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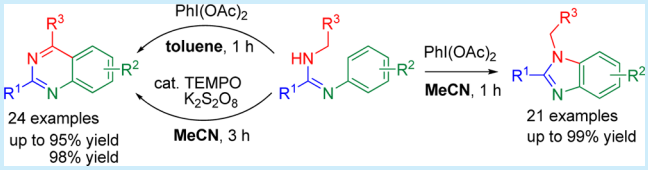
Solvent/Oxidant-Switchable Synthesis of Multisubstituted Quinazolines and Benzimidazoles via Metal-Free Selective Oxidative Annulation of Arylamidines

Jian-Ping Lin,† Feng-Hua Zhang,† and Ya-Qiu Long*

CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China

Supporting Information

ABSTRACT: A fast and simple divergent synthesis of multisubstituted quinazolines and benzimidazoles was developed from readily available amidines, via iodine(III)-promoted oxidative C(sp^3)−C(sp^2) and C(sp^2)−N bond formation in nonpolar and polar solvents, respectively. Further selective synthesis of quinazolines in polar solvent was realized by TEMPO-catalyzed sp^3C−H/sp^2C−H direct coupling of the amidine with $K_2S_2O_8$ as the oxidant. No metal, base, or other additives were needed.

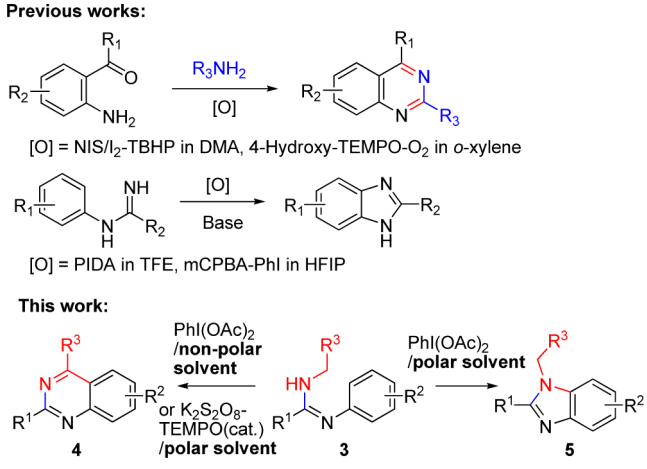


Quinazoline and benzimidazole are among the most common motifs present in drugs and bioactive compounds with a broad spectrum of pharmcological activities.[1] Typically, quinazolines constitute an important category of marketed targeted cancer therapies (e.g., Iressa, Tarceva and Tykerb). Although there are various well-established methods to construct the two privileged structures, most of them require special starting materials, multistep procedures, and harsh reaction conditions,[2] as well as the use of transition metals,[3] impeding the biological studies and therapeutic applications of these drug-like scaffolds.

In the past decade, oxidative C−H functionalization to form new C−C or C−N bonds has emerged as an elegant and robust synthetic method for interesting products, featuring atom economy and straightforwardness.[4] However, many of these methods are based on transition-metal catalysis, bringing cost and toxicity concerns. As an alternative, metal-free versions have become very important for avoiding more expenditure and environmental issues.[5] The direct construction of the nitrogen containing heterocycles via metal-free oxidative couplings is yet limited;[5] only select excellent examples were applied to quinazoline and benzimidazole synthesis (Scheme 1),[6] with a limited substrate scope and prolonged reaction time.

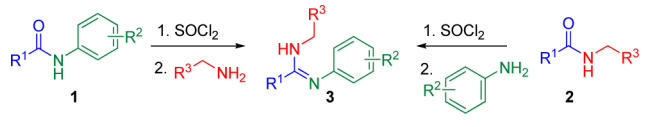
Distinct from the literature-reported one-way strategies, herein we report an unprecedented divergent synthesis of quinazolines and benzimidazoles directly from the same starting material amidine **3**, in a solvent- or oxidant-switchable manner under metal-free and base-free conditions (Scheme 1). By using iodobenzene diacetate as the only reagent, a broad range of multisubstituted quinazolines and benzimidazoles were furnished via an intramolecular oxidative C(sp^3)−C(sp^2) and C(sp^2)−N bond formation in nonpolar and polar solvents, respectively. Further selective synthesis of quinazolines in polar solvents was achieved by TEMPO-catalyzed oxidative sp^3C−H arylation.

Scheme 1. Approaches To Access Quinazolines and Benzimidazoles via Metal-Free Oxidative C−H Activation



Structurally diverse amidines **3** were easily prepared from readily available carboxylic acid, aniline, and alkyl/benzylamine, via two different condensation sequences (Scheme 2), based on the imine−enamine tautomerism,[7] ensuring a broad substrate availability scope.

Scheme 2. Two Synthetic Routes to the Designed Amidines



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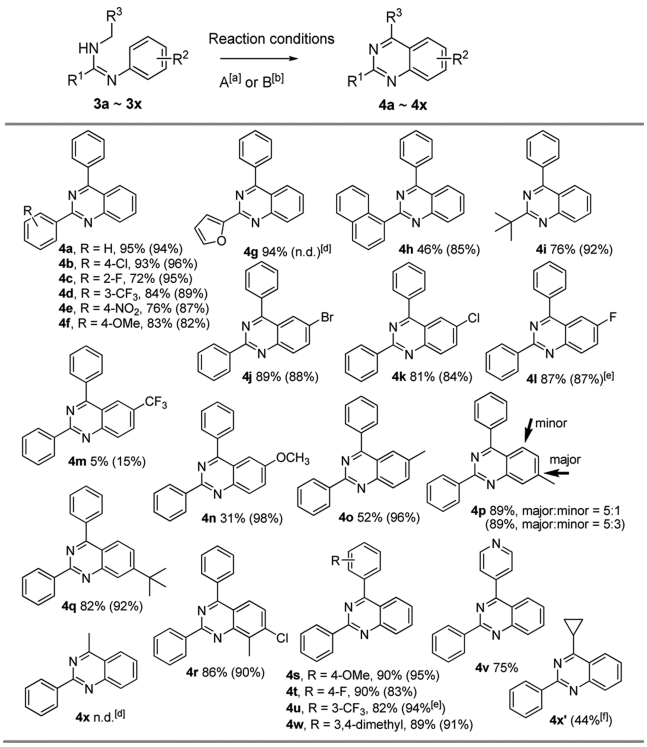
We designed the *N*-benzyl-*N*′-phenyl benzimidamide substrate **3a** to build quinazoline via a novel intramolecular C(sp^3)−H arylation strategy. Our initial effort commenced with hypervalent iodine(III), i.e. iodobenzene diacetate, as an oxidation reagent in toluene. Gratifyingly, the direct C(sp^3)−H activation/C(sp^3)−C(sp^2) bond formation occurred and the desired quinazoline product **4a** was obtained in 63% yield in the absence of a transition metal catalyst. From systematic screening of a range of solvents, oxidants and its ratio, substrate concentration, reaction temperature, and time (see Supporting Information (SI) for the details), the best result was achieved when 4 equiv of $PhI(OAc)_2$ were used as the oxidant with nonpolar solvent toluene at 120 °C for 1 h (Scheme 3, 95% for **4a**). Notably, the substrate concentration played an important role in this oxidative cyclization reaction, and a lower reaction concentration proved beneficial with 0.01 M being the best.

Scheme 3. Synthesis of Quinazolines via Metal-Free Oxidative sp^3C−H/sp^2C−H Cyclization of Amidines[a−c]



[a]Reaction conditions A: **3** (0.4 mmol), $PhI(OAc)_2$ (1.6 mmol), toluene (40 mL), 120 °C, 1 h. [b]Reaction conditions B: **3** (0.2 mmol), $K_2S_2O_8$ (0.6 mmol), TEMPO (0.04 mmol), MeCN (4 mL), 120 °C, 3 h. [c]Yield of isolated pure product under conditions A (isolated yield under conditions B). [d]n.d. = not detected. [e]*t* = 4 h. [f]*t* = 12 h, 35% starting material recovered.

Equipped with a set of optimized conditions, we explored the substrate scope of the oxidative C(sp^3)−C(sp^2) coupling reaction delivering quinazolines, as depicted in Scheme 3. First, we investigated the scope of the R^1 substituent. Various aromatic groups with electron-withdrawing and -donating substituents at various positions were well tolerated, affording the corresponding quinazolines in good to excellent yields (**4a**−**4g**). However, the bulky naphthyl group disfavored the formation of quinazoline (**4h**, 46%). Notably, this method is applicable to the synthesis of 2-alkylquinazolines; e.g., 2-*tert*-butyl substituted quinazoline was generated in a comparable yield (**4i**, 76%).

Then, the effect of the substituent attached on the aniline ring (i.e., R^2) was examined. The bromo, chloro, or fluoro group had little influence on the reaction (Scheme 3, **4j**−**4l** and **4r**), thus offering the possibility of introducing further substituents by additional coupling reactions. However, the strong electron-withdrawing group substituted at the *para* position of the aniline ring remarkably retarded the direct annulation reaction (**4m**, 5%). The electron-donating group at the *para* position of the aniline ring also adversely affected the conversion (**4n** and **4o**). But the introduction of an electron-donating group to the *meta* position marginally reduced the reaction yield (**4p** and **4q**). When the aniline ring was substituted at the *meta* position, there were two positions for the oxidative coupling to occur, favoring the less sterically hindered C−H bond, and thus the regioselectivity increased as the substituent size increased. For example, the *meta*-methyl substituted substrate produced a mixture of two regioisomers in a 5:1 ratio (**4p**), while *tert*-butyl substitution led to nearly a single product (**4q**).

Finally, we surveyed the scope of the R^3 moiety. A range of substrates bearing electron-donating or weak electron-withdrawing group substituted aromatic rings all underwent the oxidative cyclization smoothly and gave the desired quinazoline products in excellent yields (Scheme 3, **4s**, **4t**, and **4w**). Even a strong electron-withdrawing group on the aromatic ring only caused a slight decrease in the yield (**4u** and **4v**). However, this conversion was incompatible with the aliphatic substituent (**4x**).

Interestingly, from screening the reaction conditions for quinazoline synthesis, we found that benzimidazole was formed as a major product when polar solvents were used, such as EtOH, MeCN. Therefore, we were intrigued to further investigate the annulation of *N*-benzyl-*N*′-phenyl benzimidamide **3a** to generate the benzimidazole **5a** by a direct sp^2 C−H/N−H coupling (Table 2). Through reaction conditions optimization (see SI), we found that the best result was obtained by using 3 equiv of $PhI(OAc)_2$ in acetonitrile (with 0.1 M optimal concentration) at 120 °C for 1 h, furnishing 1,2-substituted **5a** in 92% yield.

To further evaluate the scope of the oxidative synthesis of benzimidazoles in the polar solvent, a survey of *N*-phenylamidine substrates **3** was conducted (Scheme 4). In general, the substrate scope was very similar to that of the quinazoline synthesis in toluene, with a diverse array of R^1, R^2, and R^3 groups being compatible with the reaction conditions in good to excellent yields (**5a**−**5i** for R^1, **5j**−**5r** for R^2, **5x**−**5z** for R^3). Notably, the alkyl group at R^3 was well tolerated for this transformation. The exception included the following: alky R^1 substituted substrate **3i** performed the sp^2 C−H amination to give **5i** in only 40% yield; strong electron-withdrawing group R^2 disfavored this conversion (**5m**). Compared to the recently reported synthesis of benzimidazole via an intramolecular oxidative coupling reaction,[6e−g] the major advantage of this new approach is the broad substrate scope with more structurally diverse substituents at position 1 and 2 thus enabling a rapid derivatization of the drug-like scaffold.

To gain insight into the reaction mechanism, we carried out several control experiments (Scheme 5). First, the *N*-methylated amidine **6** was subjected to the optimized conditions for the quinazoline synthesis, but no reaction occurred, indicating that the N−H was essential for the

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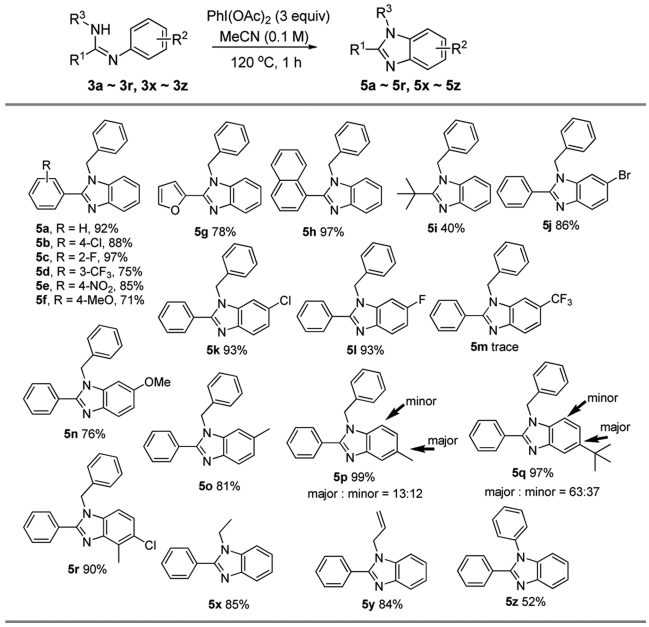
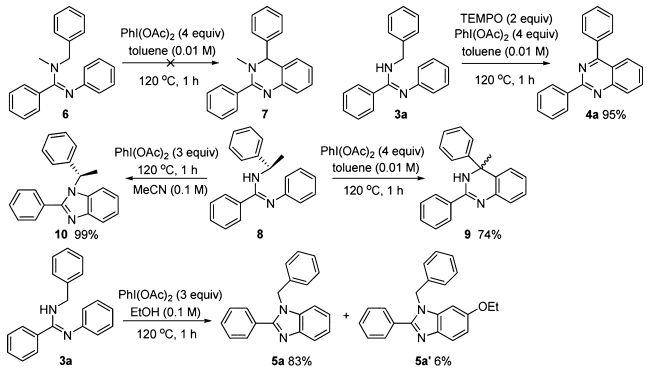
Scheme 4. Synthesis of Benzimidazoles via $PhI(OAc)_2$-Promoted Oxidative Annulation in Acetonitrile[a,b]



[a]Reaction conditions: **3** (0.4 mmol), $PhI(OAc)_2$ (1.2 mmol), MeCN (4 mL), 120 °C, 1 h. [b]Yields of isolated pure products.

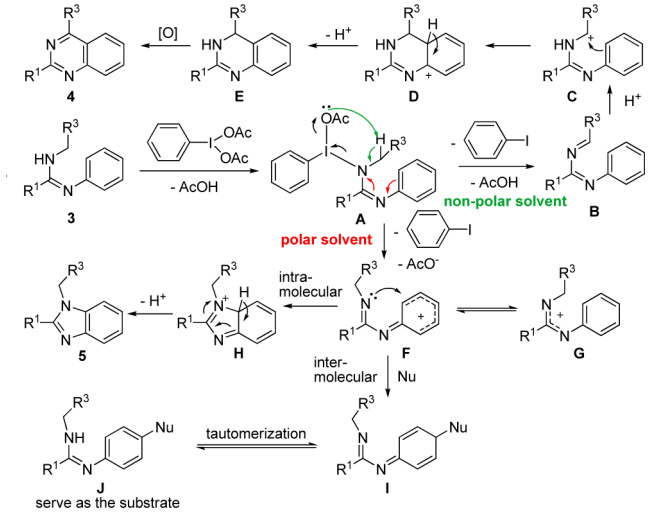
Scheme 5. Control Experiments



coupling. Second, in the presence of 2 equiv of radical trapping agent TEMPO, the quinazoline product **4a** was still formed in 95% yield, ruling out a free radical mechanism. Then a chiral substrate **8** yielded the corresponding benzimidazole **10** in polar solvent with optical activity retention, while, in the nonpolar solvent, the generated corresponding hydrogenated quinazoline **9** almost lost all optical activity (see SI). Fianlly, when using EtOH as the solvent, *para*-ethoxy substituted side-product **5a′** was isolated in 6% yield. These results imply that an aromatic cationic intermediate is involved.

Based on the observations above and previous reports on hypervalent iodine and amidine involved reactions,[8] we proposed a plausible mechanism, as shown in Scheme 6. Initially, treatment of the substrate **3** with $PhI(OAc)_2$ could furnish an *N*-(phenylacetoxyiodo)imidamido species **A**.[8b−d] Then, in a nonpolar solvent, the iodoimidamido species **A** is prone to conversion to the neutral *N*-benzylidene-*N*′-phenylcarboxamidine **B** by an intramolecular attack of the acetate ion on the benzylic C(sp^3)−H of **A**. Assisted by the proton acid formed in situ, intermediate **B** is transformed to a benzylic

Scheme 6. Proposed Mechanism for the $PhI(OAc)_2$-Mediated Oxidative Annulation



cation species **C**, which could undergo an intramolecular Friedel−Craft reaction to afford intermediate **E**, which is further oxidized to give the final product quinazoline **4**. On the other hand, when the reaction is performed in a polar solvent, due to the solvation stabilization effect, intermediate **A** is apt to be cleaved into cationic intermediate **F**, which is tautomerized to nitrenium ion **G**. Then, the nitrogen bearing lone pair electrons attack the benzene cation to generate intermediate **H**, which delivers the heteroaromatic product **5** by proton elimination. Meanwhile, cationic intermediate **F** can undergo an intermolecular nucleophilic substitution reaction to afford intermediate **I**. Intermediate **I** can be further rearranged to compound **J**, which can serve as the substrate to undergo the oxidative cyclization under the reaction conditions.

Serendipitously, when exploring the mechanism of the $PhI(OAc)_2$-mediated benzimidazole synthesis by adding 0.2 equiv of TEMPO, we were surprised to harvest the quinazoline as the major product in CH_3CN, whereas the original dominant product **5a** was obtained in a substantially lowered yield (see SI). The unusual result evoked our intense interest to develop a new synthesis for quniazolines in polar solvents via a metal-free TEMPO-catalyzed C(sp^3)−H/C(sp^2)−H coupling reaction. By carefully examining the oxidation system with respect to the oxidant species, the equivalence, the combination, the reaction temperature, and time (see SI), the best result was achieved by using 3 equiv of $K_2S_2O_8$ as the oxidant and 0.2 equiv of TEMPO as the additive in CH_3CN at 120 °C for 3 h, affording the quinazoline **4a** in 94% yield.

Then, structurally diverse substrates were subjected to the optimized conditions to evaluate the scope and generality of the new protocol (Scheme 3; the yield is in parentheses). In general, the TEMPO-catalyzed synthesis of quinazoline in acetonitrile displayed superior reaction efficiency compared to the $PhI(OAc)_2$-mediated synthesis of quinazoline in toluene, with an improved yield for the same product. The structural scope and regioselectivity were very similar to those under the $PhI(OAc)_2$−toluene system. Several exceptions occurred: furanyl as the R^1 substituent on the amidine moiety was not compatible with this procedure (**4g**); an obvious electronic effect was observed with the R^2 substituent on the aniline ring (Scheme 3, products **4j**−**4r**); an electron-donating group was beneficial for the sp^3C−H arylation (**4n**−**4q**), while the

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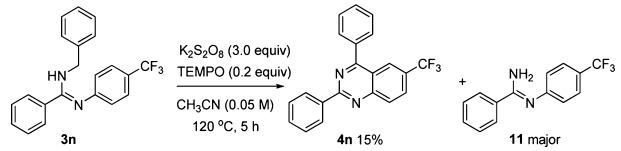
electron-withdrawing group compromised the transformation (**4m**, 15% yield), suggesting a cationic intermediate was involved. Interestingly, the pyridino and aliphatic R^3 substituted amidines were competent in giving the desired products in good yields (**4v**, **4x**′), complementary to the hypervalent iodine/nonpolar solvent protocol.

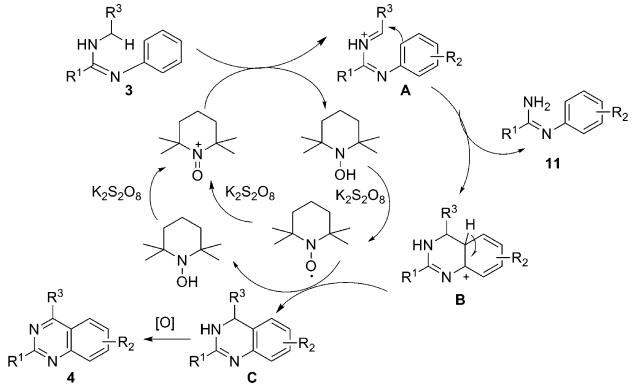
The exact mechanism of the TEMPO-catalyzed $K_2S_2O_8$-promoted oxidative Csp^3-Csp^2 coupling reaction was not clear at this stage. But the reaction condition screening experiments excluded the free radical mechanism (SI). Furthermore, the *N*-methlylated substrate **6** failed to produce 3,4-dihydroquinazoline **7**, and the electron-withdrawing *p*-CF_3-phenyl substituted amidine delivered compound **11** as a major product when extending the reaction time to 5 h (Scheme 7).

Scheme 7. Electron-Withdrawing Substituent Effect



Taken together, a possible mechanism was proposed in Scheme 8, in which the stoichiometric secondary oxidant

Scheme 8. A Possible Mechanism of the TEMPO-Catalyzed Annulation Using $K_2S_2O_8$ as the Oxidant



$K_2S_2O_8$ transformed TEMPO into an oxoammonium salt that operated as the primary oxidant and hydrogen acceptor.[9] In this oxidation system, substrate **3** was oxidized to iminium intermediate **A**, which then underwent an intramolecular Friedel–Craft reaction to give intermediate **B**. Further oxidation afforded the hydroquinone **C**, which was finally aromatized to give the stable product quinazoline **4**.

In summary, we have developed an unusual solvent- or oxidant-switchable direct synthesis of quinazolines and benzimidazoles from the common *N*-alkyl-*N*′-arylamidine under metal- and base-free conditions. This is the first example to achieve the chemoselectivity between oxidative sp^3C-H/sp^2C-H and $N-H/sp^2C-H$ coupling simply by the choice of solvent or oxidant, affording a broad range of multisubstituted quinazolines and benzimidazoles in excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, reaction conditions screening, compound characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yqlong@simm.ac.cn.

Author Contributions

†J.-P.L. and F.-H.Z. contributed equally.

Notes

The authors declare no competing financial interest.

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