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Ruthenium-Catalyzed Synthesis of 2-Ethyl-3methylquinolines from Anilines and Triallylamine

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Abstract

Anilines react with triallylamine in dioxane at 180 °C in the presence of a catalytic amount of ruthenium chloride and triphenylphosphine together with tin(II) chloride dihydrate to afford the corresponding 2-ethyl-3-methylquinolines in good yields. © 1999 Elsevier Science Ltd. All rights reserved.

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Transition metal-catalyzed heteroannulation provides a useful and convenient tool for the construction of skeletons of complex organocyclic molecules, many heterocyclic compounds being synthesized by a remarkable catalytic action of the catalysts. The formation of quinoline skeletons also has been attempted by the aid of transition metals such as palladium [1-4], rhodium [5-10], ruthenium [11-16], and iron [17] since the quinoline skeletons play an important role as an intermediate for the design of many synthetic antimalarial compounds. We recently developed and reported a synthetic method for the formation of indoles from primary aromatic amines and trialkanolamines under ruthenium-tin catalytic systems [18]. This finding prompted us to explore the similar ruthenium-catalyzed cyclization of primary aromatic amines with functionalized tertiary amines. We here report a new ruthenium-catalyzed approach for the synthesis of 2-ethyl-3-methylquinolines from primary aromatic amines and triallylamine.

A typical experimental procedure is as follows. A mixture of aniline (1) (10 mmol), triallylamine (2) (1 mmol), RuCl₃•nH₂O (0.05 mmol), SnCl₂•2H₂O (1 mmol) and PPh₃ (0.15 mmol) in dioxane (10 mL) was placed in a stainless steel autoclave. After the system was flushed with argon, the mixture was stirred at 180 °C for 20 h. The reaction mixture was poured into brine, extracted with chloroform and dried over anhydrous sodium sulfate. Removal of the solvent left an oil which was separated by column chromatography using ethyl acetate-hexane to give 2-ethyl-3-methylquinoline (3) in 51% yield (eq 1).

We employed similar reaction systems such as the molar ratio of 1 to 2 and the amount of $SnCl_2 \cdot 2H_2O$ as has been optimized in our recent ruthenium-catalyzed synthesis of indoles [18]. As expected from the previous work, the present reaction resulted in only 4% yield of the

Ruinen	A -ilinee	2 Ethyl 2 methylauinelines	Testadesiald (01)
<u>Kun</u>	Animes	2-Euryi-3-methyiquinonnes	Isolated yield (%)
1	aniline	2-ethyl-3-methylquinoline	51
2	p-toluidine	2-ethyl-3,6-dimethylquinoline	61
3	<i>m</i> -toluidine	2-ethyl-3,5-dimethyl- and 2-ethyl-3,7-dimethylquinolines	56
4	o-toluidine	N-allyl-o-toluidine	37
5	p-anisidine	2-ethyl-6-methoxy-3-methylquinoline	55
6	<i>m</i> -anisidine	2-ethyl-5-methoxy- and 2-ethyl-7-methoxy-3-methylquinolines	50
7	p-chloroaniline	6-chloro-2-ethyl-3-methylquinoline	24
8	m-chloroaniline	5-chloro- and 7-chloro-2-ethyl-3-methylquinolines	28
9	p-butylaniline	6-butyl-2-ethyl-3-methylquinoline	55
10	p-sec-butylaniline	6-(sec-butyl)-2-ethyl-3-methylquinoline	61
11	3,5-dimethylaniline	2-ethyl-3,5,7-trimethylquinoline	59

Table 1

quinoline 3 in the absence of SnCl₂•2H₂O. N-Propylaniline and N-allylaniline were obtained as by-products in 21% yield by an alkyl group transfer between 1 and 2 and hydrogenation under the ruthenium catalyst.

The present cyclization could also be applied to many primary aromatic amines, several representative results being summarized in Table 1. The quinoline yield was considerably affected by the electronic nature and the position of the substituent on aniline. With chloroanilines having electron-withdrawing Cl substituent, the product yield was generally lower than that when anilines having electron-donating character were used. In the case of otoluidine the reaction did not proceed at all toward quinoline formation, N-allyl-o-toluidine being only detectable product. In the cases of meta-substituted anilines such as m-toluidine, manisidine, and *m*-chloroaniline, the corresponding quinolines were obtained as a regioisomeric mixture in moderate yields, favoring the formation of 7-substituted isomers.

The reaction seems to proceed via an initial formation of N-allylanilines by amine exchange reactions [19,20] between anilines and 2. However, in a separate experiment, similar treatment of N-allylaniline with 2 afforded 3 in only 10% yield. The detailed mechanistic study for the present reaction and the synthesis of other quinolines using our methodology are progress.

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