A Simple, Efficient and Solvent-Free Protocol for the Friedländer Synthesis of Quinolines by Using $SnCl_2 \cdot 2H_2O$

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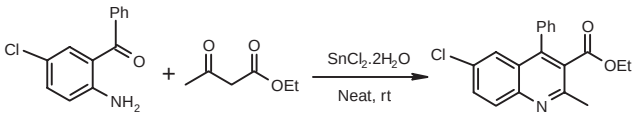
A variety of polysubstituted quinolines have been synthesized under solvent free condition by using tin(II) chloride·dihydrate. The reaction proceeds smoothly at room temperature in short reaction time. The yields and purity are excellent.

Quinoline and its derivatives display a wide spectrum of biological activities such as antimalarial, antibacterial, antidiabetic, and anti-inflammatory[1,2] behaviour. Furthermore cytotoxic agents like benzo[5,6]pyrrolizino[1,2-b]quinolines,[3] antitumor agents like camptothecin[4] also contain the quinoline nuclei. The benzo[5,6]pyrrolizino[1,2-b]quinoline system which displays potent in vitro cytotoxic activity against MCF7 cell is synthesized using the Friedländer quinoline synthesis as a key step.[3] Recently quinolines are also shown to be potential agents for the treatment of erectile dysfunction as they exhibit more potent and selective PDE5 inhibitor activity.[5]

Though numerous methods are available for the synthesis of quinolines, the synthesis reported by Friedländer is of great importance because it is simple and leads to a variety of polysubstituted quinolines. The Friedländer annulation is catalyzed by both acids and bases, but the acids are more effective.[6] The Brønsted acids like hydrochloric acid, sulfuric acid, *p*-toluene sulphonic acid, and phosphoric acids were widely used to effect the Friedländer condensation. However many of these classical methods require high temperature, prolonged reaction time and drastic reaction conditions and the yields are unsatisfactory due to the occurrence of several side reactions. The Lewis acids such as $ZnCl_2$,[7] $AuCl_3 \cdot 3H_2O$,[8] and $Bi(OTf)_3$[9] are also found to be effective in the Friedländer condensation. But the use of environmentally toxic zinc chloride, and expensive $AuCl_3 \cdot 3H_2O$ limits their application to the synthesis of quinolines.

In order to avoid the toxic and chronic effects of organic solvents, the solvent free microwave-assisted synthesis of quinolines are reported by Ranu et al.[10] and Song et al.,[11] but the microwave-assisted synthesis are not applicable to large scale production. Since quinoline derivatives are increasingly useful and important in drugs and pharmaceuticals, the development of simple, eco-benign, room temperature and high yielding protocol is desirable.

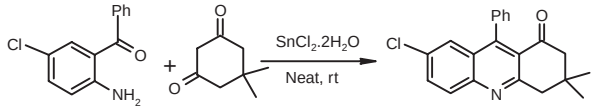
Herein we wish to report a simple, efficient and solvent free synthesis of quinolines by using tin(II) chloride. dihydrate at room temperature. Thus the treatment of *o*-amino substituted aromatic ketones with dicarbonyl compounds in the presence of tin(II) chloride·dihydrate leads to the formation of various 2,3,4-trisubstituted quinolines (Scheme 1) in excellent yields and in short reaction time.[12] In the absence of $SnCl_2 \cdot 2H_2O$ the reaction doesn't proceed. The main advantage of this solvent free, room temperature protocol is that it is operable on large scale (Entries 1 and 6), and it proceeds even when both of the precursors are solids (Entry 6).



Scheme 1.

The protocol was further extended to a various β-keto esters such as methyl acetoacetate, *t*-butyl acetoacetate, ethyl propionylacetate and dicarbonyl compound like acetylacetone. In all cases the reaction proceeds rapidly with *o*-amino substituted aromatic ketones like 5-chloro-*o*-aminobenzophenone, *o*-aminobenzophenone, and *o*-aminoacetophenone at room temperature with high efficiency. The results are summarized in Table 1. Unlike earlier reports the current protocol doesn't require heating of the reaction mixture, use of strong acids or alkalis or the use of toxic solvents to produce quinolines.

We next extended our methodology to the synthesis of fused tricyclic quinolines by using cyclic ketones such as cyclopentanone, cyclohexanone, cycloheptanone and cyclooctanone. This kind of cyclic ketones which give usually unsatisfactory yields even at 100 °C by using HCl[13] or stirring at room temperature for 48 h,[8] gave >95% yield in our reaction condition.



Scheme 2.

In the case of unsymmetrical ketone such as 2-butanone exclusively single regioisomer was obtained (Entry 6).

In conclusion we have developed a simple, efficient and ecobenign protocol for the Friedländer synthesis of quinolines. The merits of the current protocol are (a) the reaction is conducted under solvent free condition (b) the reaction proceeds at room temperature (c) the use of hazardous strong acids or bases are avoided (d) it does not require inert atmosphere or azeotropic removal of water (e) the reaction time is short (f) work up is simple (g) purifications like column chromatography or recrystallization are not needed (h) operable on large scale (i) yields are excellent.

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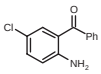
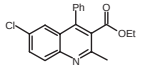
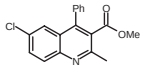
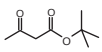
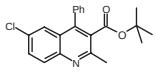
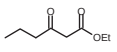
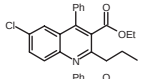
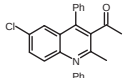
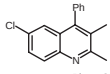
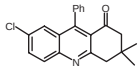
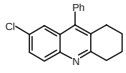
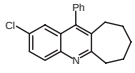
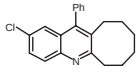
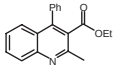
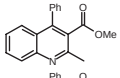
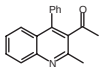
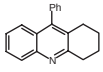
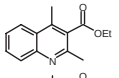
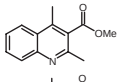
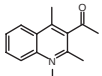
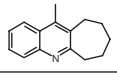
Table 1. $SnCl_2 \cdot 2H_2O$ catalyzed synthesis of polysubstituted quinolines

Entry	Compound 1	Compound 2	Product[a]	Time/min	Yield/%[b]
1				30	98[d]
2				30	98
3				40	96
4				40	95
5				30	98
6				45	98[c,e]
7				140	96[c,d]
8				140	96[c]
9				45	98[c]
10				15	98[c]
11				45	92
12				45	92
13				40	93
14				90	95[c]
15				30	93
16				30	93
17				25	92
18				15	98[c]

[a]All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, and Mass Spectra.
[b]Isolated Yields.
[c]Reactions were carried out by using 2 equiv. of $SnCl_2 \cdot 2H_2O$.
[d]Reactions were carried out in 10-g scale under mechanical stirring.
[e]Reaction was carried out at 50 °C.

References and Notes

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12 A typical procedure for quninoline synthesis is as follows: To a stirred mixture of *o*-aminobenzophenone and ethyl acetoacetate, added $SnCl_2 \cdot 2H_2O$ (1 equiv.) After the addition of $SnCl_2 \cdot 2H_2O$ and stirred, the reaction mixture became free stirring homogeneous viscous liquid. The progress of the reaction was monitered by TLC. After completion of the reaction, small amount of ethanol was added, (otherwise the reaction mixture was sticky) and stirred for 5 min. Then ice-cold water was added and the solid was obtained by filtration. The crude product was dissolved in ethyl acetate and filtered to remove the insoluble inorganic impurities. The product thus obtained was very pure as indicated by ^{1}H NMR. The product was characterized by IR, ^{1}H NMR, ^{13}C NMR, and Mass spectral data.

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