Water Mediated Synthesis of Substituted Quinolines – A New Green Approach to the Friedländer Annulation

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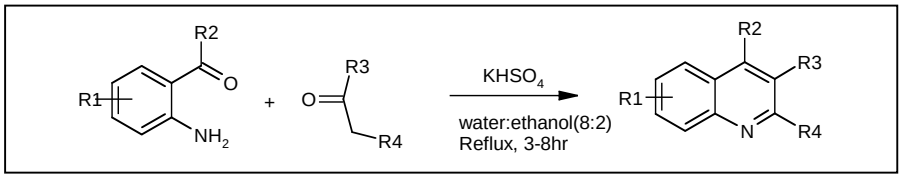

A new green approach to the Friedländer Quinoline synthesis is described for the preparation of polysubstituted quinolines from *o*-amino aryl ketones and carbonyl compounds containing active methylene group mediated by water and catalysed by $KHSO_4$ in good yields.

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Introduction.

The presence of the Quinoline scaffold in the frame work of the various pharmacologically active compounds with antimalarial, anti-inflammatory, antiasthmatic, antibacterial, antihypertensive and tyrosin kinase PDGF-RTK inhibiting properties [1-3] has enthused researchers to study their other potential biological activities. In addition, benzo [5,6] pyrrolizino[1,2-b]quinoline system is shown to display potent *in vitro* cytotoxic activity against the MCF7 cell [4]. Recently quinolines are also shown to be potential agent for the treatment of the erectile dysfunction as they exhibit more potent and selective PDE5 inhibitor activity [5]. Furthermore Quinoline scaffolds are used for the preparation of nano and mesostructures with enhanced electronic and photonic properties [6].

Despite numerous methods reported such as Skraup, Doebner, Von Miller and Combes [7,8] the Friedländer annulation is the most simple and effective method for the synthesis of polysubstituted quinolines. Friedländer method is acid or base catalyzed annulation of *o*-amino aryl ketones with carbonyl compound containing a reactive α-methylene group.

Friedländer reactions are generally carried out in alcoholic medium, in the presence of a base or by heating a mixture of the reactants at high temperature [9]. Literature reports show that acid catalysts are more effective than base catalysts for the Friedländer annulation [10]. Numerous Bronsted acid catalysts that are reported require high temperature and prolonged reaction time and moreover lead to the formation of various by-products. The Lewis acids are effective to the Friedländer condensation, but the usage of Lewis acid like $AlCl_3.3H_2O$, $ZnCl_2$ and $AuCl_3.3H_20$ limits the green approach in the large scale application. Variety of applications of quinolines in the biological and other studies necessitate the development of convenient, eco-benign synthetic routes.

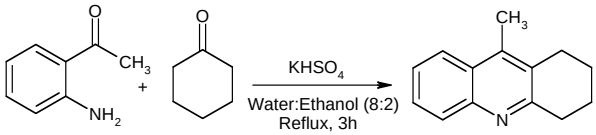
The growing awareness of the pressing need for greener and more sustainable technologies has focused attention on the use of atom efficient catalytic methodologies for the manufacture of fine chemicals and pharmaceuticals. Another aspect, which is receiving increasing attention, is the use of alternative reaction media that circumvent the problems associated with many of the traditional volatile organic solvents. The state of the art, use of alternative reaction media for green, sustainable organic synthesis is reviewed [11]. Liquid-liquid biphasic catalysis provides an alternative to the more traditional solid heterogeneous catalysts. Considering the toxicity of solvents, nowadays neat or solvent free reactions are preferred. However when a reaction medium is unavoidable, the best solvent to opt for is water. Catalysis in aqueous biphasic systems is an industrially attractive methodology, which has found broad applications.

Recently, there has been considerable interest in the $KHSO_4$ mediated organic synthesis [12] as it is water soluble as well as cost effective; moreover it is easy to handle and its separation from the reaction mixture is also easier.

Herein, we wish to report a simple, convenient and greener as well as water mediated synthesis of polysubstituted quinolines by using potassium bisulphate at reflux temperature.

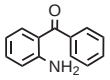
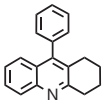
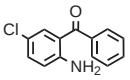
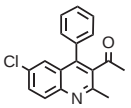
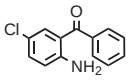
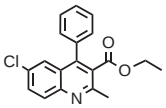
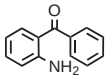
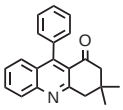
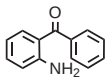
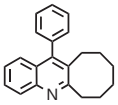
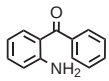
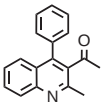
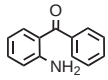
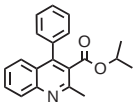
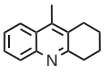
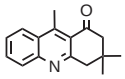
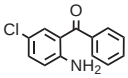
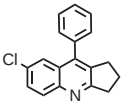
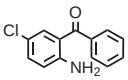
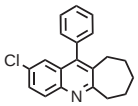
Accordingly, treatment of *o*-amino substituted aromatic ketones with carbonyl compounds in the presence of potassium bisulphate in water:ethanol (8:2) at reflux temperature resulted in the formation of various 2,3,4-trisubstituted quinolines (Scheme 1) in good yields without the need for purification.

Scheme 1



We extended our protocol to various β-ketoesters such as ethyl acetoacetate, isopropyl acetoacetate and dicarbonyl compounds like acetyl acetone and 5,5-dimethylcyclohexandione (dimedone) with *o*-amino acetophenone, 5-chloro-2-aminobenzophenone and *o*-amino benzophenone at reflux temperature to afford the corresponding substituted quinolines. Interestingly cyclic

Table 1

Entry	2-aminoketone	Ketone	Quinoline[a]	Mp(°C)	Time (h)	Yield[c] (%)
1				138(140-142)[b]	3	85
2				148(151-152)[b]	8	69
3				104(108)[b]	8	79
4				187(190-192)[b]	4	94
5				114(118-120)[b]	5	71
6				110(113-114)[b]	6	90
7				64	4	90[d]
8				75(78-79)[b]	8	94
9				94	5	61
10				98(105)[b]	8	72
11				172(175)[b]	4	93

[a]All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass Spectra. [b]Melting points reported are uncorrected. Literature values [14] are indicated in parenthesis. [c]Isolated yields. [d]Products were extracted in ethylacetate.

ketones such cyclohexanone, cyclopentanone, cycloheptanone and cyclooctanone reacted with 2-amino aryl ketones to afford the respective tricyclic quinolines. This class of cyclic ketones give usually unsatisfactory yields at room temperature or even higher temperature by using Bronsted acid [13]. However the reaction is fairly clean, rapid and efficient under the condition reported by us. The results are summarized in Table 1.

In conclusion, we have developed an expedient, potassium bisulphate catalyzed, water mediated synthesis of polysubstituted quinolines. Even though Lewis acids and other Bronsted acids are known to catalyze this reaction, this protocol offers several advantages including: (a) cleaner reactions, (b) higher yields of the products without employing any purification methods like column chromatography or recrystallisation (c) simple experimental procedure and (d) use of aqueous-ethanol medium, which makes it an useful and attractive process for the synthesis of polysubstituted quinolines.

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EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. Analytical TLC was performed on pre-coated plastic sheets of silica gel G/UV-254 of 0.2mm thickness (Machery-Nagel, Germany). IR spectra were taken as KBr pellets on a Perkin Elmer RXI FT-IR spectrometer. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded in $CDCl_3$ solutions with TMS as internal standard on a JEOL instrument. Mass spectra were recorded using JEOL DX-303 in EI ionization mode at 70eV. Elemental analysis data were recorded using Thermo Finnigan FLASH EA 1112 CHN analyzer.

Typical procedure for 9-methyl-1,2,3,4-tetrahydroacridine (**8**) synthesis is as follows: To a stirred solution of *o*-aminoacetophenone (300 mg, 2.22 mmol) and cyclohexanone (250 mg, 2.88 mmole) in water:ethanol (8:2) (5 mL), $KHSO_4$ (0.2 equiv.) was added then, reaction mixture was stirred at reflux temperature for 4 h. Reaction progress was monitored by TLC. After completion, the reaction mixture was allowed to cool to room temperature, and then the solid product was isolated by filtration and washed with water and dried. The product thus obtained was pure as indicated by ^{1}H NMR, ^{13}C NMR spectral data. 410 mg (94%), mp 75 °C (Lit [14] : 78-79 °C) ; IR (KBr): 1636, 1585, 1532, 1485 and 1883 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) : δ = 1.86(m, 4H), 2.90(m, 2H), 2.70 (s, 3H), 3.19 (m, 2H), 8.04(d, 1H, J = 7.65Hz), 7.92(t, 1H, J = 7.6Hz), 7.74(t, 1H, J = 7.65Hz), 8.33(d, 1H, J = 8.45 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): = 15.36, 20.96, 21.92, 26.16, 30.23, 122.11, 125.52, 126.78, 128.43, 130.80, 137.74, 152.83, 156.53; MS: m/z 198 (M^+)

2-Methyl-4-phenyl-quinoline-3-carboxylic acid isopropyl ester (**7**).

This compound was obtained as yellow colour solid, mp 64 °C; IR (KBr): 3012, 2914, 2800, 1807, 1710, 1569, 1471, 1230, 828, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96(d, 6H, J = 6.1Hz), 2.77(s, 3H), 4.95(heptet, 1H, J = 6.1Hz), 7.34(m, 2H), 7.38(t, 1H, J = 7.65Hz), 7.44 (d, 2H, J = 1.5Hz), 7.46(m, 1H), 7.53(d, 1H, J = 8.4Hz), 7.61(t, 1H, J = 7.65Hz), 8.05 (d, 1H, J = 8.4Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.33, 23.77, 69.12, 125.30, 126.46, 126.52, 127.81, 128.30, 128.52, 128.88, 129.56, 130.25, 135.74, 146.01, 147.69,154.58, 167.99; MS: m/z 306 (M^+).

Anal. Calcd. For $C_{20}H_{19}NO_2$: C, 78.66;H, 6.27;N, 4..39. Found: C, 78.65; H, 6.28; N, 4.38.

3,3,9-Trimethyl-3,4-dihydro-2H-acridin-1-one (**9**).

This compound was obtained as light brown colour solid, mp 94 °C; IR (KBr): 2949, 2800, 1694, 1614, 1350, 884, 830, 761cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12(s, 6H), 2.65(s, 2H), 3.06(s, 3H), 3.16(s, 2H), 7.55 (t, 1H, J = 7.65Hz), 7.74(t, 1H, J =7.65Hz), 7.97(d, 1H, J = 8.4Hz), 8.20(d, 1H, J= 9.15Hz); ^{13}C NMR (125 MHz, $CDCl_3$) : δ = 16.13, 28.31, 32.19, 48.18, 54.85, 124.29, 125.69, 126.65, 127.77, 128.71, 131.81, 147.85, 150.36, 161.09, 203.77; MS: m/z 240 (M^+).

Anal. Calcd. For $C_{16}H_{17}NO_2$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.31; H, 7.15; N, 5.84.

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