One-pot Synthesis of 6-Aza-chromone Derivatives Through Cascade Carbonylation-Sonogashira-Cyclization

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We developed an efficient synthesis of aza-chromones from 3-iodo-4-(1H)-pyridones and terminal acetylenes via a cascade carbonylation-Sonogashira-cyclization reaction. By controlling the use of bases, both 6-aza-chromones 5 and 3-(4-oxo-1,4-dihydroquinoline-3-carbonyl)-4H-pyrano[3,2-c]quinolin-4-ones 6 could be selectively obtained in moderate to good yields.

Chromone and chromone derivatives are ubiquitous structures that constitute a variety of naturally occurring and synthetic bioactive compounds¹. Among them, 6-aza-chromones are a class of interesting compounds that display various biological activities. For example (Fig. 1), compound I can inhibit bromodomain and extra terminal domain (BET) proteins with the potential as cancer therapeutic agents²; repirinast is an antiallergic drug used for bronchial asthma³; and SB236049 is a metallo-β-lactamase inhibitor that can overcome bacteria resistance to beta-lactam antibiotics⁴, ⁵. However, to date only few synthetic routes to this interesting scaffold been reported. These include the condensation of 3-acetyl-quinolinone with benzaldehyde (Fig. 2 and Eq. 1) ⁶, ⁷, the cyclization of 1-(ortho-hydroxyaryl)-1,3-diketone (Fig. 2 and Eq. 2)⁸, and the condensation of 3-carbonyl-2-(2-(dimethylamino)vinyl)-4H-pyrano-4-one with ammonium acetate (Fig. 2 and Eq. 3)⁹. The limited number of methodologies restricts the diversification and development of these compounds. In the context of our ongoing efforts to develop new methods for generating these diversified natural-product-like scaffolds¹⁰–¹⁴, we report herein a new facile synthetic method for 6-azachromone derivatives from 3-iodo-4-(1H)-pyridones and terminal acetylenes via cascade CO insertion, Sonogashira coupling and cyclization.

Recently, palladium catalyzed carbonylative Sonogashira cross-couplings have attracted much attention¹⁵–²⁰, and have been successfully applied in the synthesis of chromones using o-iodophenols and terminal acetylenes²¹–²⁷. We have envisioned that a similar strategy could be applied to 3-iodo-4-(1H)-pyridones substrates to construct diverse 6-aza-chromone derivatives (5) (Fig. 3).

Results and Discussion

Our investigation started with the reaction of 3-iodo-quinolinone (4a) and phenylacetylene (2a). Initially, 4a and 2a were treated with Et₂NH (as base and solvent)²¹ and PdCl₂(dppf) (5 mol%) under 1 atm CO at 50 °C, but only a trace amount of product 5a was observed, presumably due to the poor solubility of 4a in Et₂NH (Fig. 4, entry 1). In order to improve the solubility, we ran the reaction in DMF with an excess of Et₂NH (10 equiv) as base; under these conditions, product 5a could be obtained in 30% isolated yield, together with another unexpected compound 6a in 26% yield. (Fig. 4, entry 2, the structure of 6a was verified by single crystal X-ray diffraction, see Supplementary Information, Fig. 1S). Replacement of PdCl₂(dppf) with PdCl₂(PPh₃)₂ led to, allowed full conversion of 4a and the yields of 5a and 6a were improved to 31% and 50%, respectively (Fig. 4, entry 3). Subsequently, different bases, including Et₃N, DIPEA, DBU, DABCO, Cs₂CO₃ and K₂CO₃ were screened for this reaction. Using 5 equiv of Et₃N or DIPEA as base, 4a can be completely consumed and give 6a in good yields (76% and 86%, respectively, Fig. 4, entries 5, 6). However, when DBU, DABCO, Cs₂CO₃ or K₂CO₃ was used, 4a reacted partially react and produced 5a and 6a in low to moderate yields (23–42%, Fig. 4, entries 7–10). Reduction of the amount of DIPEA decreased the yield of 6a (Fig. 4, entries 11, 12). Next, the effect of different solvents (DMSO, DMA,
CH$_3$CN, THF) was studied. Replacement of DMF with DMSO or DMA only slightly decreased the yield of 6a (Fig. 4, entries 13, 14), while using CH$_3$CN or THF as the solvent greatly lower the yield for both 5a and 6a (Fig. 4, entries 15, 16), probably due to the poor solubility of substrate 4a in these solvents. Further replacement of CO gas (1 atm) with CO donor Mo(CO)$_6$ gave inferior results (Fig. 4, entry 17). In summary, the optimized conditions (Condition B, Fig. 4, entry 6, shown in red) for the selective preparation of 6a are PdCl$_2$(PPh$_3$)$_2$ (5 mol%), DIPEA (5 equiv) in DMF under CO (1 atm) at 50°C.

Following optimization of reaction conditions for the preparation of 6a, we began searching for the optimal conditions for the preparation of 5. It could be noted that when excessive amount of Cs$_2$CO$_3$ was used as a base...
only 5a was selectively obtained in 37% yield, albeit 35% of 4a was recovered (Fig. 4, entry 9). Our previous result indicated that DIPEA can promote the full conversion of 4a, therefore we envisioned that the addition of DIPEA and Cs₂CO₃ together might achieve better yield of 5a. Indeed, when DIPEA was used together with Cs₂CO₃ both the yield for 5a (58%) and the conversion rate of 4a were improved (Fig. 4, entry 18). When 4 equiv of DIPEA and 2 equiv of Cs₂CO₃ were used as bases, 4a was completely consumed and 5a was obtained in a yield of 74% (Fig. 4, entry 19, condition A, shown in red).

Based on the above results, a reaction mechanism has been proposed (Fig. 5). Iodoquinoline substrate 4 first undergoes a consecutive oxidative addition and CO insertion to give Pd(II) complex A. Sonogashira coupling of A with terminal alkyne can generate intermediate propynone B. Deprotonation of B and the subsequent rearrangement can provide C, which undergoes 6-endocyclization to give product 5 (Path A). Intermediate B can also coordinate with another molecule of Pd(II) complex A to form Pd(II) complex D. Cyclization of D can afford intermediate E, which is followed by reductive elimination to give product 6 (Path B).

An interesting phenomenon about this reaction is that the use of different base leads to the production of compound 5 or 6 selectively, we speculate that DIEPA might facilitate a carbonylative Sonogashira coupling process to generate intermediate B, but have less effect on the deprotonation of B to C. While Cs₂CO₃ is not an optimum base for the carbonylative Sonogashira coupling, it is a stronger base, which promotes the deprotonation of B to generate phenoxide anion intermediate C, thus favors the self-cyclization to afford product 5.

With the optimized reaction conditions for path B in hand, the substrate scope of alkynes 2 was investigated. As shown in Fig. 6, both electron-donating and electron-withdrawing groups and substituted phenyl acetylenes...
Figure 5. Plausible mechanism for the generation of product 5 and 6.

Figure 6. Synthesis of compounds 6b–k. aReaction conditions: 4 (0.2 mmol), 2 (1.8 equiv), PdCl$_2$(PPh$_3$)$_2$ (5 mol %), 5.0 equiv DIPEA, DMF (1 mL), CO (1 atm), stirred at 50 °C. bIsolated yield.
can afford the desired products in good yields (72–87%, 6b–6e), while hexyne only gave 6f in moderate yield (49%), indicating the aromatic alkynes are more favorable substrates than aliphatic alkynes for this reaction. Subsequently, phenylacetylene 2a was reacted with different substituted iodoquinolines (4g–4i) to explore the effect of substituents on the iodoquinoline ring. These reactions proceed smoothly with moderate to good yields (57%–85%), indicating the good tolerance of different substituents on iodoquinoline. In addition, using 4j or 4k as substrate also produces the corresponding product 6j or 6k with the yields of 48% and 60%, respectively, indicating the wide substrate scope of this reaction.

In a similar manner, we applied the optimized reaction conditions for path A to synthesize compounds 5b–5k (Fig. 7). All the reactions proceeded to give the corresponding products in moderate to good yields (30%–75%) except compound 5i. The inferior yield of 5c (30%) in comparison with 5d (63%) suggests that an electron donating group on phenylacetylene is unfavourable for the production of compound 5. Failure of the synthesis of compound 5i is likely due to the strong electron withdrawing effect of CF₃, which decreases the stability of 5i.

Mono heterocycle substrates 3-iodo-4-(1H)-pyridone and 5-iodopyrimidin-4(1H)-one also gave corresponding products 5j and 5k in good yields (72%, 75%), indicating the good tolerance of various substrates in this transformation.

Conclusions
In summary, we have developed an efficient method for the synthesis of 6-aza-chromone derivatives through cascade Carbonylation-Sonogashira-Cyclization reactions. Using different bases, both 6-aza-chromone derivatives 5 and 6 can be synthesized selectively in good yields. Further applications of these methods and the biological activities of these compounds are under investigation.

Experimental Section
General procedure A (Condition A): Synthesis of 5. A test tube equipped with a magnetic stir bar and fitted with a septum, was charged with 3-iodo substrates (0.2 mmol), Cs₂CO₃ (2.0 equiv), DIPEA (4.0 equiv), PdCl₂(PPh₃)₂ (5 mol%), 2.0 equiv Cs₂CO₃, 4.0 equiv DIPEA, DMF (1 mL), CO (1 atm), stirred at 50 °C.

Figure 7. Synthesis of compounds 5b–5k. Reaction condition: 4 (0.2 mmol), 2 (1.8 equiv), PdCl₂(PPh₃)₂ (5 mol %), 2.0 equiv Cs₂CO₃, 4.0 equiv DIPEA, DMF (1 mL), CO (1 atm), stirred at 50 °C. Isolated yield.
General procedure B (Condition B): Synthesis of 6. A test tube equipped with a magnetic stir bar and fitted with a septum, was charged with 3-iodo substrates (0.2 mmol), DIPEA (3.0 equiv), PdCl₂(PPh₃)₂ (5 mol%). The test tube was evacuated and backfilled with CO (repeated 3 times) and then the alkyne (0.36 mmol) was added via syringe. The reaction mixture was heated to 50 °C until the starting material was completely consumed as monitored by TLC (typically 14 h). The reaction mixture was then cooled down to room temperature, diluted with ethyl acetate, washed with water, concentrated under reduced pressure and purified by column chromatography (silica gel) to afford the corresponding compounds 6.

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Author Contributions
G.C., R.S., Y.Z.H., Y.H. designed the work. G.C., Y.Q., X.Z. carried out the experiments, analyzed the data. G.C., R.S., Y.Z.H. wrote the paper. All authors discussed the results and commented on the manuscript.

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