Efficient Synthesis of 2,3,4-Trisubstituted Quinolines via Friedländer Annulation with Nanoporous Cage-Type Aluminosilicate AlKIT-5 Catalyst

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Abstract: 2-Aminoaryl ketones undergo smooth Friedländer condensation/annulation with α-methyleneketones on the surface of nanoporous aluminosilicate catalyst to afford the corresponding quinoline derivatives in good yields with high selectivity due to its high surface area, large pore volume, and high acidity. The use of highly acidic and reusable AlKIT-5 catalyst makes the Friedländer annulation simple, convenient, and practical.

Key words: *o*-aminoaryl ketones, nanoporous catalysts, domino reactions, quinolines

Quinoline scaffolds are important heterocycles in medicinal chemistry and are found to possess a broad spectrum of biological activities such as antimalarial, antibacterial, anti-asthmatic, antihypertensive, and anti-inflammatory behavior.[1,2] The substituted quinoline are found to exhibit tyrokinase PDGF-RTK inhibiting properties.[3] In addition to pharmaceutical applications, polyquinolines derived from quinolines are found to undergo hierarchical self-assembly into a variety of nanostructures and mesostructures with enhanced electronic and photonic functions.[4] Consequently, several methods such as Skraup, Doebner–von Miller, Friedländer, and Combes have been reported for the synthesis of quinoline derivatives.[5,6] Among these methods, the Friedländer annulation is found to be the best approach for the synthesis of substituted quinolines.[6b] Generally, these annulation reactions are carried out either in the presence of a base catalyst or under thermal conditions ranging from 150–220 °C without a catalyst.[7] However, *o*-aminobenzophenone fails to react with simple ketones such as cyclohexanone, deoxybenzoin, and β-keto esters either under thermal or base catalysis.[8] Subsequently, acid catalysts were proved to be more effective than base catalysts for Friedländer annulation.[8] Acid catalysts such as hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid, and phosphoric acid have been used for this transformation.[7,9] However, many of these classical methods require high temperatures, prolonged reaction times, drastic conditions, and the conversions reported are far from satisfactory due to the occurrence of several side reactions. Therefore, new catalytic systems are being continuously explored in search of improved efficiencies and cost effectiveness.[10] Since quinoline derivatives are increasingly useful and important in drugs and pharmaceuticals, the development of simple, convenient, and high-yielding protocols is desirable.

Following our interest on the use of nanoporous aluminosilicate catalyst with 3D cage-type porous structure for the synthesis of biologically active heterocycles,[11] we herein report an efficient and straightforward approach for the synthesis of highly substituted quinolines using highly acidic nanoporous AlKIT-5 as a heterogeneous solid-acid catalyst.[12,13] In a model reaction, 2-aminobenzophenone (**1**) was treated with ethyl acetoacetate (**2**) in the presence of AlKIT-5. Initially the reaction was carried out with AlKIT-5 catalyst with different Al content. It was found that the amount of Al in the catalyst plays a significant role in controlling the activity of the catalyst. The catalytic activity increases with increasing the amount of Al in the catalyst. Among the catalysts studied, AlKIT-5(10) where the number in the parenthesis indicates the Si/Al molar ratio in the final product, was found to be the best, affording the product in high yield. This was mainly due to the fact that the acidity, surface area, and the specific pore volume of AlKIT-5(10) are much higher than that of the other AlKIT-5 catalysts.[11] Thus, AlKIT-5(10) was used for the rest of the study. To start with, we have investigated the reaction with different weight of the AlKIT-5(10) catalyst. To our surprise, we noticed that 50 mg catalyst was sufficient for the reaction of 2-aminobenzophenone with ethyl acetoacetate in ethanol at 80 °C for obtaining the final product ethyl 2-methyl-4-phenyl-quinoline-3-carboxylate (**3a**) with a yield of 92% (Scheme 1).

In order to investigate the scope and limitation of this transformation using the AlKIT-5, we turned our attention to various β-keto esters and ketones. Notably, various β-keto esters including methyl acetoacetate and ethyl benzoylacetate participated effectively in this annulation reaction (entries 2, 3, 8, and 9, Table 1). We also found that the reaction gave excellent yield with 1,3-diketones such as acetyl acetone and 1,3-cyclohexanedione (entries 4, 7, and 10, Table 1). This transformation was also extended

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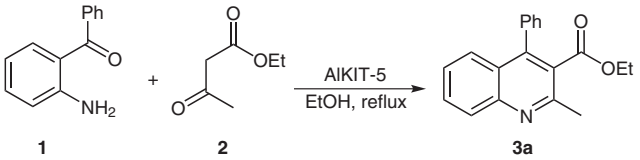
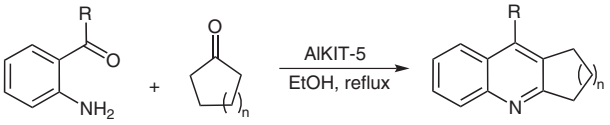
to the reaction of cyclic ketones and 2-aminoketones. Both cyclohexanone and cyclopentanone (entries 5, 6, 11, and 12, Table 1) reacted well with 2-aminoketones under the influence of AlKIT-5 to furnish the corresponding annulated quinoline derivatives in a 86–91% yield (Scheme 2). Mechanistically, the reaction proceeds via the activation of 1,3-diketone by AlKIT-5 to give the corresponding enamine. Thus formed enamine subsequently reacts with keto group to undergo cyclodehydration resulting in the formation of quinoline as depicted in Scheme 3.



Scheme 1 Friedländer condensation of 2-aminobenzophenone with β-keto ester

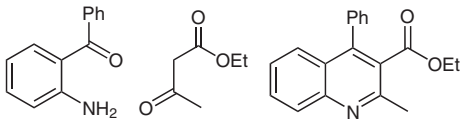
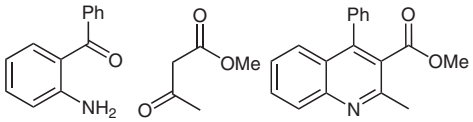
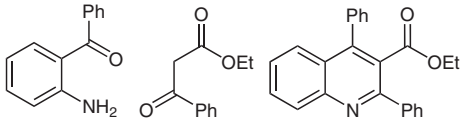
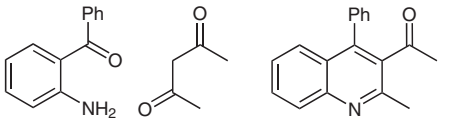
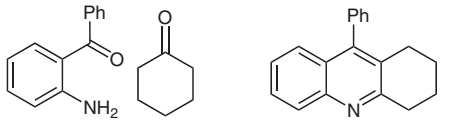
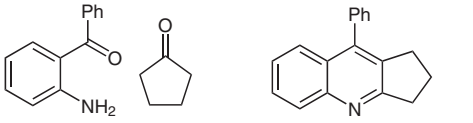
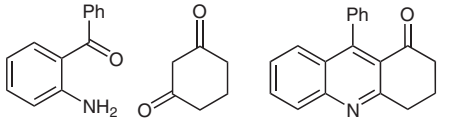
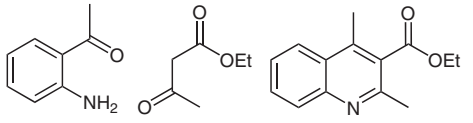
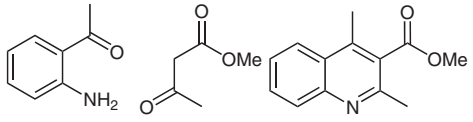
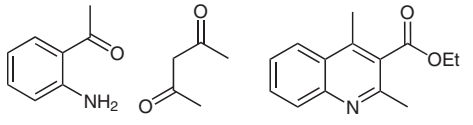
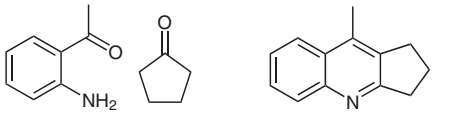
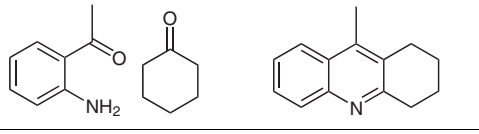


Scheme 2 Friedländer annulation of cyclic ketones

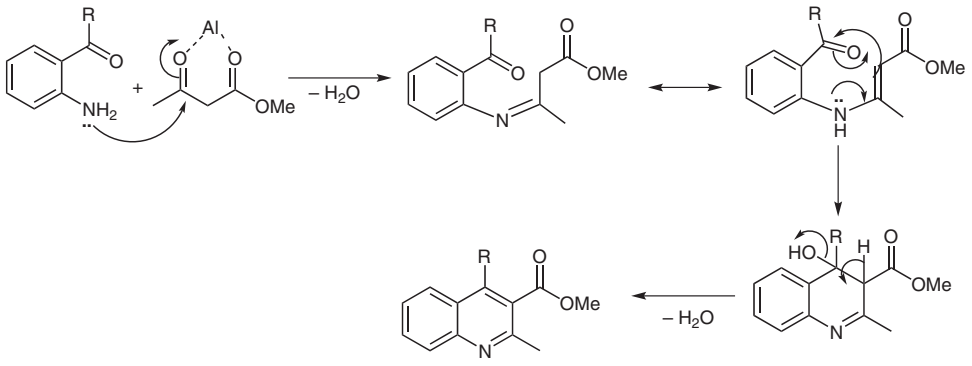
Notably, no reaction was observed at room temperature or reflux conditions in the absence of a catalyst. However, our catalyst was highly active and effective for both cyclic and acyclic ketones in ethanol under reflux conditions. Several examples illustrating the scope and generality of this process with respect to various α-methylene ketones and 2-aminoaryl ketones, and the results are summarized in Table 1. The structures of the products were determined from their spectral data (NMR, IR, and MS) and also by comparison with authentic samples.[7] These data confirm that the present method is clean and free from side reactions such as self-condensation of ketones which is normally observed under basic conditions. Interestingly, the catalyst showed excellent recyclable capability. The catalyst was easily separated by filtration and reused after activation at 500 °C for three to four hours. The efficiency of the recovered catalyst was verified in the coupling of 2-aminobenzophenone with ethyl acetoacetate (entry 1, Table 1). Using the fresh catalyst, the yield of product **3a** was 92%, while the recovered catalyst gave the yield of 92%, 89%, and 86% over three cycles, respectively.

In summary, we have demonstrated for the first time the Friedländer annulation using a highly acidic 3D nanoporous aluminosilicate nanocage catalyst for the synthesis of substituted quinolines. The heterogeneous nature, high surface area, large pore volume, high acidity, and reusability of the catalyst make the Friedländer annulation simple, convenient, and practical. This method avoids the use of hazardous acids or bases and harsh reaction conditions.

Table 1 AlKIT-5-Catalyzed Synthesis of Quinolines via Friedländer Annulation

Entry	2-Aminoketone	1,3-Diketone	Quinoline[a]	Time (h)	Yield (%)[b]
1				2.5	92
2				3.0	90
3				2.5	89
4				3.5	90
5				3.0	91
6				2.5	86
7				3.0	88
8				3.0	89
9				3.0	86
10				4.0	90
11				2.5	90
12				3.0	91

[a] All products were characterized by NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after column chromatography.



Scheme 3 A plausible reaction mechanism

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(12) **General Procedure**
A mixture of 2-aminoaryl ketone (1.0 mmol), α-methylene ketone (1.0 mmol), and AlKIT-5 (50 mg) in EtOH (5 mL) was stirred at 80 °C for the specified time (see Table 1). After completion of the reaction, as monitored by TLC, the catalyst was separated by filtration, and the residue was washed with EtOH (10 mL). The combined organic layers were concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography using EtOAc–*n*-hexane (1:9) as eluent to afford the pure quinoline derivative.
Spectral Data for Selected Products
Ethyl 2-Methyl-4-phenylquinoline-3-carboxylate (3a)
Solid, mp 98 °C. IR (KBr): ν = 3030, 2960, 1700, 1605, 1568, 1482, 905 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.0 Hz, 3 H), 2.80 (s, 3 H), 4.05 (q, *J* = 7.0 Hz, 2 H), 7.35–7.50 (m, 6 H), 7.55 (d, *J* = 8.1 Hz, 1 H), 7.70 (t, *J* = 7.9 Hz, 1 H), 8.05 (d, *J* = 8.1 Hz, 1 H). MS (EI): *m/z* = 291 $[M]^+$, 85, 263, 246, 218, 176, 150.
3-Acetyl-2-methyl-4-phenylquinoline (3d)
Solid, mp 115 °C. IR (KBr): ν = 3027, 2960, 1705, 1610, 1569, 1485, 705 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.95 (s, 3 H), 2.60 (s, 3 H), 7.25–7.30 (m, 2 H), 7.35 (t, *J* = 8.0 Hz, 1 H), 7.40–7.50 (m, 3 H), 7.55 (d, *J* = 8.2 Hz, 1 H), 7.65 (t, *J* = 8.0 Hz, 1 H), 8.00 (d, *J* = 8.2 Hz, 1 H). MS (EI): *m/z* = 261 $[M]^+$, 246, 218, 176, 150, 43.
9-Phenyl-1,2,3,4-tetrahydroacridine (3e)
Solid, mp 137 °C. IR (KBr): ν = 3057, 2945, 1609, 1575, 1480, 1210, 708 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.75–1.85 (m, 2 H), 1.95–2.05 (m, 2 H), 2.60 (t, *J* = 6.7 Hz, 2 H), 3.20 (t, *J* = 6.9 Hz, 2 H), 7.20–7.32 (m, 3 H), 7.40–7.60

(m, 5 H), 8.00 (d, J = 8.2 Hz, 1 H). MS (EI): m/z = 259 $[M]^+$, 230, 182, 176, 57.

(13) **Syntheses of AlKIT-5 Catalyst with Different n_{Si}/n_{Al} Ratio**

The AlKIT-5 materials with different n_{Si}/n_{Al} ratios were synthesized using Pluronic F127 as the template in an acidic medium. In a typical synthesis, 5.0 g of F127 was dissolved in 3 g of HCl (35 wt%) and 240 g of distilled H_2O. To this mixture, 24.0 g of TEOS and the required amount of the aluminium isopropoxide were added, and the resulting mixture was stirred for 24 h at 45 °C. Subsequently, the reaction mixture was heated for 24 h at 100 °C under static conditions for hydrothermal treatment. After hydrothermal treatment, the final solid product was filtered off and then dried at 100 °C without washing. The product was calcined at 540 °C for 10 h. The samples are denoted as AlKIT-5 (x)where x denotes the n_{Si}/n_{Al} ratio in the final product. The molar gel composition of the reaction mixture was SiO_2/Al_2O_3/F127/HCl/H_2O = 1.0:0.041–0.071:0.0035:0.25:116.6.