One-pot Synthesis of Substituted Quinolines by Iridium-catalyzed Three-component Coupling Reaction

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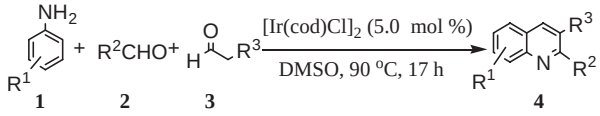
A convenient and efficient synthesis of substituted quinolines in a simple one-pot reaction of an arylamine **1**, an aromatic aldehyde or aliphatic aldehyde **2** and an aliphatic aldehyde **3** in the presence of transition metal complexes or Lewis acids was developed. Among them, the iridium catalyst $[Ir(cod)Cl]_2$ catalyzed the reaction most efficiently.

Development of quinoline synthesis has been of considerable interest in organic synthesis because of their wide occurrence in natural products[1] and usefulness for drug design.[2] Classical methods for the synthesis of quinolines, such as the Skraup,[3] Doebner-von Miller,[4] Conrad-Limbach,[5] Combes,[6] Pfitzinger,[7] and Friedländer[8] quinoline syntheses, require harsh reaction conditions and the yields are unsatisfactory in most cases. Therefore, a simple, general and efficient method for the preparation of quinoline ring system is in demand and modern synthetic methods for quinoline using a transition metal-catalyst have been investigated.[9,10] Dzhemilev reported that 2,3-disubstituted quinolines were synthesized with a $PrCl_3$ catalyst at 190 °C from arylamine **1**, an aromatic or aliphatic aldehyde **2** and aliphatic aldehyde **3**.[9] In our synthetic studies utilizing iridium-catalysts we have found the three-component coupling reaction proceeds at lower temperature 90 °C (Scheme 1). We present here the results of the iridium-catalyzed quinoline synthesis.



Scheme 1. Iridium-catalyzed quinoline synthesis.

In a typical experiment, a mixture of an aniline **1a** and a benzaldehyde **2a** in a 1:1 ratio in DMSO was stirred in the presence of iridium catalyst (5 mol %) at room temperature for 1 h. Butanal **3a** was added and the resulting mixture was heated at 90 °C for 17 h. The usual work up and chromatographic purification gave **4a** and **5a** in 42 and 28% yields (Table 1, Entry 1). Using *N*-benzylideneaniline as the starting material instead of an aniline and a benzaldehyde gave a satisfactory result (**4a**: 63% yield, **5a**: 8%) (Table 1, Entry 5). However, mostly imines are hygroscopic and difficult to purify by distillation or column chromatography. Therefore three-component coupling reaction using an aromatic amine, and two aldehydes directly without isolation of imines is desirable for practical synthesis. When two equiv. of **2a** was used, the ratio of the desired quinoline **4a** was raised and **4a** was obtained in 51% yield. When 5 equivalents or 10 equivalents of **2a** was used, the desired quinoline **4a** was obtained in 61 or 58% yields with small amounts of **5a** (Table 1, Entries 3 and 4). The 1:2 adduct **5a** of aniline and butanal was obtained in good yield (73%) by the reaction in the absence of a benzaldehyde **2a** (Table 1, Entry 6).

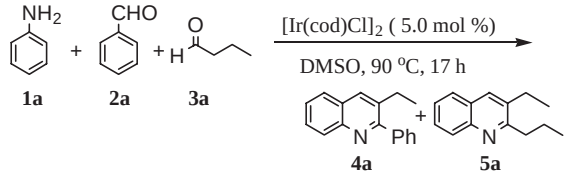


Table 1. Synthesis of quinoline **4a** by iridium-catalyzed three-component coupling reaction

Entry	Equivalent			Yield/%[a]	
	1a	**2a**	**3a**	**4a**	**5a**
1	1.0	1.0	1.0	42	28
2	1.0	2.0	1.0	51	22
3	1.0	5.0	1.0	61	11
4	1.0	10	1.0	58	9
5[b]	1.0	1.0	1.0	63	8
6	1.0	0	2.5	0	73

[a]Isolated yield based on aniline **1a**. [b]*N*-Benzylideneaniline was used in stead of **1a** and **2a**.

Formation of quinoline is expected to be catalyzed by various acids.[11] In this case, Lewis acids such as $AlCl_3$, $TiCl_4$, $HfCl_4$, and $Yb(OTf)_3$ exhibit also considerable activities for the synthesis of quinoline **4a** as shown in Table 2. However, the iridium catalyst gave the best result for the one-pot quinoline synthesis (Table 2, Entry 2).

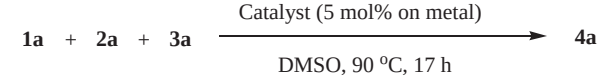


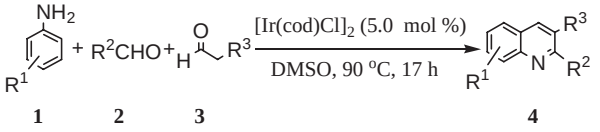
Table 2. Effect of catalysts on three-component coupling reaction

Entry	Catalysts	Yield/%[a]
1	blank	N.R.
2	$[Ir(cod)Cl]_2$	61
3	$AlCl_3$	45
4	$TiCl_4$	55
5	$HfCl_4$	54
6	$Yb(OTf)_3$	61
7[b]	$PrCl_3/3\ PPh_3$	17

[a]Isolated yield based on aniline **1a**. [b]Reaction at 190 °C in DMF.[9] No formation of **4a** at 90 °C in DMF, but **5a** was obtained in 35% yield.

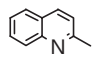
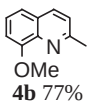
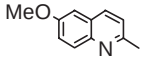
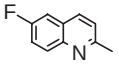
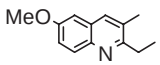
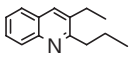
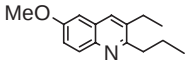
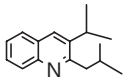
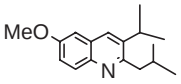
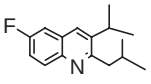
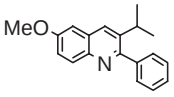
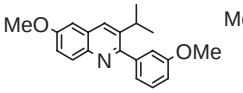
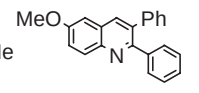
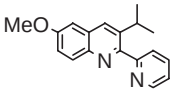
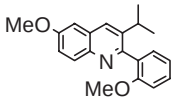
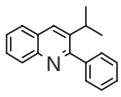
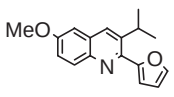
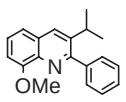
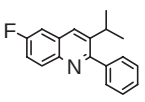
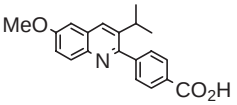
Various substituted quinolines were obtained using iridium-catalyzed three-component coupling reaction in a one pot. A wide range of substituted anilines, aromatic aldehydes, and ali-

phatic aldehydes were subjected to this procedure to synthesize the corresponding quinolines in yields as shown in Table 3. Functional groups such as methoxy, fluoro, carboxylic acid and heterocycles as a pyridine and a furan are incorporated in this synthesis.



1 **2** **3** **4**

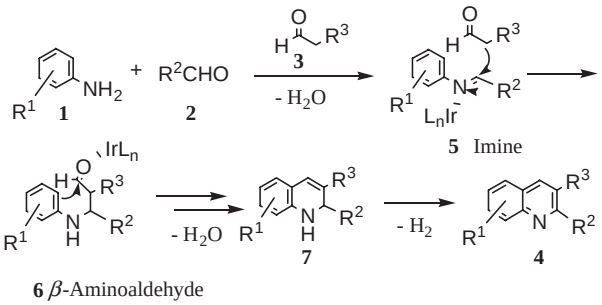
Table 3. Synthesis of substituted quinolines by iridium-catalyzed three-component coupling reaction

Products[a]		
		
4a 69%	**4b** 77%	**4c** 41%
		
4d 74%	**4e** 40%	**4f** 45%
		
4g 73%	**4h** 59%	**4i** 99%
		
4j 83%	**4k** 78%	**4l** 61%
		
4m 53%	**4n** 52%	**4o** 7%
		
4p 75%	**4q** 53 %	**4r** 44%
		
4s 37%	**4t** 45%	**4u** 47%

[a]The reactions were carried out using conditions of Entry 6 in Table 1 for **4a**–**4k** and those of Entry 2 for **4l**–**4u**.

The mechanism for the conversion of the three components to a quinoline is ambiguous but can be explained tentatively as in Scheme 2. A β-amino aldehyde **6** is preformed by three-component direct-Mannich reaction, followed by subsequent cyclization and aromatization under the catalyst of $[Ir(cod)Cl]_2$.

In summary, we have developed an efficient and general route to substituted quinolines in a one-pot synthesis from an arylamine, an aromatic aldehyde and an aliphatic aldehyde in the presence of catalytic amount of iridium complex.



Scheme 2. Plausible reaction mechanism.

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