012, **77**, 1136.
6 J. Fang, J. Zhou and Z. Fang, *RSC Adv*., 2013, **3**, 334.
7 C. U. Maheswari, G. S. Kumar, M. Venkateshwar, R. A. Kumar, M. L. Kantam and K. R. Reddy, *Adv. Synth. Catal*., 2010, **352**, 341.
8 J. J. Vanden Eynde, J. Godin, A. Mayence, A. Maquestiau and E. Anders, *Synthesis*, 1993, 867.
9 Y. Peng, Y. Zeng, G. Qiu, L. Cai and V. W. Pike, *J. Heterocycl. Chem*., 2010, **47**, 1240.
10 For selected recent examples and reviews, see: (*a*) A. S.-K. Tsang, A. Kapat and F. Schoenebeck, *J. Am. Chem. Soc*., 2016, **138**, 518; (*b*) A. Bechtoldt, C. Tirler, K. Raghuvanshi, S. Warratz, C. Kornhaaβ and L. Ackermann, *Angew. Chem., Int. Ed*., 2016, **55**, 264; (*c*) A. Gonzalez-de-Castro and J. Xiao, *J. Am. Chem. Soc*., 2015, **137**, 8206; (*d*) Y. Tan, W. Yuan, L. Gong and E. Meggers, *Angew. Chem., Int. Ed*., 2015, **54**, 13045; (*e*) J. Li, M. J. Lear, Y. Kawamoto, S. Umemiya, A. R. Wong, E. Kwon, I. Sato and Y. Hayashi, *Angew. Chem., Int. Ed*., 2015, **54**, 12986; (*f*) Z. Zhang, Y. Gao, Y. Liu, J. Li, H. Xie, H. Li and W. Wang, *Org. Lett*., 2015, **17**, 5492; (*g*) Y. Qin, L. Zhang, J. Lv, S. Luo and J.-P. Cheng, *Org. Lett*., 2015, **17**, 1469; (*h*) J. Liu, F. Liu, Y. Zhu, X. Ma and X. Jia, *Org. Lett*., 2015, **17**, 1409; (*i*) Q. Huang, X. Zhang, L. Qiu, J. Wu, H. Xiao, X. Zhang and S. Lin, *Adv. Synth. Catal*., 2015, **357**, 3753; (*j*) N. Bagi, J. Kaizer and G. Speier, *RSC Adv*., 2015, **5**, 45983; (*k*) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int.*

View Article Online
DOI: 10.1039/C6RA04073J

Ed., 2011, **50**, 11062. (*l*) J. Piera and J.-E. Bäckvall, *Angew. Chem., Int. Ed*., 2008, **47**, 3506.
11 T. Nobuta, A. Fujiya, T. Yamaguchi, N. Tada, T. Miura and A. Itoh, *RSC Adv*., 2013, **3**, 10189.

View Article Online
DOI: 10.1039/C6RA04073J

Table of contents



We disclose a novel and efficient synthesis of 2-substituted quinazolines by aerobic photooxidative reaction catalyzed by magnesium iodide.