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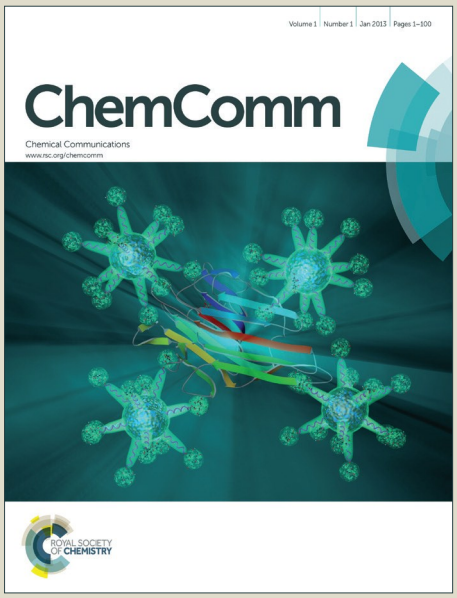

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ARTICLE TYPE

A palladium-catalyzed intramolecular carbonylative annulation reaction to form 4,5-fused tricyclic 2-quinolones

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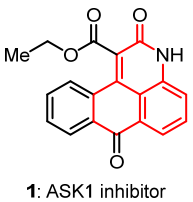
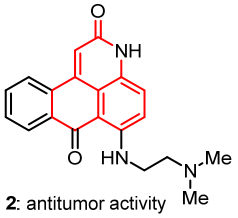
A concise and efficient synthetic route to 4,5-fused tricyclic 2-quinolones through a palladium-catalyzed carbonylative annulation of alkyne-tethered *N*-substituted *o*-iodoanilines has been developed. This reaction proceeds smoothly under mild reaction conditions and exhibits exceptional tolerance to a variety of functional groups. It has been successfully applied to the efficient synthesis of BI 224436, an HIV integrase inhibitor.

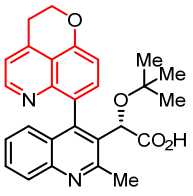
The 2-quinolone nucleus is one of the most important heterocycles since they are found in various natural products and pharmaceutically active compounds.[1,2] In addition, 2-quinolones are also valuable synthetic intermediates that can be easily converted into 2-haloquinoline derivatives, which could undergo further modifications.[3] Accordingly, a variety of well-documented traditional and modern methods have been developed for the construction of 2-quinolines.[4-6] Among the members of the 2-quinolone family, 4,5-fused tricyclic 2-quinolones have been considered attractive synthetic targets because of their unique molecular skeletons and potential pharmaceutical activities (Figure 1).[7-9] For example, compound **1** exhibits highly specific inhibitory activity toward apoptosis signal-regulating kinase 1 (ASK1) and could be used for the treatment of cardiac and neurodegenerative disorders.[7a] In addition, 4,5-fused tricyclic 2-quinolones have been used as synthetic intermediates and converted into 4,5-fused tricyclic 2-chloro- quinolines or 4,5-fused tricyclic quinolines.[8] Moreover, the tricyclic quinoline derivatives have also been reported to have interesting biological activities.[8] Compound **3** (BI 224436) is the first noncatalytic site integrase inhibitor of HIV-1 to undergo a phase Ia clinical trial.[8a,b] Compound **4** shows a noticeable cytotoxic activity against HT-29 with an IC_{50} value of 0.16 μM.[7d]



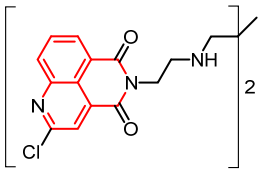
1: ASK1 inhibitor



2: antitumor activity



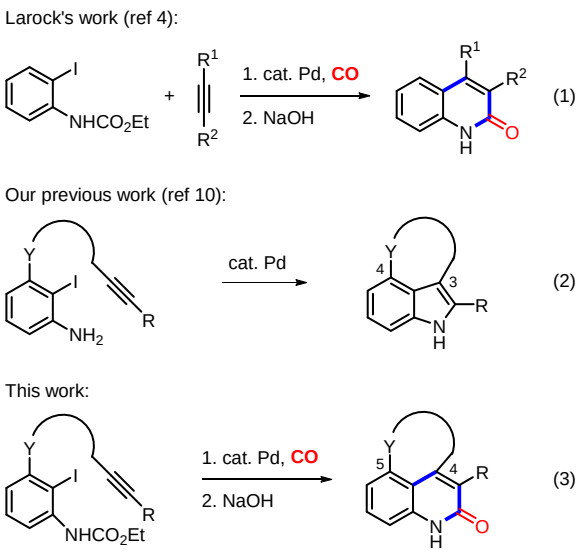
3 (BI 224436): HIV integrase inhibitor



4: antitumor activity

Figure 1 Selected biologically active 4,5-fused tricyclic 2-quinolones and 4,5-fused tricyclic quinolines.

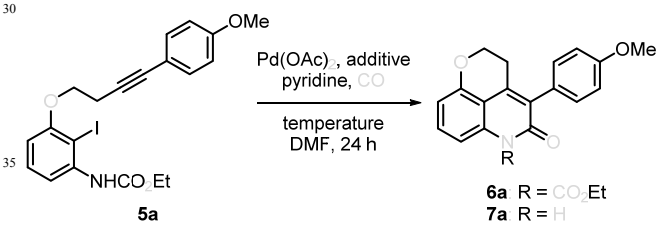
In 2004, Larock and Kadnikov reported a concise and efficient synthetic route to 2-quinolones through a palladium-catalyzed carbonylative annulation of *N*-substituted *o*-iodoanilines with internal alkynes (Scheme 1, eqn (1)).[4] The nature of the substituent on the nitrogen is crucial for obtaining high yields of 2-quinolones, and the nitrogen substituent is lost during the course of the reaction. This multicomponent process is significant because it involves the formation of two carbon-carbon and one carbon-nitrogen bonds. During the course of our studies on the total synthesis of 3,4-fused indole alkaloids, we have recently developed a new strategy for the construction of 3,4-fused tricyclic indoles by intramolecular Larock indolization of alkyne-tethered *o*-iodoanilines (Scheme 1, eqn (2)).[10] This general strategy can be widely applied to the total synthesis of 3,4-fused alkaloids and related systems. Encouraged by these results, we were curious whether an intramolecular carbonylative annulation of alkyne-tethered *o*-iodoaniline derivatives could be applied for the construction of 4,5-fused tricyclic 2-quinolones (Scheme 1, eqn (3)). Herein, we report our early results.



Scheme 1 Intramolecular annulation strategies for the synthesis of 4,5-fused tricyclic 2-quinolones.

Initially, compound **5a** was chosen as a model substrate and subjected to Larock's 2-quinolone synthesis conditions [$Pd(OAc)_2$ (0.1 equiv.), pyridine (2.0 equiv.), TBAC (1.0 equiv.) in DMF (0.01 M) under 1 atm CO at 100 °C for 24 h]. The desired 4,5-fused tricyclic 2-quinolone **6a** was obtained in only 25% yield accompanied with a recovery of 53% starting material **5a** (Table 1, entry 1). Interestingly, replacement of additive TBAC with LiCl gave better result and the unprotected product **7a** was also obtained in 34% yield, which was generated in situ by deprotection of the nitrogen substituent (Table 1, entry 2). Considering the low boiling point of pyridine and its diluted concentration, the amount of pyridine was increased to 5 equivalents. To our delight, the yield of **6a** was increased to 69% and the yield of **7a** was 21% (Table 1, entry 3). Next, the effect of reaction temperature was examined. When the temperature was decreased to 80 °C, the reaction was notably slower. **6a** was obtained in 60% yield accompanied with a recovery of 28% starting material **5a**, and no **7a** was generated (Table 1, entry 4). Increasing the temperature to 120 °C led to the completely consume of **5a**, but the yields of **6a** and **7a** were only 30% and 39%, respectively (Table 1, entry 5). Finally, we found that the phosphine ligand was effective for this process. When 0.2 equivalent of PPh_3 was added, the desired product was obtained in 95% overall yield (Table 1, entry 6), although the exact role of PPh_3 is not clear.[11] Thus, the optimized conditions is: 10 mol % $Pd(OAc)_2$, 5 equivalent of pyridine, 1 equivalent of LiCl, and 0.2 equivalent of PPh_3 in DMF at 100 °C for 24 h.

Table 1 Optimization of reaction conditions[a]

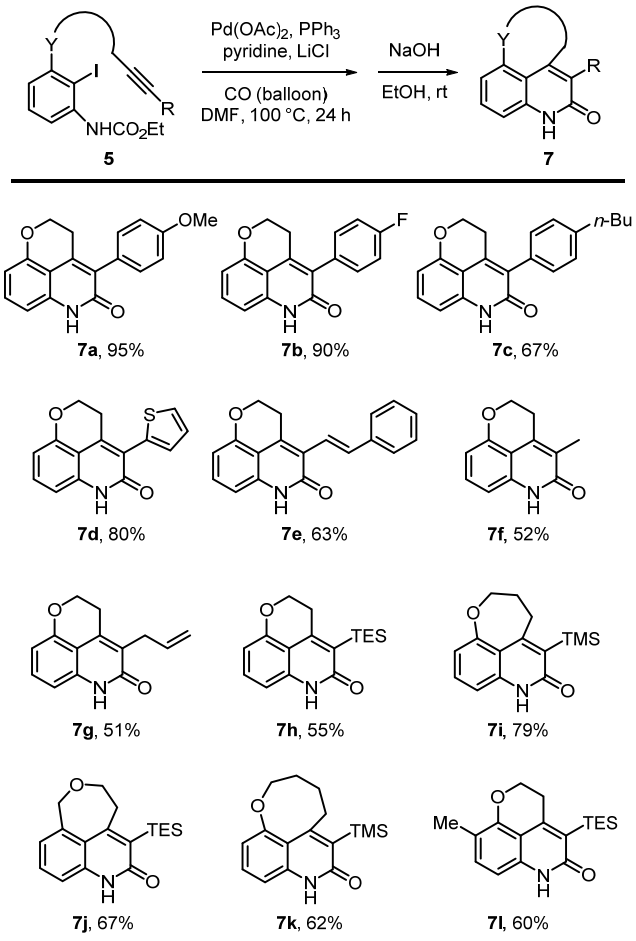


Entry	Additive	Equiv. of pyridine	Temp.	Yield (%) of **6a**, **7a**, and recovery of **5a**
1	TBAC	2	100 °C	25:0:53
2	LiCl	2	100 °C	33:34:28
3	LiCl	5	100 °C	69:21:5
4	LiCl	5	80 °C	60:0:28
5	LiCl	5	120 °C	30:39:0
6[b]	LiCl	5	100 °C	70:25:0

[a] Reaction conditions: **5a** (0.3 mmol), $Pd(OAc)_2$ (10 mmol%), pyridine (as indicated), additive (as indicated) in DMF (30 mL) under 1 atm CO for 24 h. [b] 0.2 equiv of PPh_3 was added.

Under the optimized reaction conditions, we next examined the substrate scope of this reaction. Considering that most substrates afforded the cyclized products **6** and **7** as a mixture in different ratios, the crude products were treated with 1 M ethanolic NaOH for 1 h at room temperature to hydrolyze **6** completely and the yield of **7** was obtained. The results of this study are summarized in Table 2. Under our optimized reaction conditions, the reaction proceeded smoothly to yield a series of 4,5-fused tricyclic 2-quinolones in moderate to excellent yields. Firstly, the electronic effects of aryl groups attached to the internal alkyne were first examined (Table 2, **5c**-**7c**). We found that there was no significant electronic effect of aryl groups on the internal alkyne. To explore the substituent effects of internal alkyne, a variety of internal alkynes bearing TES, alkyl, alkene, aryl and heteroaryl groups were examined (Table 2, **7c**-**7h**). They all gave the expected products in moderate to good yields. These results indicated that the substituents did not affect the reactivity of this transformation. The substrates leading to 7- and 8-membered ring fused 2-quinolones were then examined and gave the desired products in good yields (Table 2, **7i**-**7k**). In addition, *o*-methyl substituent on the *o*-iodoaniline was well tolerated, giving corresponding product in 60% yield (Table 2, **7l**).

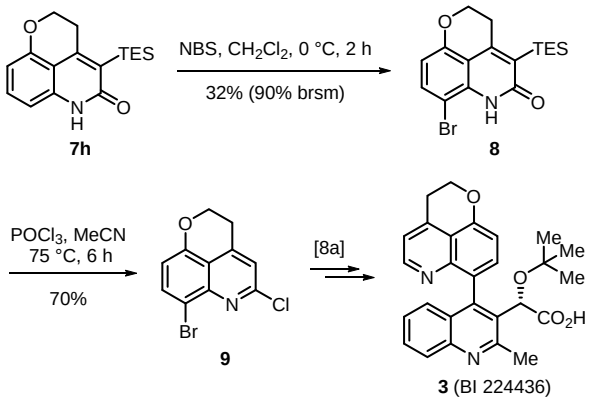
Table 2 Substrate scope for the formation of 4,5-fused tricyclic 2-quinolones[a]



[a] Reaction conditions: **5a** (0.3 mmol), $Pd(OAc)_2$ (10 mmol%), pyridine (5 equiv.), additive (2 equiv.), and PPh_3 (20 mmol%) in DMF (30 mL) under 1 atm CO for 24 h.

The utility of this new process was demonstrated by a rapid formal synthesis of compound **3**, a HIV integrase inhibitor

(Scheme 1). Treatment of **7h** with NBS afforded the desired 8-bromo **8** in 32% yield (brsm 90%). Chlorination of **8** with $POCl_3$ in CH_3CN at 75 °C resulted in the formation of quinoline chloride and deprotection of 3-TES group, yielding the known compound **9**, which could be transformed to **3** following the literature protocol.[8a]



Scheme 2 Formal synthesis of compound **3** (BI 224436).

In summary, we developed a novel and efficient strategy for the construction of 4,5-fused tricyclic 2-quinolones via palladium-catalyzed intramolecular carbonylative annulation of alkyne-tethered *N*-substituted *o*-iodoanilines. A variety of 4,5-fused tricyclic 2-quinolones have been successfully prepared. Its utility has been demonstrated with the rapid synthesis of BI 224436. We expect that this intramolecular protocol will find use in broad chemical synthesis.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental details and spectroscopic characterization. See DOI: 10.1039/b000000x/

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