DOI: 10.1002/adsc.200600527

Friedländer Synthesis of Quinolines Using a Lewis Acid-Surfactant-Combined Catalyst in Water

Liang Zhang[a] and Jie Wu[a,b,*]

[a] Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, People's Republic of China
Fax: (+86)-216-510-2412; e-mail: jie_wu@fudan.edu.cn
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, People's Republic of China

Received: October 13, 2006

Abstract: In water, Friedländer annulation using Lewis acid-surfactant-combined catalyst provides a mild and efficient route for the synthesis of quinolines. Employing a catalytic amount of scandium tris(dodecyl sulfate) [$Sc(O_3SOC_{12}H_{25})_3$], various polysubstituted and polycyclic quinolines were obtained in exellent yields.

Keywords: Friedländer annulation; Lewis acids; quinoline; surfactant

Lewis acid catalysis has attracted much attention in organic synthesis.[1] Recently, a new type of catalyst, "Lewis acid-surfactant-combined catalyst (LASC)", has shown high efficiency in various organic transformations. These reactions are promoted in water without organic cosolvents.[2] Proposed by Kobayashi,[3] this kind of catalyst acts both as a Lewis acid to activate the substrate molecules and as a surfactant to form emulsions in water. The high efficiency of LASC in reactions, as well as creation of environmentally benign processes promoted us to explore the possibility of methodological development in the scaffold construction of natural product-like compounds.

The availability of a practical route for the generation of small molecules-based natural products is of utmost urgency and importance in biomedical research. As a privileged fragment, quinoline is a ubiquitous subunit in many quinoline-containing natural products with remarkable biological activities.[4] Members of this family have wide applications in medicinal chemistry.[4] Because of their importance as substructures in a broad range of natural and designed products, a significant effort continues to be given over to the development of new quinoline-based structures[5] and new methods for their construction.[6]

As part of a continuing effort in our laboratory toward the development of new methods for the expeditious synthesis of biologically relevant heterocyclic compounds,[7] we became interested in the possibility of developing a novel and efficient method to construct the quinoline scaffold. It is well-known that the protocol reported by Friedländer is one of the most simple and straightforward methods for the synthesis of polysubstituted quinolines, although some methods such as Skraup, Doebner von Miller, and Combes reactions[8] are available. Brønsted acids like sulfamic acid, hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid and phosphoric acid were widely used as reagents or catalysts.[9] Recently, various Lewis acids have been reported to be effective for the synthesis of quinolines.[10] However, many of these procedures are complicated by harsh reaction conditions, low yields, difficulties in work-up, and the use of stoichiometric and/or relatively expensive reagents. And in some cases, high catalyst loadings had to be employed in order to obtain respectable yields. Since quinoline derivatives are increasingly useful and important in pharmaceuticals and industry, the development of a simple, eco- and environmentally benign protocol is still desirable. Inspired by the recent advances of "Lewis acid-surfactant-combined catalysts (LASC)", we envisioned that we could exploit the property of LASC to effect the Friedländer annulation in water. Herein, we disclose our preliminary results for this transformation.

Our studies commenced with reaction of 2-aminobenzophenone **1a** with ethyl acetoacetate **2a** catalyzed by various Lewis acid-surfactant-combined catalysts (10 mol%) in water at room temperature (Table 1). Among the LASC screened, scandium tris(dodecyl sulfate) [$Sc(O_3SOC_{12}H_{25})_3$] shows the best result. Complete conversion and a 90% isolated yield of ethyl 2-methyl-4-phenylquinoline-3-carboxylate **3a** was obtained. Further studies showed that the result was improved when the reaction was performed at 40°C (12 h, 99% yield). Next, we examined the catalytic requirement of $Sc(O_3SOC_{12}H_{25})_3$ (1–10 mol%) for the reaction in water at 40°C. Reducing the amount of catalyst retarded the reaction. For example, only a trace amount of desired product **3a** was

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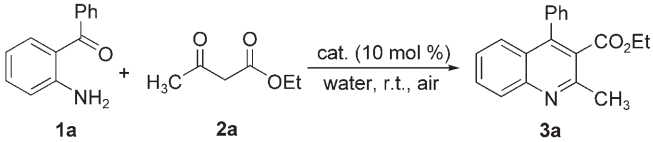
Table 1. Reaction of 2-aminobenzophenone **1a** with ethyl acetoacetate **2a** catalyzed by various Lewis acid-surfactant-combined catalysts (10 mol%) in water at room temperature.



Entry	LASC (catalyst)	Yield [%][a]
1	$In(O_3SOC_{12}H_{25})_3$	67
2	$In(O_3SC_{12}H_{25})_3$	50
3	$Sm(O_3SOC_{12}H_{25})_3$	82
4	$Gd(O_3SOC_{12}H_{25})_3$	56
5	$Dy(O_3SOC_{12}H_{25})_3$	45
6	$Fe(O_3SOC_{12}H_{25})_3$	58
7	*$Sc(O_3SOC_{12}H_{25})_3$*	*90*

[a] Isolated yield based on 2-aminobenzophenone **1a**.

observed after 5 days when 1 mol% of $Sc(O_3SOC_{12}H_{25})_3$ was employed in the reaction. Gratifyingly, 94% yield of **3a** was generated when 5 mol% of catalyst was used although a prolonged reaction time was needed for completion (24 h). When $Sc(OTf)_3$ alone was used under these conditions, the reaction did not go to completion even after 5 days. The desired product was only obtained in 56% yield.

To demonstrate the generality of this method, we next investigated the scope of this reaction under the optimized conditions [5 mol% of $Sc(O_3SOC_{12}H_{25})_3$, air, 40°C] and the results are summarized in Table 2. The operation was simple: A mixture of the 2-aminoaryl ketone (0.25 mmol), α-methylene ketone (1.5 equivs.) and $Sc(O_3SOC_{12}H_{25})_3$ (5 mol%) in water (4 mL) was stirred at 40°C. After completion of the reaction as indicated by TLC, the reaction mixture was extracted with EtOAc (2×10 mL). Evaporation of the solvent followed by purification on silica gel afforded the pure quinoline. As shown in Table 2, this method is equally effective for both cyclic and acyclic ketones. The reaction employing ethyl 4-chloro-3-oxobutanoate also proceeded efficiently to provide the desired product which is ready for further elaboration. Various substituted 2-aminoaryl ketones such as 2-aminoacetophenone, 2-aminobenzophenone, and 2-amino-5-chlorobenzophenone reacted smoothly with α-methylene ketones to produce a range of quinoline derivatives. Complete conversion and good to excellent isolated yields were observed for all substrates employed. This reaction is very clean and free from side reactions such as self-condensation of ketones which are normally observed under basic conditions.

In conclusion, we have described the Lewis acid-surfactant-combined catalyst, scandium tris(dodecyl sulfate) [$Sc(O_3SOC_{12}H_{25})_3$], as an efficient catalyst for Friedländer annulation in water. This simple system offers a mild and very efficient route for the synthesis of polysubstituted and polycyclic quinolines. It not only provides an excellent complement to quinoline synthesis *via* Friedländer annulation, but also avoids the use of hazardous acids or bases and harsh reaction conditions. The advantages of this method include excellent yields, the use of a catalytic amount of catalyst under mild conditions, environmentally benign and simple experimental operations.

Experimental Section

Scandium Tris(dodecyl Sulfate)

Scandium tris(dodecyl sulfate) was synthesized according to the literature method.[11]

General Procedure

A mixture of the 2-aminoaryl ketone (0.25 mmol), α-methylene ketone (1.5 equivs.) and scandium tris(dodecyl sulfate) (5 mol%) in water (4 mL) was stirred at 40°C. After completion of the reaction as indicated by TLC, the reaction mixture was extracted with EtOAc (2×10 mL). Evaporation of the solvent followed by purification on silica gel afforded pure quinoline. (All the products are known compounds. The characterizations of these compounds are identical with the literature reports.[10])

Ethyl 2-methyl-4-phenylquinoline-3-carboxylate (3a)[10s]: ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.94 (t, *J*=7.1 Hz, 3H), 2.79 (s, 3H), 4.04–4.09 (m, 2H), 7.36–7.72 (m, 8H), 8.07 (d, *J*=8.4 Hz, 1H).

1-(2-Methyl-4-phenylquinolin-3-yl)ethanone (3b)[10s]: ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.97 (s, 3H), 2.67 (s, 3H), 7.32–8.06 (m, 9H).

9-Phenyl-3,4-dihydroacridin-1(2H)-one (3c)[10k]: ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.23–2.26 (m, 2H), 2.68 (t, *J*=6.7 Hz, 2H), 3.36 (t, *J*=6.4 Hz, 2H), 7.18–8.07 (m, 9H).

3,3-Dimethyl-9-phenyl-3,4-dihydroacridin-1(2H)-one (3d)[10s]: ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.15 (s, 6H), 2.55 (s, 2H), 3.26 (s, 2H), 7.16–8.07 (m, 9H).

Methyl 2-methyl-4-phenylquinoline-3-carboxylate (3e)[10j]: ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.76 (s, 3H), 3.55 (s, 3H), 7.32–8.06 (m, 9H).

Ethyl 2-(chloromethyl)-4-phenylquinoline-3-carboxylate (3f)[10u]: ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.90 (t, *J*=7.3 Hz, 3H), 4.01–4.05 (m, 2H), 5.03 (s, 2H), 7.33–8.14 (m, 9H).

Ethyl 6-chloro-2-methyl-4-phenylquinoline-3-carboxylate (3g)[10k]: ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.93 (t, *J*=7.1 Hz, 3H), 2.75 (s, 3H), 4.04–4.07 (m, 2H), 7.33–8.00 (m, 8H).

1-(6-Chloro-2-methyl-4-phenylquinolin-3-yl)ethanone (3h)[10k]: ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.96 (s, 3H), 2.65 (s, 3H), 7.31–7.98 (m, 8H).

7-Chloro-9-phenyl-3,4-dihydroacridin-1(2*H*)-one (3i)[10k]: ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.21–2.26 (m, 2H), 2.69 (t, *J*=6.6 Hz, 2H), 3.34 (t, *J*=6.4 Hz, 2H), 7.14–7.98 (m, 8H).

7-Chloro-3,3-dimethyl-9-phenyl-3,4-dihydroacridin-1(2*H*)-one (3j)[10s]: ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.14 (s, 6H),

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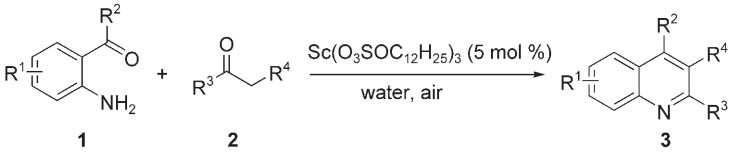
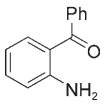
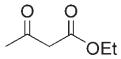
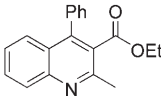
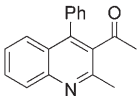
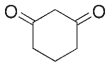
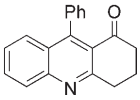
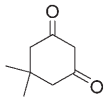
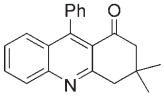
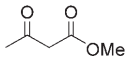
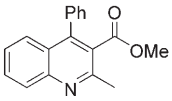
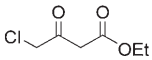
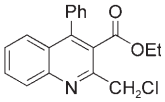
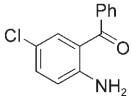
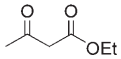
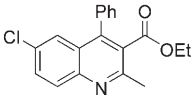
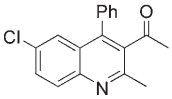
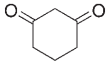
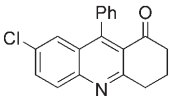
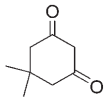
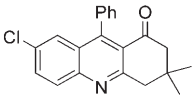
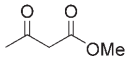
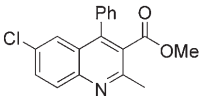
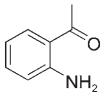
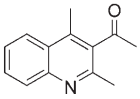
Table 2. Scandium tris(dodecyl sulfate)-catalyzed Friedländer annulation in water.[a]



Entry	Substrate **1**		Ketone **2**		Quinoline **3**		Yield [%][b]
1	**1a**		**2a**		**3a**		94
2	**1a**		**2b**		**3b**		99
3[c]	**1a**		**2c**		**3c**		96
4[c]	**1a**		**2d**		**3d**		99
5	**1a**		**2e**		**3e**		99
6	**1a**		**2f**		**3f**		96
7	**1b**		**2a**		**3g**		99
8	**1b**		**2b**		**3h**		95
9[c]	**1b**		**2c**		**3i**		98
10[c]	**1b**		**2d**		**3j**		93
11	**1b**		**2e**		**3k**		97
12	**1c**		**2b**		**3l**		89

[a] *Reaction conditions:* 2-amino ketone (0.25 mmol), ketone (1.5 equivs.), $Sc(O_3SOC_{12}H_{25})_3$ (5 mol%), water (4 mL), 40°C.
[b] Isolated yield based on 2-aminoaryl ketone **1**.
[c] The reaction was performed at 60°C.

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2.55 (s, 2H), 3.24 (s, 2H), 7.14–7.16 (m, 2H), 7.42–7.99 (m, 6H).

Methyl 6-chloro-2-methyl-4-phenylquinoline-3-carboxylate (3k)[10s]: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.73$ (s, 3H), 3.55 (s, 3H), 7.33–7.99 (m, 8H).

1-(2,4-Dimethylquinolin-3-yl)ethanone (3l)[10k]: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.54$ (d, $J = 12.3$ Hz, 6H), 2.62 (s, 3H), 7.49 (t, $J = 7.6$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.91 (d, $J = 8.3$ Hz, 1H), 7.99 (d, $J = 8.4$ Hz, 1H).

Acknowledgements

We thank Professor Pengyuan Yang for his invaluable advice during the course of this research. Financial support from National Natural Science Foundation of China (20502004) and the Science and Technology Commission of Shanghai Municipality (05ZR14013) is gratefully acknowledged.

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