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GREEN PROTOCOL FOR THE FRIEDLÄNDER SYNTHESIS: $KAl(SO_4)_2{\cdot}12H_2O$-SiO_2 (ALUM-SiO_2) A HIGHLY EFFICIENT CATALYST IN THE SYNTHESIS OF QUINOLINES

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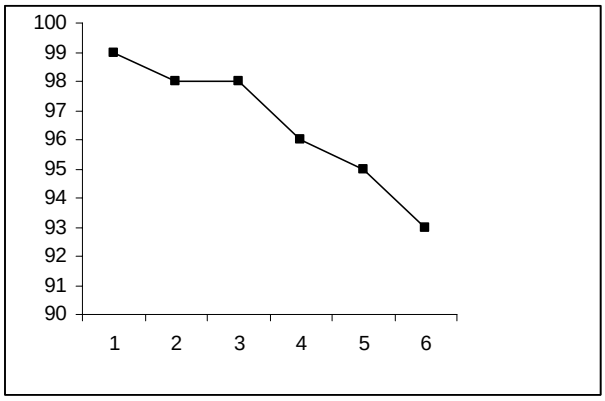
Abstract – In this letter, an efficient synthesis of an array of poly-substituted quinolines from 2-aminoaryl ketones and β-ketoester, β-diketones and α-methylene ketones using $KAl(SO_4)_2{\cdot}12H_2O$-SiO_2 (Alum-SiO_2) under solvent-free conditions is described. Compared with the classical Friedländer synthesis this new synthetic method has the advantage of excellent yields (90-98%), shorter reaction time, and reusability of the catalyst.

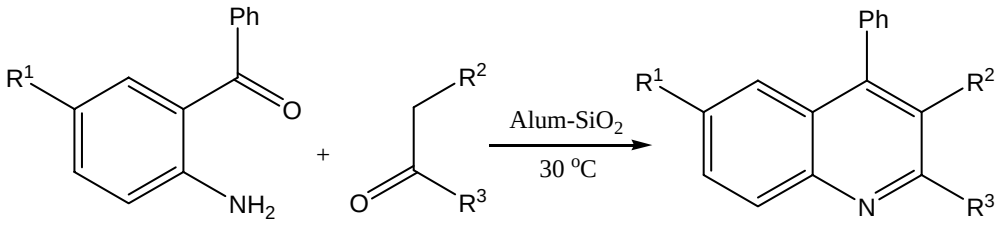
Quinolines are an important class of heterocyclic compounds having remarkable biological activities such as antimalarial, antibacterial, antiasthmatic, antibacterial, antihypertensive, anti-inflammatory and tyrosine kinase PDGF-RTK inhibiting agents.[1,2] In addition, they are also applied for the preparation of nano-structures and polymers that combine enhanced electronic, optoelectronic or non-linear optical properties with excellent mechanical properties.[3] Thus, the synthesis of quinolines is an important and useful task in organic chemistry. Various methods such as the Skraup,[4] Friedländer,[5] Pfitzinger,[6] Combes,[7] and Conrad-Limpach-Knorr [8] have been developed for the synthesis of quinoline derivatives.
However, the Friedländer annulation is one of the most simple and straightforward methods that is employed to produce poly-substituted quinolines. This method involves the acid or base catalyzed or thermal condensation (150-220 °C) between a 2-aminoaryl ketone and a second carbonyl compound possessing a reactive α-methylene group followed by cyclodehydration.[9-12] Subsequent works showed that acid catalysts are more effective that base catalysts for the Friedländer annulation. Several acids such as *p*-toluenesulphonic acid,[13] $SnCl_2$,[14] $Bi(OTf)_3$,15 $AuCl_3$,[16] $NaAuCl_4{\cdot}2H_2O$,[17] HCl,[18] NH_2SO_3H,[19] $Sc(O_3SOC_{12}H_{25})_3$,[20] silica sulfuric acid,[21] and ionic liquids [22] have also recently been utilized for this synthesis.

In connection with our ongoing work on synthesis of heterocyclic compounds [23] and in view of our interest in the $KAl(SO_4)_2{\cdot}12H_2O$-SiO_2 catalyzed reactions,[24] we now wish to report a facile and rapid procedure of preparation of quinolines derivatives *via* Friedländer synthesis with SiO_2-Alum as a non-toxic, reusable, inexpensive, and easily available reagent under solvent-free conditions at 30 °C. This method not only affords excellent yields, but also avoids problems associated with catalyst cost, handling, safety, and pollution.

The reaction of 2-amino-5-chlorobenzophenone **1a** (1 mmol) and 5,5-dimethyl-1,3-cyclohexanedione **2a** (1.2 mmol) in the presence of 25 mol% Alum-SiO_2 [Alum- SiO_2 contains 25% of $KAl(SO_4)_2{\cdot}12H_2O$ (see EXPERIMENTAL)] under solvent-free conditions at 30 °C in 99, 98, 98, 96, 95, and 93% yields over six cycles.(Scheme 1, Figure 1)

Figure 1: The same catalyst was used for each of the six runs





1 **2** **3**

Scheme 1

Promoted by this success, we extended this reaction of 2-aminoaryl ketones **1** with a range of other α-methylene ketones **2** under similar conditions; furnishing the respective poly-substituted quinolines **3** in excellent yields. Several examples that illustrate this novel and generally usable method for the synthesis of the quinolines are summarized in Table 1.

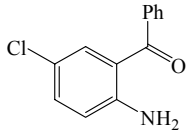
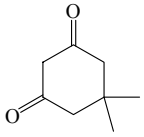
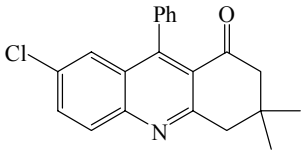
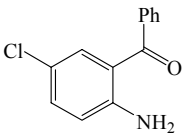
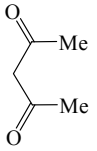
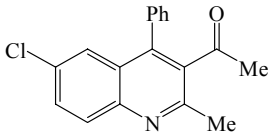
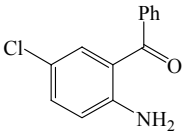
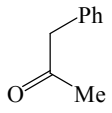
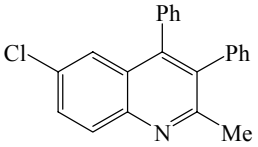
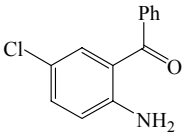
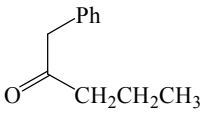
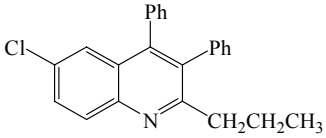
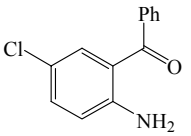
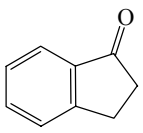
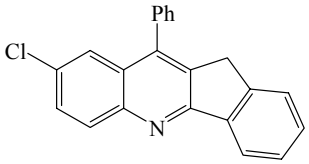
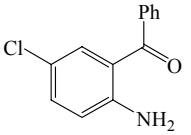
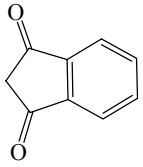
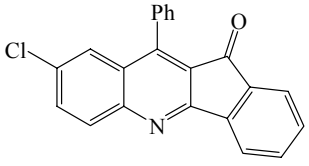
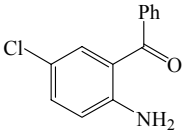
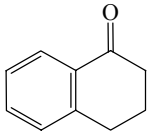
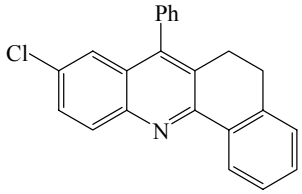
In summary, we have developed a simple, convenient, and effective method for the synthesis of quinolines employing $KAl(SO_4)_2{\cdot}12H_2O$-SiO_2 under mild conditions. The catalyst can be prepared easily with readily available inexpensive regents that are heterogeneous, reusable, and non-hazardous. To the

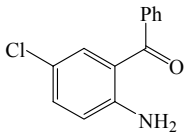
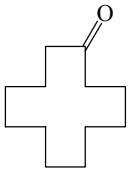
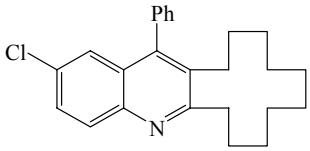
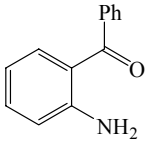
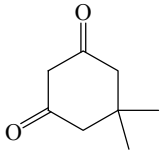
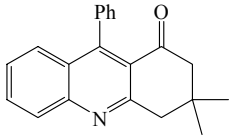
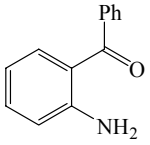
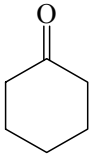
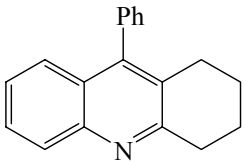
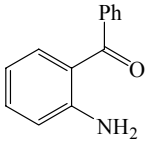
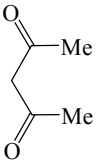
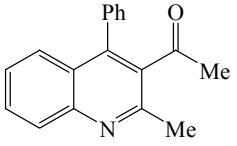
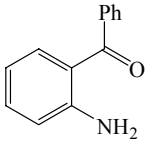
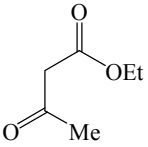
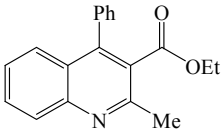
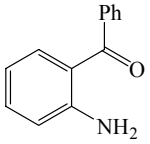
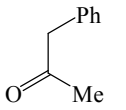
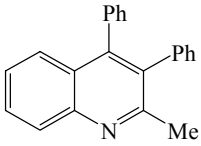
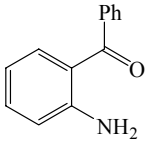
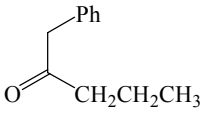
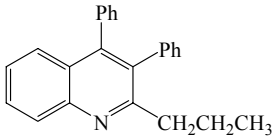
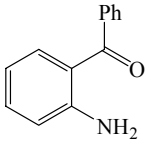
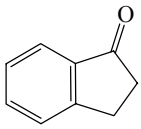
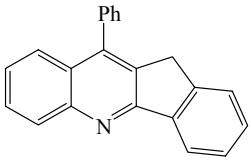
best of our knowledge, this is the first report of an efficient general method for the synthesis of some new quinolines by using a simple catalyst.

EXPERIMENTAL

Melting points were measured on the Electrothermal 9100 apparatus and are uncorrected. IR spectra were measured on a Shimadzu IR-470 Spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined on Bruker 300 DRX Avance instrument at 300 and 75MHz. respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

Table 1: $KAl(SO_4)_2{\cdot}12H_2O$-SiO_2 catalyzed Friedländer reaction under solvent free conditions[a]

Entry	2-Aminoaryl Ketone **1**	α-Methylene Ketone **2**	Time (h)	Product **3**	Yield (%)[b]	MP (°C)
a			1.5		99	208-9[21]
b			1.5		97	152-4[21]
c			2.45		93	-
d			2.45		91	-
e			2.5		95	-
f			2		90	-
g			2.45		90	-

h			2.45		85	-
i			1.45		97	191-3[21]
j			2.45		85	224-6[18]
k			2		96	113-4[25]
l			2		97	100-1[25]
m			2.45		92	-
n			2.45		93	-
o			2.5		94	-

[a]Reaction conditions: 2-aminoaryl ketone (1 mmol), α-methylene ketone (1.2 mmol), Alum-SiO_2 (25 mol%), under solvent-free conditions at 30 °C.
[b]Isolated products.

General procedure: A mixture of *o*-aminobenzophenones (1 mmol), ketones (1.2 mmol), and $KAl(SO_4)_2{\cdot}12H_2O$-SiO_2 (0.6 g, 25 mol%) was heated with stirring at 30 °C for the time periods that are recorded in Table 1. After completion of the reaction, as indicated by TLC (AcOEt/*n*-hexane, 1/1), the reaction mixture was washed with hot EtOH and filtered through a sinter funnel to recover the catalyst. The organic portion from filtrate was separated and concentrated under reduced pressure. The crude product was recrystallized from EtOH to afford the quinolines derivatives.

The recovered catalyst was washed with acetone and dries at rt and used consecutively six times to afford

the products with minimum variation of the yields.

Preparation of the supported catalyst: To a suspension of silica gel (7.5 g, Merck, Silica gel 0.063–200 mm) in water (20 mL) $KAl(SO_4)_2 \cdot 12H_2O$ (2.5 g) was added. The suspension stirred at rt for 6 h, then was water evaporated under reduced pressure and the residue dried at 50 °C.

Spectral data for new product:

6-Chloro-2-methyl-3,4-diphenylquinoline (3c): White powder; mp 200-201 ˚C; IR (KBr), ν_{max} 3015, 2909, 1602, 1568 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 2.54 (s, CH_3), 7.05 (m, 5H, ArH), 7.24 (m, 5H, ArH), 7.48 (s, ArH), 7.62 (d, *J*=8.8 Hz, ArH), 8.05 (d, *J*=8.8 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ_C: 25.40, 125.39, 127.04, 127.13, 127.56, 127.93, 128.01, 129.88, 129.99, 130.04, 130.25, 131.69, 134.93, 136.05, 138.20, 145.38, 145.95, 158.30; MS (*m/z*, %): 329 (M^+, 100). Anal. Calcd for $C_{22}H_{16}ClN$: C, 80.11; H, 4.89; N, 4.25. Found: C, 80.02; H, 4.78; N, 4.13.

6-Chloro-3,4-diphenyl-2-propylquinoline (3d): White powder; mp 148-150 ˚C; IR (KBr), ν_{max} 3055, 2956, 1603, 1559 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 0.87 (t, *J*=7.2 Hz, CH_3), 1.71 (m, CH_2), 2.78 (t, *J*=8.0 Hz, CH_2), 7.06 (m, 5H, ArH), 7.25 (m, 5H, ArH), 7.46 (s, ArH), 7.62 (d, *J*=8.8 Hz, ArH), 8.08 (d, *J*=8.9 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ_C: 14.22, 22.82, 39.20, 125.35, 126.96, 127.06, 127.46, 127.76, 127.87, 129.98, 130.16, 130.21, 130.45, 131.65, 134.81, 136.25, 137.98, 145.48, 146.22, 161.66; MS (*m/z*, %): 357 (M^+, 35). Anal. Calcd for $C_{24}H_{20}ClN$: C, 80.55; H, 5.63; N, 3.91. Found: C, 80.42; H, 5.52; N, 3.83.

8-Chloro-10-phenyl-11*H*-indeno[1,2-*b*]quinoline (3e): White powder; mp 172-173 ˚C; IR (KBr), ν_{max} 3053, 1602, 1562 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 3.85 (d, *J*=4.0 Hz, CH_2), 7.48 (m, 5H, ArH), 7.62 (m, 4H, ArH), 7.66 (s, 1H, ArH), 8.18 (d, *J*=8.5 Hz, ArH), 8.31 (d, *J*=7.2 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ_C: 34.01, 122.22, 124.66, 125.38, 127.12, 127.61, 128.58, 128.94, 129.18, 129.53, 130.27, 130.73, 131.42, 133.89, 135.81, 140.12, 142.85, 145.19, 146.83,161.31; MS (*m/z*, %): 327 (M^+, 90). Anal. Calcd for $C_{22}H_{14}ClN$: C, 80.61; H, 4.30; N, 4.27. Found: C, 80.52; H, 4.21; N, 4.16.

8-Chloro-10-phenyl-11*H*-indeno[1,2-*b*]quinolin-11-one (3f): White powder; mp 238-239 ˚C; IR (KBr), ν_{max} 3051, 1712, 1617, 1588 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 7.42-7.75 (m, 10H, ArH), 8.13 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$) δ_C: 121.81, 123.39, 123.90, 124.00, 127.36, 128.38, 128.68, 129.32, 131.27, 131.86, 132.16, 132.39, 133.13, 135.50, 137.44, 143.36, 147.18, 159.98, 162.20, 189.88; MS (*m/z*, %): 341 (M^+, 90). Anal. Calcd for $C_{22}H_{12}ClNO$: C, 77.31; H, 3.54; N, 4.10. Found: C, 77.19; H, 3.42; N, 4.01.

9-Chloro-5,6-dihydro-7-phenylbenzo[*c*]acridine (3g): White powder; mp 139-140 ˚C; IR (KBr), ν_{max} 3050, 2951, 1566, 1549 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 2.83-2.91 (m, 2 CH_2), 7.25-7.61 (m, 10H, ArH), 8.12 (d, *J*=8.9 Hz, ArH), 8.60 (d, *J*=7.4 Hz, ArH); ^{13}C NMR $CDCl_3$) δ_C: 26.53, 28.11, 124.86, 126.36, 127.35,

127.77, 128.00, 128.25, 128.80, 129.11, 129.41, 129.93, 131.16, 131.74, 134.71, 136.19, 139.30, 144.69, 145.51, 153.39; MS (*m/z*, %): 341 (M^+, 70). Anal. Calcd for $C_{23}H_{16}ClN$: C, 80.81; H, 4.72; N, 4.10. Found: C, 80.72; H, 4.59; N, 4.01.

2-Chloro-6,7,8,9,10,11,12,13,14,15-decahydro-16-phenylcyclododeca[*b*]quinoline (3h): White powder; mp 114-116 ˚C; IR (KBr), ν_{max} 3052, 2929, 2851, 1602, 1563 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 1.31 (brod, CH_2), 1.57 (m, 6 CH_2), 2.03 (brod, CH_2), 2.64 (t, *J*=7.5 Hz, CH_2), 3.07 (t, *J*=7.6 Hz, CH_2), 7.17-7.51 (m, 7H, ArH), 7.96 (d, *J*=8.8 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ_C: 22.77, 23.22, 26.87, 27.07, 27.75, 28.01, 28.38, 28.47, 28.78, 33.73, 124.89, 127.66, 127.98, 128.50, 129.26, 129.28, 129.98, 131.23, 133.24, 136.96, 144.36, 146.64; MS (*m/z*, %): 377 (M^+, 80). Anal. Calcd for $C_{25}H_{28}ClN$: C, 79.45; H, 7.47; N, 3.71. Found: C, 79.32; H, 7.38; N, 3.60.

2-Methyl-3,4-diphenylquinoline (3m): White powder; mp 173-175 ˚C; IR (KBr), ν_{max} 3056, 2911, 1562 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 2.56 (s, CH_3), 7.09 (m, 4H, ArH), 7.21 (m, 6H, ArH), 7.41 (m, 1H, ArH), 7.50 (d, *J*=7.7 Hz, ArH), 7.70 (m, 1H, ArH), 8.15 (d, *J*=7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ_C: 25.42, 125.90, 126.31, 126.63, 126.85, 127.24, 127.70, 127.93, 128.55, 129.18, 130.04, 130.10, 134.09, 136.76, 138.61, 146.70, 146.95, 157.86; MS (*m/z*, %): 295 (M^+, 95). Anal. Calcd for $C_{22}H_{17}ClN$: C, 89.46; H, 5.80; N, 4.74. Found: C, 89.33; H, 5.68; N, 4.63.

3,4-Diphenyl-2-propylquinoline (3n): White powder; mp 125-127 ˚C; IR (KBr), ν_{max} 3059, 2968, 2932, 1601, 1565 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 0.87 (t, *J*=7.1 Hz, CH_3), 1.71 (m, CH_2), 2.80 (t, *J*=7.8 Hz, CH_2), 7.09 (m, 4H, ArH), 7.20 (m, 6H, ArH), 7.39 (m, 1H, ArH), 7.48 (d, *J*=7.1 Hz, ArH), 7.70 (m, 1H, ArH), 8.15 (d, *J*=7.8 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ_C: 14.25, 23.01, 39.27, 125.85, 126.15, 126.61, 126.76, 127.13, 127.65, 128.74, 129.07, 130.08, 130.32, 133.95, 136.97, 138.39, 147.07, 161.28; MS (*m/z*, %): 323 (M^+, 45). Anal. Calcd for $C_{24}H_{21}N$: C, 89.12; H, 6.54; N, 4.33. Found: C, 89.02; H, 6.42; N, 4.24.

10-Phenyl-11*H*-indeno[1,2-*b*]quinoline (3o): White powder; mp 138-140 ˚C; IR (KBr), ν_{max} 3058, 1616,1599, 1568 cm^{-1}; ^1H NMR ($CDCl_3$) δ_H: 3.89 (s, CH_2), 7.43-7.66 (m, 9H, ArH), 7.71-7.76 (m, 2H, ArH), 8.29 (d, *J*=8.5 Hz, ArH), 8.38 (d, *J*=6.9 Hz, ArH); ^{13}C NMR ($CDCl_3$) δ_C: 34.00, 122.25, 125.35, 125.70, 125.81, 126.39, 127.52, 128.28, 128.73, 129.18, 129.28, 130.03, 132.98, 136.52, 140.45, 143.70, 145.26, 148.41, 161.01; MS (*m/z*, %): 293 (M^+, 85). Anal. Calcd for $C_{22}H_{15}N$: C, 90.07; H, 5.15; N, 4.77. Found: C, 90.01; H, 5.13; N, 4.66.

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