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# An aerobic oxidative aza-[4+2] cycloaddition induced by radical cation salt: Synthesis of dihydroquinazoline derivatives

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## ABSTRACT

A facile and efficient radical cation salt-induced approach to dihydroquinazoline derivatives has been developed by $sp^3$ C—H oxidation, and the method uses readily available glycine esters as the starting material under aerobic oxidation conditions without addition of any additive. The present method provides a convenient and practical route for construction of quinazoline skeleton.

In the past decade, construction of C—C and C—heteroatom bonds through the dehydrogenative or oxidative coupling via functionalization of C—H bonds are established as a powerful and more efficient method in modern synthetic organic chemistry.[1] These approaches avoid prefunctionalizations and tedious purification steps for the synthesis of complex organic compounds, enhancing the atom and step economy of the transformation. Generally, organic peroxides, DDQ, TEMPO oxoammonium salt and other stoichiometric oxidants are typically used as oxidants for accomplishing such transformations.[2] An attractive alternative is the use of molecular oxygen as the terminal oxidant, which only leads to concomitant water loss. However, examples are still limited.[3] In 2012, our group introduced a triarylamine radical cation salt ($TBPA^{+\cdot}$, tris (4-bromophenyl)aminium hexachloroantimonate)[4] as an efficient and mild promoter for aerobic oxidation of C—H bonds.[5a] This catalyst has been used widely in oxidation of *N*-arylglycines, *N*-benzylanilines and *N*-protected tetrahydroisoquinoline (THIQ), building a series of heterocycles in high yields.[5]

The quinazoline skeleton is a kind of medicinally and pharmaceutically important heterocyclic motif present in various synthetic and natural alkaloids with an extensive spectrum of biological and medicinal activities, such as s anticancer, anti-inflammatory, antibiotic, antiviral activity and others.[6] A variety of drug molecules contain quinazoline ring as the core structural skeletons such as prazosin,[7] erlotinib[8] and iressa[9] (Fig. 1).

Due to the demand of quinazoline derivatives in various fields, different synthetic methods have been described.[10] For example, Buchwald et al. reported an efficient domino process to quinazolines through the Pd-catalyzed *N*-arylation of amidines followed by addition of aldehydes.[10a] Benzamides and alkylnitriles could also be used to construct quinazoline skeleton in the presence of $Tf_2O$ and a base additive.[10e] In 2012, Han and coworkers developed a copper catalyzed aerobic oxidative reaction of 2-(aminomethyl) benzenamines with aldehydes for the synthesis of quinazolines.[10g] Although these reported elegant methods for synthesis of quinazolines are efficient, it would still be highly desirable to exploit a more convenient and straightforward approach.

In 2013, Mancheño's group developed a straightforward iron-catalyzed oxidative tandem synthesis of dihydroquinazolines from *N*-arylglycines, in which a TEMPO oxoammonium salt was used as a mild, nontoxic oxidant.[11] So we wondered whether the triarylamine radical cation salt can also be applied to induce the aerobic oxidation of *N*-arylglycines, avoiding the use of stoichiometric oxidant. Herein we describe an efficient synthesis of dihydroquinazolines from an aerobic oxidation of *N*-arylglycines followed by domino aza-[4+2] cycloaddition. In this transformation, two C—X bonds and one heterocyclic ring were constructed in one step, and $TBPA^{+\cdot}$ was employed as a mild and nontoxic catalyst under additive free conditions.

We investigated the reaction by selecting *N*-arylglycine **1a** as the model substrate in the presence of $TBPA^{+\cdot}$ (10 mol%) and $O_2$

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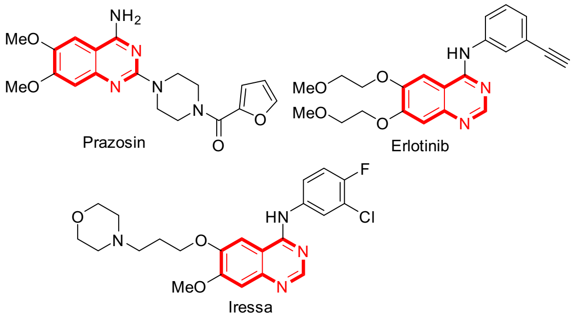


**Fig. 1.** Drugs Containing the Quinazoline Skeleton.

in MeCN at 60 °C (Table 1, entry 1). The desired dihydroquinazoline was obtained in 62% yield. Various solvents such as DCE, $CHCl_3$, DCM and THF were also screened, and the desired product was isolated in lower yield (entries 2–5). Further optimization of the conditions showed that the reaction was significantly affected by catalyst loading (entries 6–8), and the highest yield was obtained in the presence of 15 mol% $TBPA^{+\cdot}$ (entry 8). Addition of acidic additive decreased the reaction efficiency, giving the dihydroquinazoline in lower yields (entries 9–10). Then the evaluation of reaction temperature was performed, and the results indicated that the aerobic oxidation was not efficient at lower temperature (entries 11–12), and the conversion of the starting material was less than 50% (8% and 33%, respectively). Higher temperature is beneficial to accelerate the oxidation of *N*-arylglycine, but resulted in complicated products, providing the desired product in 56% yield (entry 13).

The scope of this aza-[4+2] cycloaddition of substituted *N*-arylglycines was then investigated under the optimized conditions. As shown in Table 2, all the substrates examined provided the desired products in moderate to good yields. Both electron-donating and withdrawing groups substituted *N*-arylglycines showed good reactivity, yielding the corresponding dihydroquinazolines in 60–75% isolated yields (entries 1–5). The 2,4-disubstituted substrates could also be tolerated in this reaction, and the desired products were obtained in 42–64% yields (entries 6–8). However, in accord with the reported results,[11] the absence of *para*-groups would decrease the reaction efficiency and led to a complex reaction mixture, in which only trace of the expected quinazoline **2** was detected.

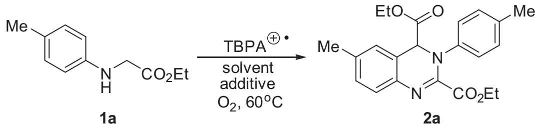
Then, different ester groups were varied to test the functional group tolerance. To our delight, the reaction efficiency was not decreased when various alkyl groups were connected (entries 11–16), and even the bulky esters gave the desired product **2** in comparable yields (entries 13–16). When benzyl and allyl esters were employed, in which other active $sp^3$ C—H bonds might also be oxidized under the oxidative reaction conditions, the reaction was not disturbed, delivering the corresponding quinazoline **2q** and **2r** in 68% and 73% isolated yields, respectively. Moreover, the acid labile three-membered ring could also be well tolerated in this mild oxidation, and the desired product **2s** was isolated in 67% yield.

To elucidate the reaction mechanism, several control experiments were performed, as shown in Scheme 1. In the absence of dioxygen and $TBPA^{+\cdot}$, respectively, the reactions were totally inhibited, and only trace amount of the desired product was detected by crude $^1H$ NMR (Eqs. 1 and 2. These results show that both dioxygen and $TBPA^{+\cdot}$ are crucial to the $sp^3$ C—H bond oxidation. It was also found that the addition of TEMPO (1 equiv) interrupts the reaction process (Eq. 3), implying that a radical intermediate might be involved in this reaction.

Based on our and Mancheño's research on C—H oxidation of glycines,[5,11] a radical intermediate mechanism was proposed (Scheme 2). Initially, the glycine **1** is oxidized by $TBPA^{+\cdot}$ under aerobic atmosphere,[12] generating a radical intermediate **A**, which is further oxidized to an iminium ion **B**. A nucleophilic attack of the nitrogen of another glycine **1** takes place, giving an adduct **C**. Under the oxidative conditions, the intermediate **C** can again be oxidized to another iminium ion **D**, followed by a Friedel-Crafts type cyclization. After the terminal deprotonation and oxidation, the desired dihydroquinazoline derivative **2** is formed.

In conclusion, we have developed a simple and efficient method for construction of quinazoline derivatives. In this protocol, an

**Table 1**
Optimization of Reaction Conditions.[a]



| Entry | $TBPA^{+\cdot}$ (mol%) | Additive (mol%) | Solvent | Yield (%) [b] |
|---|---|---|---|---|
| 1 | 10 | None | MeCN | 62 |
| 2 | 10 | None | DCE | 52 |
| 3 | 10 | None | $CHCl_3$ | 40 |
| 4 | 10 | None | DCM | 10 [c] |
| 5 | 10 | None | THF | trace |
| 6 | 2 | None | MeCN | 12 [c] |
| 7 | 5 | None | MeCN | 47 [c] |
| **8** | **15** | **None** | **MeCN** | **74** |
| 9 | 15 | $Incl_3$ | MeCN | 17 [c] |
| 10 | 15 | TsOH | MeCN | 40 [c] |
| 11 | 10 | None | MeCN | trace [c,d] |
| 12 | 10 | None | MeCN | 25 [c,e] |
| 13 | 10 | None | MeCN | 56 [f] |

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.5 mmol) in the presence of $TBPA^{+\cdot}$ (10 mol%) and anhydrous solvent (3.0 mL) at 60 °C for 24 h.
[b] Isolated yields.
[c] Low conversion of the starting material.
[d] Room temperature.
[e] At 40 °C.
[f] At 80 °C.