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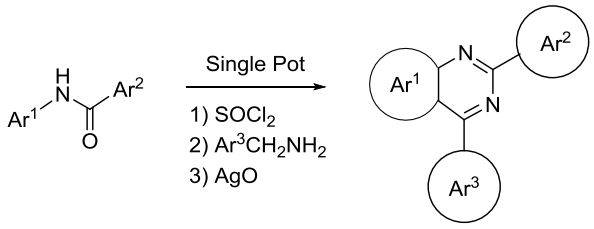
Graphical Abstract



Silver(II) Oxide-Mediated Synthesis of 2,4-Diarylquinazolines

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ABSTRACT: A single-pot procedure for the synthesis of 2,4-diarylquinazolines is described which involves a silver oxide-mediated C-H activation/C-N bond formation process. The generality of this method with respect to substituent effects is presented along with studies leading to process optimization. Mechanistic investigations provide support for the involvement of radical intermediates in the reaction process.

KEYWORDS: Diarylquinazoline, *N*-arylbenzamidine, silver oxide, radical oxidation

In support of a drug discovery research program, we were interested in developing a focused compound library of 1,2-diarylbenzimidazoles, as exemplified by compound **1**. As a prelude to the development of this library, a retrosynthetic analysis was performed, in which a double disconnection of the imidazole ring system was considered (Figure 1). In this case, imidoyl chloride **3** was envisioned to undergo a nucleophilic substitution reaction with aniline **4** to generate intermediate **2**, which would subsequently be cyclized under a palladium-mediated

C-H activation/C-N bond formation reaction to produce the target benzimidazole **1**.[1] It also seemed reasonable to anticipate that this reaction sequence could be carried out in a single pot operation. To test this hypothesis, anilide **5** was first converted to the corresponding imidoyl chloride **3** by heating with thionyl chloride (Scheme 1). After removal of excess thionyl chloride, the residue was dissolved in DMPU, treated with **4** (1.5 eq), palladium acetate (10 mol %), potassium phosphate (3 eq), and silver (I) oxide (4 eq) as an oxidant, and heated to 120 °C for 12 h. Following reaction work-up, benzimidazole **1** was isolated in 44% yield.

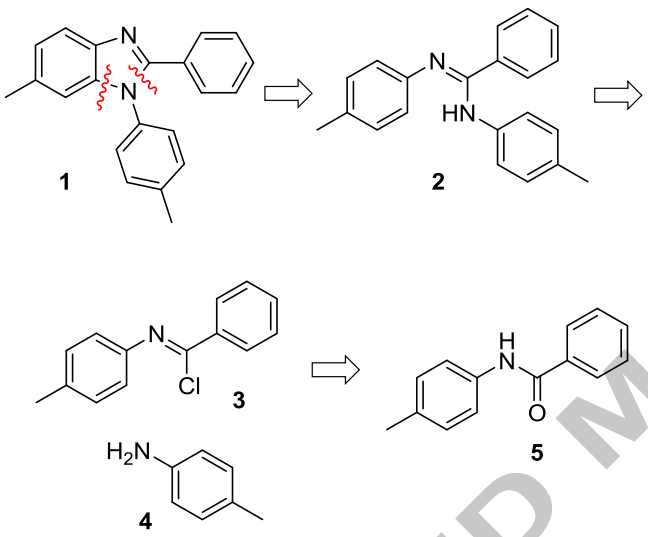
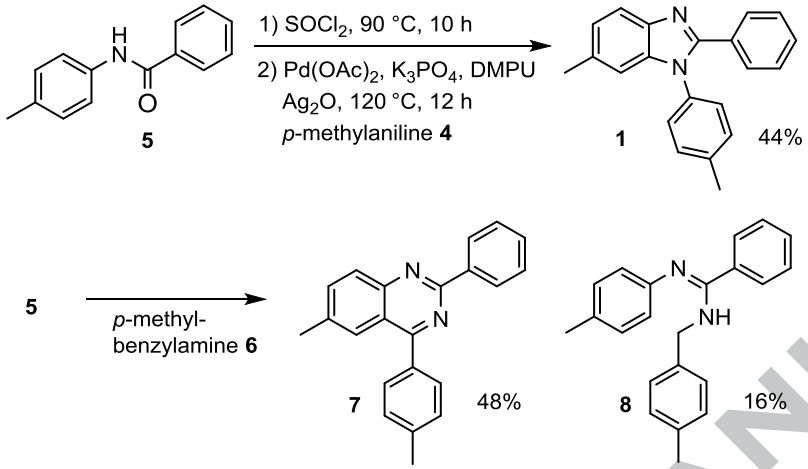


Figure 1. Retrosynthetic analysis of benzimidazole synthesis.

In an attempt to expand the substrate scope, aniline **4** was replaced with *p*-methylbenzylamine **6** and subjected to the same reaction conditions. However, in this case, the corresponding *N*-1-benzyl-substituted benzimidazole was not obtained; rather, 2,4-diarylquinazoline **7** was isolated in 48% yield along with amidine adduct **8**, in a ratio of 3 to 1.[2, 3] At the time this work was under investigation, there were few methodologies described for delivering 2,4-diarylquinazolines based upon this type of bond disconnection strategy (Scheme 1).[4] Movassaghi and Hill reported a closely related conversion, in which arylnitriles were reacted with activated *N*-arylbenzamides to produce the corresponding substituted quinazolines in a single-step procedure.[4c] More recently, Lin described a methodology in which arylamidines were converted to quinazolines using hypervalent iodine-mediated oxidative annulation.[4d] Most recently, Lv and colleagues have reported on the preparation of quinazolines from *N,N'*-disubstituted amidines via I_2/KI-mediated oxidative C-C bond formation under basic

conditions.[4e] Herein we report on a complementary one-pot approach to convert readily available *N*-arylbenzamides to 2,4-diarylquinazolines via the corresponding *N*-arylbenzamidines by way of an oxidative reaction with silver(II) oxide under neutral conditions.

Scheme 1. Initial syntheses of benzimidazole **1** and quinazoline **7**.



With the above result in hand, subsequent experiments were conducted to optimize reaction conditions and to examine the substrate scope. During exploratory studies, it was found that 2,4-diarylquinazoline **7** formed even in the absence of palladium acetate, which we had initially presumed would be necessary for inducing a C-H-activated ring closure. Moreover, under thermal conditions in the absence of both the palladium catalyst and the silver oxidant, only substitution adduct **8** was obtained. Potassium phosphate was similarly found to be nonessential; thus, silver(I) oxide alone in DMPU was sufficient for effecting cyclization. Elevation of the reaction temperature (ca. to 170 °C) did not affect product distribution, nor did it enhance cyclization. Since it was noted that the reaction is accompanied by the formation of water along with reduced silver (mirrored walls of the flask), the addition of molecular sieves was investigated as a means of driving the removal of water. Indeed, the incorporation of molecular sieves (powdered, 4Å) during the reaction (3:1 w/w relative to amide) resulted in an increased conversion to **7** (from 48% to 76%). The use of greater amounts of molecular sieves proved deleterious to the process, leading to reduced product recovery.

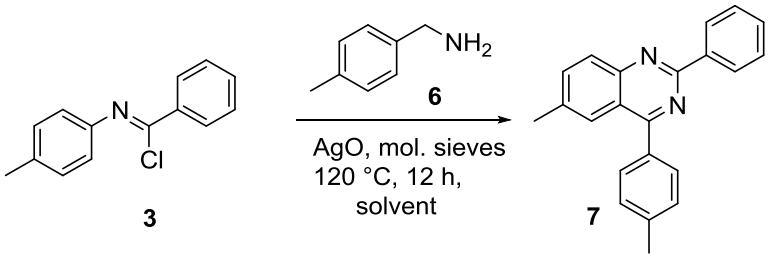
Reasoning that the cyclization of **8** may have proceeded through a radical pathway, several oxidants known to operate via radical mechanisms were thus investigated as potential replacements for silver(I) oxide. However, none of the inorganic metal salts studied, e.g.

$Cu(OAc)_2$,[5] CuO,[6] $Mn(OAc)_2$,[7] and MnO,[8] effected cyclization; in each case, only amidine adduct **8** was formed. Other oxidants such as iodobenzene diacetate, 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate[9] and DDQ also failed to provide cyclized product **7**. In addition, several silver salts including $Ag(OAc)_2$, $AgBF_4$, $AgNO_3$, Ag(OAc), $PhCO_2Ag$, $MeSO_3Ag$, Ag_2PO_4, and $AgSO_4$ were found to be ineffective at inducing ring closure under these reaction conditions. And while AgF and $Ag(CO_3)_2$ afforded modest yields of cyclized product **7** (21 and 52% respectively), AgO was identified as an equally efficacious substitute for Ag_2O in this reaction. Furthermore, by increasing the stoichiometry of either silver oxide to 6 eq, complete consumption of adduct **8** was realized, and improved isolated yields of **7** (~ 84%) were obtained.

Finally, the effects of various solvents on this process were investigated (Table 1). Amongst the polar aprotic solvents evaluated, only dioxane provided results comparable to those obtained in DMPU. In DMF, only marginal conversion to product **7** was obtained, whereas DMSO proved to be incompatible with this reaction, as neither quinazoline **7** nor amine adduct **8** were detected. In other polar aprotic solvents (DME, ethyl acetate, NMP, HMPA) yields of the target quinazoline were moderate, whereas in the protic solvent, tert-butanol, the reaction progressed poorly. In non-polar solvents such as benzene and toluene, moderate product conversion was realized, whereas in fluorinated solvents, product yields were improved. Thus, in benzotrifluoride, a 68% yield of quinazoline product was obtained; in hexafluorobenzene, the conversion was almost quantitative. This dramatically improved conversion in hexafluorobenzene could reflect the favorable stabilization of a putative radical intermediate(s) resulting from π–π stacking interactions with this solvent.[10c] In order to overcome potential solubility limitations of various substrate reagents in this solvent, a co-solvent mixture with DMPU (1:1) was used for investigating the scope of this reaction. It was determined that in this solvent mixture, a reaction temperature of 100 °C was sufficient for effecting complete cyclization. Thus, in a typical experiment, a mixture of the imidoyl chloride (100 mg; prepared as described above), molecular sieves (300 mg) and DMPU (2 mL) was treated with the benzylic amine (1.5 eq) and the resulting solution was heated to 80 °C for 0.5 h to allow for adduct formation. After cooling the solution to rt, hexafluorobenzene (2 mL) and silver(II) oxide (6 eq) were subsequently introduced and the resulting mixture was heated at 100 °C for 12 h. After filtration and concentration of the filtrate, the product quinazoline was purified by silica gel chromatography. Using these optimized reaction conditions, the substrate scope was then

explored to examine the general versatility of this approach. Because adducts derived from meta-substituted anilides were not expected to cyclize regiospecifically, these were not included in the anilide test set (Table 2).

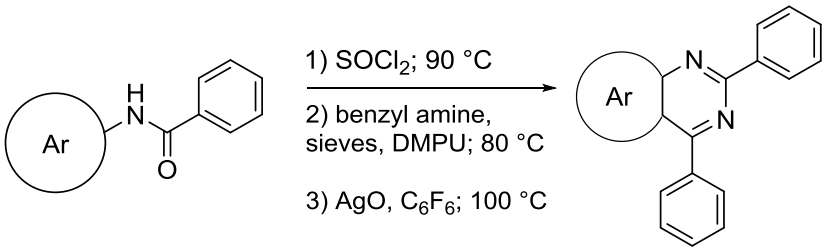
Table 1. Optimization of Reaction Conditions: Solvent Screen.



Solvent	Yield (%)	Solvent	Yield (%)
DMPU	**84**	**EtOAc**	**57**
DMF	**9**	**DCE**	**28**
NMP	**43 (incomplete)**	**Benzene**	**44**
DME	**31**	**C_6F_6**	**93**
Dioxane	**85**	**Toluene**	**55**
DMSO	**No adduct or product**	**F_3CPh**	**68**
HMPA	**73 (incomplete)**	***t*-BuOH**	**26**

Investigation of substituent effects of the amide N-aryl ring revealed that the reaction accommodates a range of substituents in this region of the molecule; success of the reaction is more dependent on the steric nature of a substituent than on its electronic effects. Thus, at the para position, halo (**10-12**), alkoxy (**13**) and alkyl (**14**) moieties are well tolerated (yields of biarylquinazolines > 90%). However, with ortho-substituted anilides (entries 7 and 8), modest decreases in product yields were obtained (**15** and **16**; 85% and 72%, respectively). The reaction can also extend to heteroarylamines, as exemplified by the anilide derived from 5-amino-1,3-dimethylpyrazole (entry 9). Reaction with benzylamine under the above conditions provided the corresponding pyrazolopyrimidine **17** in good yield (80%).

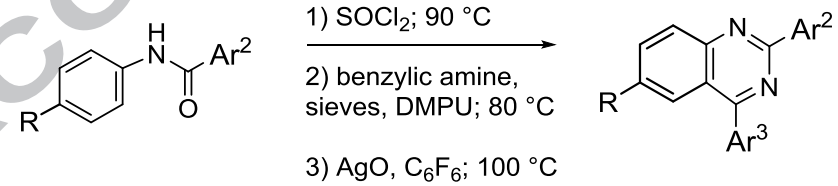
Table 2. Substrate Scope: Aniline Ring Substituents.



Entry	Ar	Product	Yield (%)
1	Ph	9	93
2	4-F-Ph	10	86
3	4-Cl-Ph	11	93
4	4-Br-Ph	12	91
5	4-MeO-Ph	13	89
6	4-Me-Ph	14	92
7	2-Me-Ph	15	85
8	2-MeO-Ph	16	72
9	1,3-Dimethylpyrazol-5-yl	17	80

Substituent effects of the aroyl ring were next examined (Table 3). Again, while para-substituents were well tolerated regardless of their electronic nature (**18**-**23**), ortho-substituents negatively impacted the overall process (entries 7 and 8; 62% and 44%, respectively). In the case of an isonicotinoyl amide (entry 9), the significant reduction in yield is the result of partial degradation of the pyridyl ring that occurred under the reaction conditions employed for imidoyl chloride formation. Nonetheless, a moderate yield of the corresponding quinazoline **26** (42%) could still be obtained from this process.

Table 3. Substrate Scope: Aroyl Ring and Benzylic Amine Substituents.



Entry	R	Ar^2	Ar^3	Product	Yield (%)
1	H	4-MePh	Ph	18	91
2	H	4-F-Ph	Ph	19	88
3	H	4-Cl-Ph	Ph	20	93

4	**H**	**4-Br-Ph**	**Ph**	**21**	**90**
5	**H**	**4-MeO-Ph**	**Ph**	**22**	**83**
6	**H**	**4-F_3C-Ph**	**Ph**	**23**	**87**
7	**H**	**2-Me-Ph**	**Ph**	**24**	**62**
8	**H**	**2-Cl-Ph**	**Ph**	**25**	**44**
9	**H**	**Pyrid-4-yl**	**Ph**	**26**	**42**
10	**Me**	**Ph**	**4-F-Ph**	**27**	**88**
11	**Me**	**Ph**	**4-Cl-Ph**	**28**	**94**
12	**Me**	**Ph**	**4-F_3C-Ph**	**29**	**95**
13	**Me**	**Ph**	**4-MeO-Ph**	**30**	**92**
14	**Me**	**Ph**	**4-Me_2N-Ph**	**31**	**91**
15	**Me**	**Ph**	**4-CN-Ph**	**32**	**65**
16	**Me**	**Ph**	**4-AcHN-Ph**	**33**	**47**
17	**H**	**Ph**	**4-MePh**	**34**	**87**
18	**H**	**Ph**	**2-F-Ph**	**35**	**92**
19	**H**	**Ph**	**2-Cl-Ph**	**36**	**94**
20	**H**	**Ph**	**2,6-di-MeO-Ph**	**37**	**67**
21	**H**	**Ph**	**2,5-di-Me-Ph**	**38**	**85**
22	**H**	**Ph**	**Naphth-1-yl**	**39**	**82**
23	**H**	**Ph**	**Pyrazin-2-yl**	**40**	**84**

Finally, the benzylamine component could also be varied with respect to steric and electronic effects without adversely affecting the overall process, albeit with a few notable exceptions (Table 3). Whereas electron-donating substituents such as methoxy and dimethylamino were well tolerated (entries 13 and 14, respectively), as were some electron-withdrawing substituents (halo; entries 10, 11, 18, 19 and trifluoromethyl; entry 12), the reaction proved to be less suited for the 4-cyano and 4-acetamido benzylamines (entries 15 and 16, respectively). And while this process accommodated a single ortho substituent (entries 18, 19, 21 and 22), the presence of two (2, 6-dimethoxy; entry 20) resulted in a modest reduction in overall yield (67%). Heterocyclic benzylic amines may also be compatible reaction partners, as exemplified by 2-pyrazinemethanamine (entry 23), from which quinazoline **40** was obtained in good yield (84%). It is important to point out that even in those cases where the presence of certain substituents adversely affected the overall yield of the reaction, the process still provided an expeditious means of generating the corresponding diarylquinazolines in practical amounts.

In order to determine if a radical mechanism was operational during this silver(II) oxide-mediated transformation, the optimized two-step reaction sequence was carried out with

benzamidine **41** and *p*-methylbenzylamine (**6**) in the presence of radical scavengers (2 eq.), e.g. 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO),[11] 1,1-diphenylethylene,[12a] or 2,6-di-*tert*-butyl-4-methylphenol (BHT).[12] The first two inhibitors significantly suppressed the formation of the diarylquinazoline **34** (42% and 39% yields, respectively (vs. 87% in the absence of the scavenger), while the presence of BHT completely inhibited the transformation.[13] These results are consistent with the involvement of a radical-induced oxidative cyclization mechanism, as depicted in Figure 3. In this proposed mechanism, oxidation of benzamidine **41** could proceed through a benzyl amidinium radical (**42a**),[14] which in turn would be further oxidized to the corresponding diimine (**42b**) with concomitant loss of water and reduction of the silver(II) to silver(0). Ring formation could ensue by way of a 6π-electrocyclization rearrangement to afford the dihydroquinazoline and related tautomers (**42c-e**), which would then undergo rapid oxidative aromatization to provide the quinazoline product, **34**.[15]

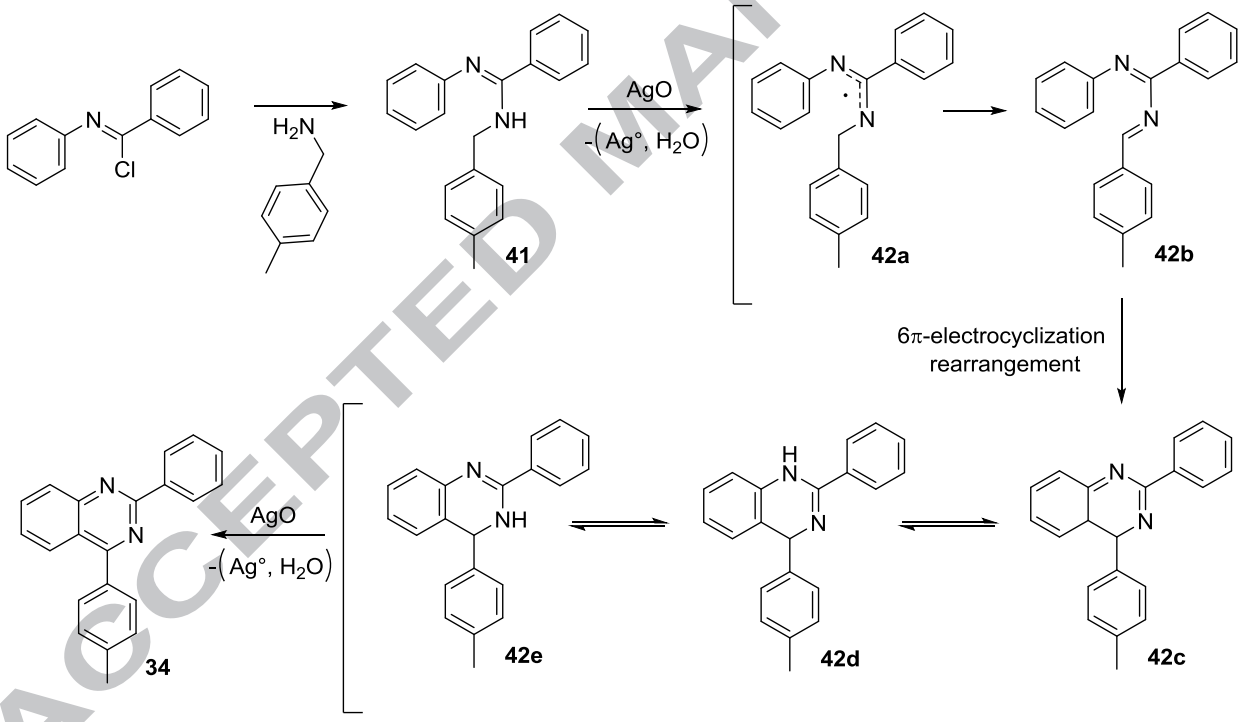


Figure 3. Proposed Mechanistic Pathway.

In conclusion, we have demonstrated a facile one-pot synthesis 2,4-diarylquinazolines, starting from readily available aryl anilides and benzylic amines. Under mild oxidative reaction conditions employing silver(II) oxide as oxidant, the reaction was found to likely proceed through a radical mechanism. The reaction tolerates a broad range of substituents, though

sterically demanding ortho-substituents in the aroyl and benzylamine reaction components may compromise the cyclization efficiency. Notwithstanding this limitation, the method reported herein appears to have otherwise broad application, and provides mild, neutral reaction conditions for accessing the 2,4-diarylquinazoline ring system. This complementary approach may be particularly useful in cases where alternative methods may not be tolerated.

Acknowledgement

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Supplementary data

Experimental details; characterization data (HRMS summary data and ^{1}H NMR) of final compounds.

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(13) Though not structurally characterized, a putative BHT-benzamidine **41** adduct was detected in the reaction mixture by LC/MS (m/e = 519.5^{+}), along with mostly unreacted benzamidine **41**. Similarly, a putative diphenylethylene-benzamidine **41** adduct (minor peak) was detected in its reaction mixture by LC/MS (m/e = 480.4^{+}), along with unreacted benzamidine **41** and quinazoline **34**. However, a TEMPO-benzamidine **41** adduct could not be detected in its reaction mixture.

(14) An analogous *N*-arylbenzimidamidyl radical species has recently been postulated as a plausible reaction intermediate, generated by a silver(I) carbonate-mediated oxidation of an *N*-arylbenzamidine: He, C-L; Liu, R.; Li, D-D.; Zhu, S-E.; Wang, G-W. *Org. Lett*. **2013**, *15*, 1532.

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HIGHLIGHTS

- One-pot synthesis of 2,4-diarylquinazolines from *N*-arylbenzamides and benzylamines
- Proceeds under neutral reaction conditions
- Silver oxide-mediated 6π-electrocyclization/oxidation process
- Broad scope with respect to *N*-arylbenzamides and benzylamine components