ONE-POT PALLADIUM-CATALYZED LIGAND- AND METAL-OXIDANT-FREE AEROBIC OXIDATIVE ISOCYANIDE INSERTION LEADING TO 2-AMINO-SUBSTITUTED-4(3H)-QUINAZOLINONES

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GRAPHICAL ABSTRACT

Abstract An efficient, ligand- and metal-oxidant-free, one-pot, cascade aerobic oxidative, palladium-catalyzed, multicomponent reaction has been developed through isocyanide insertion of less active secondary amide and aromatic amine, which leads to 2-amino-substituted-4(3H)-quinazolinones. This approach proves to be one of the simplest methods for the synthesis of this class of valuable bioactive heterocyclic scaffolds.

Keywords 2-Amino-substituted-4(3H)-quinazolinones; isocyanide insertion; Pd-catalyzed aerobic oxidation

INTRODUCTION

Heterocyclic compounds are well noted for their wide presence among natural products and more importantly for their potent biological and medicinal properties.[1] It is quite interesting to know that 2-amino-substituted-4(3H)-quinazolinone has two biologically potent functionalities, the 4(3H)-quinazolinone and...
guanidine groups present within it, which might enhance its bioactivity.\[2\] Examples include methaqualone (antimalarial),\[3\] afloqualone (muscle relaxant),\[3\] anagrelide (thrombocytosis),\[4\] and norastemizole (rhinitis).\[5\] 2-Amino-substituted-4(3\(H\))-quinazolinones have antibacterial, anti-inflammatory, antimalarial, and antiviral properties. It is worth mentioning that 2-amino-substituted-4(3\(H\))-quinazolinone moieties also have potent activity against Parkinson's and hypokinetic conditions,\[6\] such as nolatrexed (anticancer)\[7\] and acyclovir (antiviral)\[8\] (Fig. 1). Thus, the major role these privileged molecules possess in the drug discovery sector was an impetus for us to work toward their synthesis.

Even though several strategies that employ quite different approaches for the synthesis of 2-amino-substituted-4(3\(H\))-quinazolinones are reported, exploring newer and more efficient protocols would always be in demand. A few of them include (a) solid-phase synthesis of 2-amino-substituted-4(3\(H\))-quinazolinones,\[9\] (b) palladium-catalyzed cyclocarbonylation of \(o\)-iodoanilines with heterocumulenes,\[10\] (c) efficient synthesis by tandem palladium-catalyzed addition/cyclocarbonylation,\[11\] (d) molybdenum-mediated synthesis of quinazolin-4(3\(H\))-ones via cyclocarbonylation using microwave irradiation,\[12\] and (e) synthesis of 2-aminobenzimidazoles starting from \(o\)-phenylenediamines.\[13\] However, these methodologies require either the use of strong base, expensive ligand, hazardous CO gas, or preparation of starting material.

Recent development of multicomponent reactions (MCRs)\[14\] in heterocyclic synthesis is mainly based on employment of transition metals, among which palladium occupies a prominent position because it catalyses a variety of organic transformations.\[15\] The previous decades used carbonylation (CO insertion) reaction in heterocyclic synthesis, which now has been replaced by imidoylation (isocyanide insertion) reaction. Even though isocyanides are known for their obnoxious odor, their synthetic utility is so enormous that it outweighs it.\[15\] The replacement of CO with isocyanide can be easily done because of their similar isoelectronic natures. Moreover, isocyanides also have several advantages over CO, such as ease in handling, being less hazardous, and ability to bring about high diversity and further transformations with the use of functionalized isocyanides. Nowadays, the importance of isocyanide insertion reactions using palladium is realized by the number of reports
that are being published for the synthesis of various heterocyclic molecules, including (a) multicomponent synthesis of oxazoline and benzoxazole,[16] (b) synthesis of pyridopyrimidines by isocyanide insertion,[17] (c) synthesis of 4-aminophthalazine-1(2H)-ones by isocyanide insertion,[18] (d) synthesis of 2-amino-benzoazinones by aerobic oxidative coupling,[19] and (e) synthesis of isoquinolin-1(2H)-ones.[20] In continuation of our work in developing newer and efficient methodologies for the synthesis of novel and bio-potent heterocyclic molecules,[21] herein we desired to synthesize 2-amino-substituted-4(3H)-quinazolinones via isocyanide insertion between less reactive secondary amide and an aromatic amine utilizing palladium as catalyst and molecular oxygen as an oxidant in one-pot fashion.

During the preparation of our article, a closely related approach was described by other researchers,[22] who used metal oxidant Ag2CO3. However, the present cascade oxidative isocyanide insertion protocol is different from that report in the sense that it utilizes the cheaply available molecular oxygen as an oxidant under metal-oxidant-free conditions. Moreover, we have demonstrated the wide substrate scope for the present strategy.

RESULTS AND DISCUSSION

To reach our goal, we treated isatoic anhydride (1) with an amine (2) in dimethylsulfoxide (DMSO) and 4ÅMS as additive at 110 °C to give the desired dinucleophile (3) under inert conditions, which then serves as a substrate for isocyanide insertion (Table 1).

Initially, to optimize the reaction conditions, we employed various bases such as K2CO3, Cs2CO3, KtOBu, NaOBU, and NaOMe as additive/oxidant (Table 1). Because the yields were not appreciable with bases, we thought of using molecular oxygen for the regeneration of catalyst and surprisingly observed a drastic increase in the yield and also reduction in the time (entries 9 and 11, Table 1). Thus, we noticed that reaction went smoothly without any metal oxidant and afforded very good yields of the product with molecular oxygen (Table 1). Simultaneously, we also screened for solvents (Table 1), and found DMSO and toluene to be suitable for the reaction (Table 1). It is worth mentioning that use of molecular sieves enhanced the yield of product.

To expand the scope of reaction, we chose DMSO as solvent with 1.5 equiv of cyclohexyl isocyanide and oxygen as oxidant at 110 °C as the optimum conditions (entry 11, Table 1). We proved the generality of reaction by employing various amines such as benzylic, aliphatic, and aromatic amines, isocyanides, and isatoic anhydrides. We observed that formation of dinucleophile took 30–60 min with aliphatic and benzylic amines but 2–4 h with aromatic amines. The second step of the reaction takes 15–17 h, and increasing the reaction time has no effect on the conversion of intermediate. During the second step of the reaction, we found that benzylic amines gave very good yields while aromatic and aliphatic amines gave poor or no yields. In the case of 4-nitroaniline, it failed to give the desired product, which can result due to its lesser nucleophilicity (Table 2). So far most of the previous approaches for isocyanide insertion reactions have demonstrated that the scope of reaction with respect to isocyanide is limited to tert-butylisocyanide.[16–20] In contrast, we obtained better results with secondary cyclohexyl isocyanide, whereas tert-butyl isocyanide and others gave very poor or no yields of the desired products (Table 2).
Plausible Mechanism

The mechanism for the coupling of dinucleophile and isocyanide is given based on the previous reports for aerobic oxidative isocyanide insertion reactions using palladium (Figure 2)\textsuperscript{[13]} At first, a dinucleophile (3) is formed from isatoic anhydride (1) and amine (2). Complex (a) is formed by coordination of isocyanide to palladium acetate, which reacts with the dinucleophile to form intermediate I. This is followed by migratory insertion of coordinated isocyanide, which affords intermediate II, which eventually undergoes reductive elimination to give Pd\textsuperscript{0}, which is then stabilized by coordination of multiple isocyanides. It is worth mentioning that regeneration of the catalyst for further reactions does not require any metal oxidant; rather, it is smoothly oxidized by molecular oxygen.

CONCLUSION

In summary, we were successful in developing a novel and facile one-pot palladium-catalyzed isocyanide insertion by the newly evolving sustainable strategy of aerobic oxidation for the synthesis of biologically important 2-amino-substituted-4(3\textit{H})-quinazolinones. The advantages of the present protocol are operational simplicity, readily available starting materials, and relatively inexpensive catalyst. Here,
Table 2. Scope of various starting materials for the synthesis of 2-amino-substituted-3(3H)-quinazolinones (5a–5w)
Reaction conditions: 1 (0.609 mmol), 2 (0.609 mmol), 4 (0.913 mmol), 5 mol% of Pd(OAc)$_2$, 0.913 mmol of base.
it is worth mentioning that molecular oxygen is employed as oxidant in place of metal oxidant for regeneration of catalyst, and it eliminates the use of additional ligands. Our strategy is ecofriendly because of the reduction of the amount of waste generated and has an easier workup. Thus, this protocol should prove more efficient for the synthesis of 2-amino-substituted-4(3H)-quinazolinones than the existing ones.

**EXPERIMENTAL**

In an oven-dried Schlenk tube under argon atmosphere, isatoic anhydride (1 equiv, 0.609 mmol), amine (1 equiv, 0.609 mmol), and activated 4 Å molecular sieves (150 mg) were added, followed by dry dimethylsulfoxide (DMSO; 2 mL). The reaction mixture was stirred at 110 °C for 30 min to 4 h. The completion of first step was monitored by thin-layer chromatography (TLC). Once the dinucleophile was formed Pd(OAc)$_2$ (5 mol%) and CyNC (1.5 equiv., 0.913 mmol) were added in the same pot under an argon atmosphere. It was evacuated and filled with O$_2$ by using a balloon. The resulting reaction mixture was heated at 110 °C. Progress of the reaction was monitored by TLC, which took 15–17 h. The reaction mixture was then
quenched with water and the product was extracted with ethyl acetate. The organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as eluent, which afforded the desired product (5a–5w).

3-Benzyl-2-(cyclohexylamino)quinazolin-4(3H)-one (5a): White solid (75%), mp 106–108 °C [TLC control $R_f$(1) = 0.30, $R_f$(5a) = 0.70 (petroleum ether/ethyl acetate 8:2, UV detection)]. IR (MIR-ATR, 4000–600 cm$^{-1}$): $\tilde{v}_{\text{max}}$ = 3324, 3059, 2921, 1627, 1584, 1517, 1487, 1384, 1230, 1198, 1029, 951, 751, 640. $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$H = 8.18 (dd, 1H, $J_a$ = 8.1 and $J_b$ = 1.2 Hz), 7.60–7.56 (m, 1H), 7.38–7.30 (m, 4H), 7.29–7.26 (m, 1H), 7.17 (t, 1H, $J$ = 7.6 Hz), 5.32 (s, 2H), 4.36 (d, 1H, $J$ = 6.8 Hz), 3.99–3.91 (m, 1H), 1.83 (dd, 2H, $J_a$ = 8.6 and $J_b$ = 3.7 Hz), 1.53–1.46 (m, 3H), 1.40–1.29 (m, 2H), 1.18–0.98 (m, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$C = 163.2, 149.5, 149.2, 135.3, 134.4, 129.4, 128.2, 127.4, 126.6, 124.9, 122.4, 116.9, 49.7, 44.6, 42.5, 25.6, 24.2. HR-MS (ESI$^+$) m/z calculated for [C$_{21}$H$_{24}$N$_3$O]$^+$ = [M + H]$^+$: 334.1914; found: 334.1901.

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**SUPPORTING INFORMATION**

Supplemental data for this article can be accessed on the publisher’s website.

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