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An efficient, high yielding protocol for the synthesis of functionalized quinolines via the tandem addition/annulation reaction of *o*-aminoaryl ketones with α-methylene ketones

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Dedicated to Dr. A. V. Rama Rao on the occasion of his 70th birthday

Abstract—A mild and efficient method has been developed for the condensation of 2-aminoaryl ketones with α-methylene ketones in the presence of a catalytic amount of reusable catalyst $CeCl_3 \cdot 7H_2O$ (25 mol %) at ambient temperature to afford the corresponding poly-substituted quinolines in high yields under mild conditions.

The presence of a quinoline scaffold in the framework of various pharmacologically active compounds possessing antimalarial, anti-inflammatory, antiasthmatic, antibacterial and antihypersensitive activities[1,2] and tyrosine kinase PDGF-RTK inhibiting properties[3] continues to spur synthetic efforts regarding their acquisition.[4] In addition, quinolines are valuable synthons used for the preparation of nanostructures and polymers that combine enhanced electronic, optoelectronic or non-linear optical properties with excellent mechanical properties.[5] In spite of their importance from industrial, pharmacological and synthetic points of view, relatively few methods for their preparation have been reported. Although other methods such as the Skraup, Doebner von Miller and Combes procedures have been reported,[6,7] the Friedländer annulation is one of the most simple and straightforward methods used to produce poly-substituted quinolines. Classically, the process consists of an acid or base catalyzed condensation followed by a cyclodehydration between a 2-aminoaryl ketone and a second carbonyl compound possessing a reactive α-methylene group. The Friedländer reaction is carried out either by refluxing an aqueous or alcoholic solution of reactants in the presence of base or by heating a mixture of the reactants at high temperature ranging from 150 to 220 °C in the absence of catalysts.[8] Under thermal or base catalysis conditions, *o*-aminobenzophenone fails to react with simple ketones such as cyclohexanone and β-keto esters.[9] Subsequent work showed that acid catalysts are more effective than base catalysts for the Friedländer annulation. Several acid catalysts have been used in the Friedländer reaction including $ZnCl_2$, phosphoric acid, sodium fluoride, silver phosphotungstate and $AuCl_3 \cdot 3H_2O$ amongst others.[10] However, many of these methods have significant drawbacks such as low yields of the products, prolonged reaction times, harsh conditions, difficulties in work-up and the use of stoichiometric quantities of reagents. Consequently, there is scope for further development of milder conditions, increased variation of the substituents in both components and better yields.

Over recent years, lanthanide salt-mediated Lewis acid reactions have attracted tremendous interest throughout the scientific community.[11] Their low toxicity, ease of handling and low cost make lanthanide derivative species attractive alternatives to their classical counterparts such as $TiCl_4$. In continuation of our ongoing studies towards the development of new environmentally friendly syntheses of heterocycles through transition metal catalyzed tandem reactions,[12] we observed the high efficiency of $CeCl_3$ catalysis (25 mol %) in sequential condensation/

Keywords: 2-Aminoaryl ketones; α-Methylene ketones; $CeCl_3 \cdot 7H_2O$; Friedländer; Quinolines.
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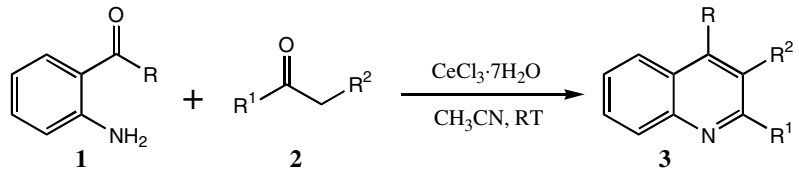
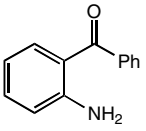
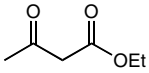
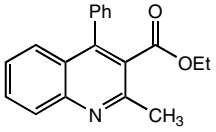
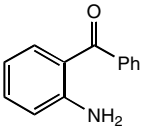
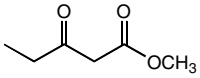
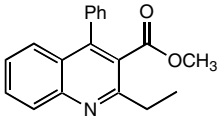
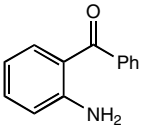
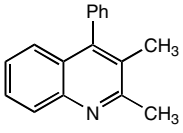
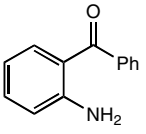
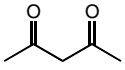
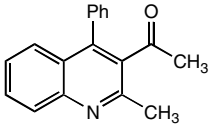
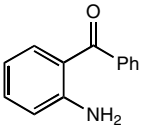
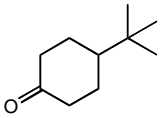
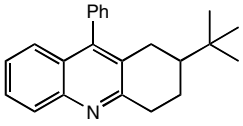
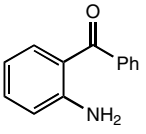
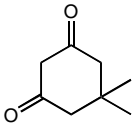
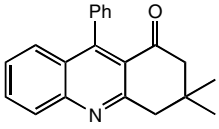
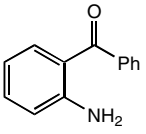
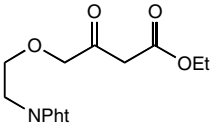
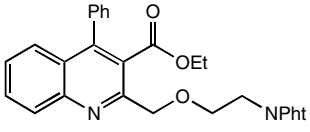
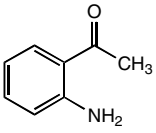
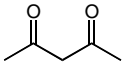
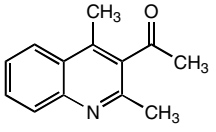
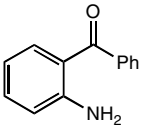
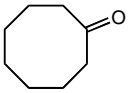
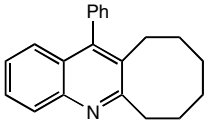


Scheme 1.

annulation reactions of *o*-aminoaryl carbonyls **1** and ketones containing an active methylene group **2** for the synthesis of substituted quinolines **3** (Scheme 1). The reaction proceeds efficiently in high yields at ambient temperature within a few minutes. Similarly, various 1,3-dicarbonyl compounds including alkyl acetoacetates and acetylacetone, cyclic β-diketones such as 5,5-dimethylcyclohexanedione (dimedone) and acyclic ketones, for

Table 1. $CeCl_3$-catalyzed synthesis of quinolines and polycyclic quinolines

Entry	2-Aminoketone	Ketone	Time (h)	Quinoline[a]	Yield (%)[b]
1[c]			1.5		95 (1st run) 91 (2nd run) 88 (3rd run) 65[d]
2			2.0		92
3			5.0		72
4			2.5		88
5			3.0		90
6			2.5		93
7			3.5		86
8			4.0		80
9			5.0		65

[a] All products were characterized by mp, IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.
[b] Yields refer to pure isolated products after chromatography.
[c] Catalyst was reused at least three times.
[d] Concd H_2SO_4 used instead of $CeCl_3·7H_2O$.

example, 2-butanone reacted with 2-aminoaryl ketones to give the corresponding substituted quinolines without any side products (Table 1, entry 3). Interestingly, cyclic ketones such as 4-*tert*-butylcyclohexanone and cyclooctanone reacted with 2-amino aryl ketones to afford the respective tricyclic quinolines in good yields. In general, the reaction is very clean, rapid, efficient and involves a simple work-up procedure.[13,14] Unlike previous methods, the reported protocol does not require high temperatures to produce quinoline derivatives. In order to improve the yields, we performed reactions using different quantities of reagents. The optimum results were obtained with a 0.1:1:1 ratio of $CeCl_3{\cdot}7H_2O$, *o*-aminoaryl ketone, α-methylene ketone or β-diketones. Higher amounts of catalyst did not improve the results to any greater extent. Solvents such as CH_3CN, THF and EtOH proved to be effective. After the reaction was complete as monitored by TLC, the product was isolated by simple filtration. When the filtered solution containing $CeCl_3$ catalyst was reused, only a slight decrease in the yield from 95% to 88% was observed after the third run (Table 1, entry 1). In another experiment, when the filtered solution containing the catalyst was used after 3 months of storage, it was observed that the catalyst was still quite active (no appreciable change in the yield of the product was apparent), which demonstrated that $CeCl_3$ is stable and does not undergo any deterioration. This study demonstrates that $CeCl_3$ can be effectively employed as a reusable catalyst for Friedländer annulation. In the absence of catalyst, the reaction did not yield any product even after longer reaction times (10–15 h). Furthermore, the condensation of *o*-aminobenzophenone with ethyl acetoacetate in the presence of concd H_2SO_4 afforded the quinoline product in only 65% yield (entry 1).

In conclusion, we have demonstrated a simple and efficient procedure for the synthesis of quinolines, including polycyclic quinolines, by employing $CeCl_3{\cdot}7H_2O$ as a reusable catalyst. The salient features of this method include operational simplicity, improved reaction rates, high yields of products and avoidance of the use of hazardous acids or bases.

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13. Typical procedure: A mixture of *o*-aminobenzophenone (1.97 g, 10 mmol), ethyl acetoacetate (1.30 g, 10 mmol) and $CeCl_3{\cdot}7H_2O$ (930 mg, 25 mol %) in acetonitrile (5 mL) was stirred at room temperature for 90 min. After completion of the reaction (monitored by TLC), the mixture was diluted with ethyl acetate (30 mL), and washed with water (15 mL), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford the pure product (2.76 g). The aqueous layer containing the catalyst could be evaporated under reduced pressure to give a white solid. The catalyst was recovered and reused in subsequent reactions, three times without losing any significant activity (reaction yields 95%, 92% and 88%).
14. Selected analytical data for the products from entries 4, 5 and 7: Entry 4: mp 105–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.96 (s, 3H), 2.65 (s, 3H), 7.33–7.72 (m, 8H), 8.04 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ

23.3, 29.2, 31.4, 124.5, 125.6, 126.0, 128.1, 128.4, 129.5, 134.7, 147.0, 153.0, 205.6; EIMS: *m*/*z* (%) 261 (M^+ 46), 246 (100), 218 (57), 176 (35). Entry 5: mp 132–133 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (s, 9H), 1.48–1.62 (m, 2H), 2.12–2.38 (m, 2H), 2.61–2.75 (m, 1H), 3.02–3.39 (m, 2H), 7.17–7.33 (m, 4H), 7.42–7.64 (m, 4H), 8.02 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 27.0, 29.3, 32.5, 34.8, 44.7, 125.5, 125.7, 126.6, 127.7, 128.2, 128.3, 128.5, 128.6, 128.9, 129.1, 137.0, 146.3, 146.5, 159.3; EIMS: *m*/*z* (%) 315 (M^+ 43), 258 (100), 57 (28). Entry 7: mp 98–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, $J = 7.0$ Hz, 3H), 3.65–3.69 (m, 2H), 3.82–3.92 (m, 2H), 4.06 (q, $J = 7.0$ Hz, 2H), 4.92 (s, 2H), 7.26–7.88 (m, 12H), 8.02 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 37.4, 60.9, 67.2, 73.7, 96.1, 123.0, 123.1, 126.2, 126.3, 126.4, 126.9, 127.9, 128.2, 129.4, 129.6, 129.9, 132.2, 132.4, 133.4, 133.6, 135.8, 146.7, 147.1, 154.7, 167.3, 167.5; FABMS: 481 (M+1).