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Tetrahedron Letters 46 (2005) 1647–1649
Tetrahedron Letters

A mild and efficient one-step synthesis of quinolines

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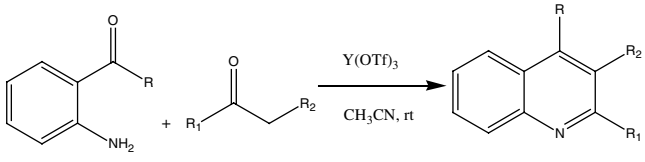
Received 8 December 2004; revised 12 January 2005; accepted 17 January 2005
Available online 29 January 2005

Abstract—*2*-Aminoaryl ketones undergo condensation with α-methylene ketones in the presence of a catalytic amount of $Y(OTf)_3$ at room temperature under mild conditions to afford the corresponding polysubstituted quinolines in excellent yields.

Quinolines are very important compounds because of their pharmacological properties. Members of this family have wide applications in medicinal chemistry, being used as antimalarial, antiinflammatory agents, antiasthamatic, antibacterial, antihypertensive, and tyrosine kinase inhibiting agents.[1–3] In addition, quinolines are valuable synthons used for the preparation of nano and mesostructures with enhanced electronic and photonic properties.[4] Despite their importance from pharmacological, industrial, and synthetic point of views, comparatively few methods for their preparation have been reported. Although other methods such as Skraup, Doebner von Miller, and Combes procedures have been reported[5,6] for the preparation of quinolines, the Friedlander annulation is one of the most simple and straightforward methods for the synthesis of poly-substituted quinolines. The Friedlander synthesis is an acid or base catalyzed condensation followed by a cyclodehydration between 2-aminoaryl ketone and a second carbonyl compound containing a reactive α-methylene group. Generally, this reaction is carried out by refluxing an aqueous or alcoholic solution of reactants in the presence of base at high temperature.[7] Under thermal or base catalysis conditions, *o*-aminobenzophenone fails to react with simple ketones such as cyclohexanone and β-keto esters.[8] Recently, modified methods employing $ZnCl_2$, phosphoric acid, $Bi(OTf)_3$, silver phosphotungstate, sodium fluoride, and $AuCl_3$ have been reported for the synthesis of quinolines.[9] However, many of these procedures have significant drawbacks such as low yields of the products, long reaction times, harsh reaction conditions, difficulties in work-up, and the use of stoichiometric and/or relatively expensive reagents. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Thus, the development of more efficient procedures for the synthesis of quinolines is still needed.

Recently, there has been growing considerable interest in the use of lanthanide triflates in organic synthesis[10] as they are water stable and reusable. The reagent $Y(OTf)_3$ is commercially available and significantly less expensive than $Sc(OTf)_3$. Like lanthanide triflates, $Y(OTf)_3$ is also water tolerable, reusable, and efficient catalyst[11] and can be used for the preparation of quninoline derivatives.

As part of a continuing effort in our laboratory toward the development of new methods in organic synthesis,[12] we became interested in the possibility of developing a one pot synthesis of 2,3,4-trisubstituted quinolines. The Friedlander condensation of 2-aminobenzophenone with ethyl acetoacetate in the presence of a catalytic amount of yttrium triflate at room temperature results in the formation of ethyl 2-methyl-4-phenylquinoline-3-carboxylate in 92% yield (Scheme 1). Similarly, various 1,3-diketones reacted with 2-aminoaryl ketones



Scheme 1.

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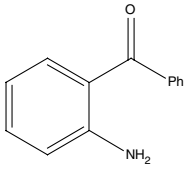
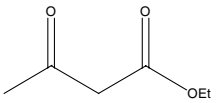
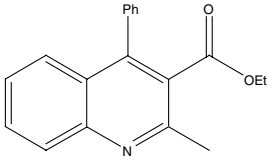
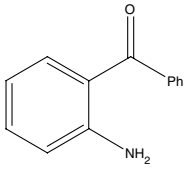
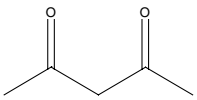
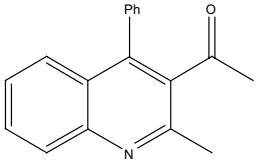
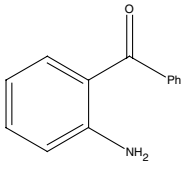
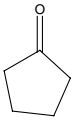
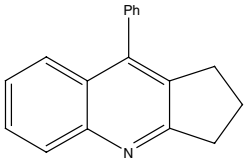
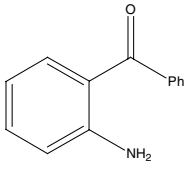
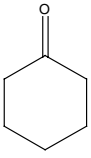
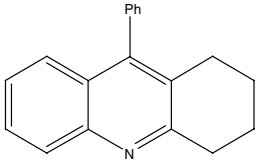
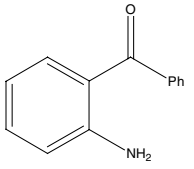
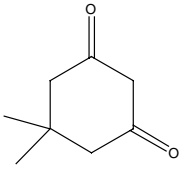
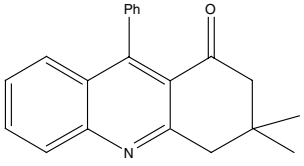
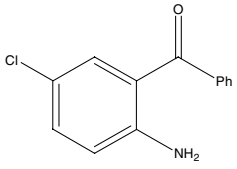
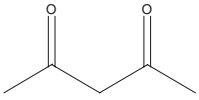
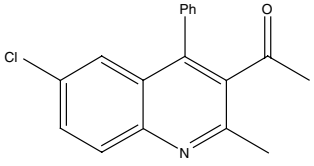
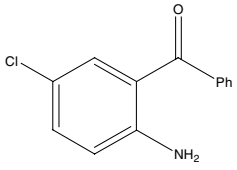
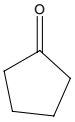
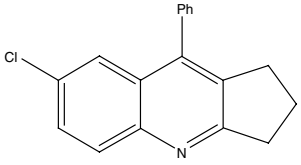
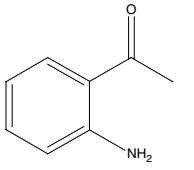
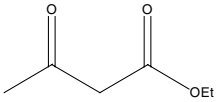
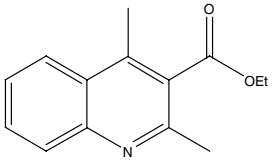
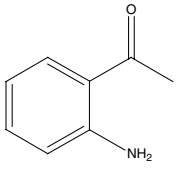
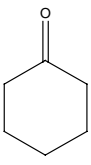
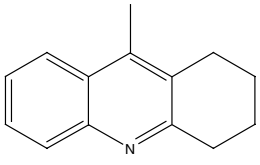
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2005.01.075

Table 1. $Y(OTf)_3$-catalyzed synthesis of quinolines

Entry	2-Aminoketone	Ketone	Quinoline	Time (h)	Yield[a] (%)
1				4	89(65)[b]
2				5	85
3				4	91
4				4	92
5				5	83
6				6	81
7				6	76
8				6	83
9				5	91

[a] Yields refer to pure products and were characterized by comparison of their mp, IR, and ^1H NMR spectra with those of authentic samples.
[b] Concd H_2SO_4 used instead of $Y(OTf)_3$.

to give the corresponding substituted quinolines. Interestingly, cyclic ketones such cyclohexanone and cyclopentanone reacted with 2-aminoaryl ketones to afford the respective tricyclic quinolines. The reaction is fairly general, clean, rapid, and efficient.[13,14] The experimental procedure is very simple. The high yield transformation

did not form any significant amounts of undesirable side products. Unlike previously reported methods, the present method does not require high temperatures to produce quinoline derivatives. The condensation of 2-aminobenzophenone with ethyl acetoacetate in the presence of concd H_2SO_4 afforded the quinoline product only in 65% yield (entry 1). Among the various metal triflates such as $Nd(OTf)_3$, $Lu(OTf)_3$, $Cu(OTf)_2$, $Yb(OTf)_3$, $Ce(OTf)_3$ studied for this reaction, $Y(OTf)_3$ employed here gave better yields with short reaction times. It should be mentioned that the $Sc(OTf)_3$ gave similar results under identical conditions but it is more expensive than $Y(OTf)_3$. The results shown in Table 1 clearly indicate the scope and generality of the reaction with respect to various 2-aminoaryl ketones and a wide array of α-methylene ketones.

In conclusion, we have demonstrated a simple and efficient procedure for the synthesis of quinolines, including polycyclic quinolines, using ytrrium triflate as a reusable catalyst. The significant features of this method include (a) operational simplicity, (b) inexpensive reagents, (c) high yields of products, and (d) the use of relatively nontoxic reagents and solvents.

Acknowledgements

We thank the reviewers for their valuable suggestions and comments.

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13. *Typical procedure*: A mixture of 2-aminobenzophenone (197 mg, 1 mmol), ethyl acetoacetate (169 mg, 1.3 mmol), and $Y(OTf)_3$ (108 mg, 0.2 mmol) in ethanol or acetonitrile (5 mL) was stirred at room temperature for 4 h. After completion of the reaction (TLC), the reaction mixture was diluted with ethyl acetate (30 mL), and washed with water (15 mL), dried ($MgSO_4$), and concentrated. The residue was purified by silica gel column chromatography (10% ethyl acetate in hexane) to afford a pure product. The aqueous layer containing the catalyst could be evaporated under reduced pressure to give a white solid. The IR spectrum of the recovered catalyst was identical to that of the commercially available catalyst (Aldrich), which could be reused for the next reaction, without losing any significant activity. The catalyst has been recovered and reused for four times (reaction yields 89%, 82%, 77%, and 61%).
14. Spectral data for selected products: *Ethyl 2-methyl-4-phenylquinoline-3-carboxylate* (entry 1): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, $J = 7$ Hz, 3H), 2.81 (s, 3H), 4.06 (q, $J = 7$ Hz, 2H), 7.28–7.56 (m, 7H), 7.66–7.71 (m, 2H), 8.02 (d, $J = 8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 23.3, 60.8, 96.1, 125.1, 126.1, 126.4, 127.8, 128.2, 129.1, 129.5, 135.7, 145.7, 147.8, 153.7, 167.7; EIMS *m/z* 291 (M^+), 247, 218, 177, 75, 43. *9-Phenyl-1,2,3,4-tetrahydroacridine* (entry 4): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72–1.89 (m, 2H), 1.92–2.03 (m, 2H), 2.58 (t, $J = 7$ Hz, 2H), 3.17 (t, $J = 7.2$ Hz, 2H), 7.17–7.32 (m, 4H), 7.41–7.63 (m, 4H), 7.96 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7, 23.1, 27.8, 34.1, 96.1, 1252, 125.6, 126.6, 127.5, 127.9, 128.2, 128.5, 128.7, 129.2, 137.3, 146.1, 146.5, 158.4; EIMS *m/z* 259 (M^+), 230, 183, 77. *7-Chloro-9-phenyl-2,3-dihydro-1H-cyclopenta[b]quinoline* (entry 7): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16–2.27 (m, 2H), 2.96 (t, $J = 7.2$ Hz, 2H), 3.26 (t, $J = 7.2$ Hz, 2H); 7.24–7.37 (m, 2H), 7.46–7.62 (m, 5H), 8.21 (d, $J = 8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.2, 30.3, 35.1, 124.2, 126.9, 128.5, 129.2, 130.2, 131.2, 134.4, 135.6, 141.9, 146.3, 167.8; EIMS *m/z* 279 (M^+), 244, 202, 167, 121, 114, 94, 77. *Ethyl 2,4-dimethylquinoline-3-carboxylate* (entry 8): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (t, $J = 7$ Hz, 3H), 2.97 (s, 3H), 3.11 (s, 3H), 4.78 (q, $J = 7$ Hz, 2H), 7.80–8.06 (m, 3H), 8.41 (d, $J = 8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 15.5, 23.6, 61.2, 123.6, 125.7, 126.1, 127.8, 129.7, 141.1, 147.2, 154.2, 168.9; EIMS *m/z* 229 (M^+), 186, 158, 125, 77.