A facile one-pot Friedländer synthesis of quinoline derivatives

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A facile one-pot Friedländer synthesis has been developed for quinolines using $GdCl_3.6H_2O$ as the novel catalyst. The method is simple, efficient and rapid to afford the quinolines in very good yields.

Keywords: quinolines, carbonyl compounds, $GdCl_3.6H_2O$

Quinolines are important heterocyclic compounds and are present in many biological systems. They possess anti-malarial, anti-bacterial, anti-asthmatic, anti-hypertensive and anti-inflammatory properties.[1-3] Because of their importance in natural products, a straight forward quinoline synthesis was developed by Friedländer.[4-9] The Friedländer[10] annulation is a condensation reaction between an aromatic *ortho*-aminoaldehyde and an aldehyde or ketone bearing α–methylene group. In the presence of Lewis acids.[11-15] However many of these procedures have drawbacks such as expensive reagents, harsh reaction conditions, low yields, high temperature and a tedious work-up. Therefore, a practical, simple and environmentally benign method is required.

Our continuing interest[16,17] in bioactive compounds and on heterocyclic compounds led us to report a facile and an efficient method for the synthesis of various quinolines from *o*-aminobenzophenones, or *o*-aminoacetophenones with α-methylene carbonyl compounds in presence of catalytic amount of $GdCl_3.6H_2O$ (3 mol%) in ethyl alcohol (5 ml) under reflux. Organic reactions using mild catalysts that tolerate water have received attention in recent years as they are eco-friendly and can conveniently be handled in the laboratory for various organic transformations. $GdCl_3.6H_2O$[18,19] has received attention for a few organic transformations such as those of homoallylic alcohols, α-aminonitriles and Diels–Alder reactions,[20-22] and there is further scope to develop synthetic methodologies using $GdCl_3.6H_2O$ as catalyst. However, to the best of our knowledge there is no report on Friedländer synthesis of quinolines using the $GdCl_3.6H_2O$. Initially we have carried out the reaction of *o*-aminobenzophenone (**1a**) and ethyl acetoacetate (**2b**) in the presence of $GdCl_3.6H_2O$ (3 mol%) in ethyl alcohol under reflux. The reaction was monitored by TLC (25 min) and upon workup afforded ethyl-2-methyl-4-phenyl-3-quinolinecarboxylate (entry **3b**) in 97% yield (Scheme 1). The product was characterised by its spectral data (^{1}H NMR, IR and MS) and compared with an authentic sample. A similar reaction at room temperature was slower and did not give good yields.

We have conducted similar reactions of substituted benzophenones with various active methylene ketones such as methyl acetoacetate, 2,5-pentanedione, 2,5-hexanedione; cyclic ketones such as cyclopentanone, cyclohexanone and 5,5-dimethyl-1,3-cyclohexanedione to give the corresponding quinolines in good yields (entries **3a–h**). The results encouraged us to study further reactions with *o*-aminoacetophenone and 5-chloro-*o*-aminobenzophenone with active methylene ketones such as methyl acetoacetate, ethyl acetoacetate, 2,5-pentanedione, 2,5-hexanedione; cyclic ketones such as cyclopentanone, cyclohexanone and 5,5-dimethyl-1,3-cyclohexanedione gave corresponding quinolines (entries **3i–x**). All the products were characterised by ^{1}H NMR, IR and mass spectra and compared with authentic samples. The results were tabulated in Table 1and show the efficiency of the catalyst.

In conclusion, we have developed a mild, rapid and efficient Friedländer protocol for the synthesis of quinolines using catalytic amounts of $GdCl_3.6H_2O$. The present method offers several advantages such as a short reaction times, cleaner reaction products, simple experimental and work up procedures making this an attractive alternate method compared to reported methods.

Experimental

^{1}H NMR spectra were determined on Varian Gemini 200 MHz spectrometer using TMS as internal standard. IR spectra were recorded on Nicollet 740 FT spectrometer. Mass spectra were recorded on Agilent LCMS 1100 instrument. Flash column chromatography was performed with 100–200 silicagel and analytical TLC was performed on precoated silica- gel plates (60F-254). Melting points were measured on Buchi-510 apparatus and are uncorrected. C, H and N analysis was carried out using Elementar Vario EL, Germany instrument.

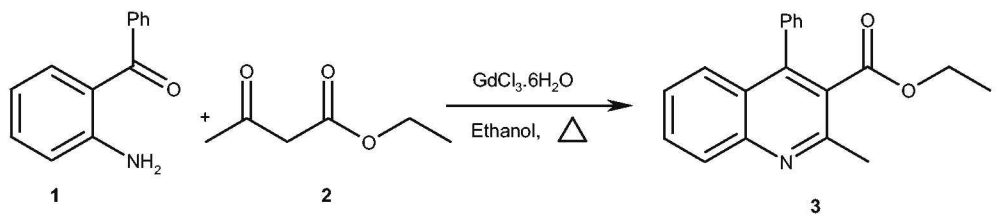
General procedure

A mixture of 2-aminoacetophenone (1 mmol), α-methylene carbonyl compound (1.2 mmol) and $GdCl_3.6H_2O$ (3 mol%) in ethyl alcohol (5 mL) was refluxed for an appropriate time (Table 1). After completion of the reaction (TLC), the solvent was removed under reduced pressure and the crude product was purified by column chromatography to afford pure quinolines in very good yields.

The spectral data (^{1}H NMR, IR and MS) of some of the representative compounds are given below.

(3a): IR (KBr): 3070, 2930, 1725, 1614, 1590, 1485, 1405, 1295, 579 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.08 (d, J = 8.0 Hz, 1H), 7.80–7.23 (m, 8H), 3.55 (s, 3H), 2.72 (s, 3H); Mass (LCMS): *m/e* 278 [M$^+$ + H].

(3c): IR (KBr): 3027, 2960, 1725, 1614, 1590, 1485, 1405, 1295, 704 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.03 (d, J = 8.2 Hz, 1H, aromatic), 7.80–7.23 (m, 8H, aromatic), 2.69 (s, 3H), 1.94 (s, 3H). ^{13}C NMR: δ 203.56, 153.57, 147.56, 143.96, 135.23, 134.86, 130.29, 130.29, 130.13, 129.12, 128.93, 128.90, 128.73, 126.54, 126.19, 125.07, 31.97, 23.90; Mass (LCMS): *m/e* 262 [M$^+$ + H].



Scheme 1

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Table 1 $GdCl_3.6H_2O$ catalysed Friedländer synthesis of quinolines

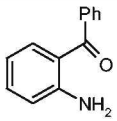
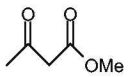
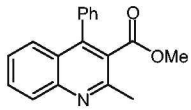
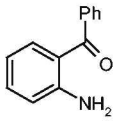
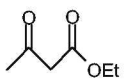
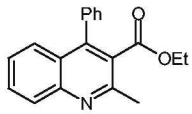
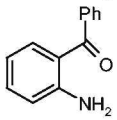
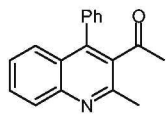
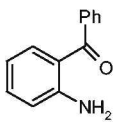
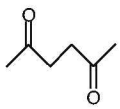
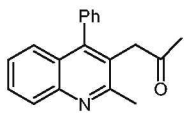
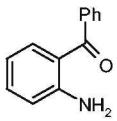
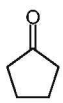
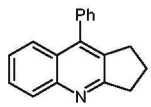
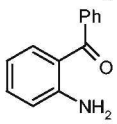
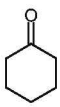
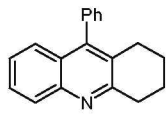
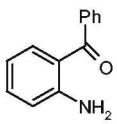
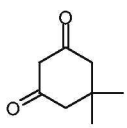
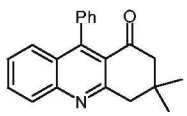
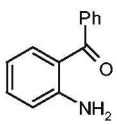
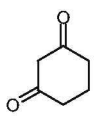
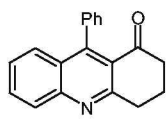
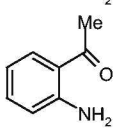
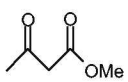
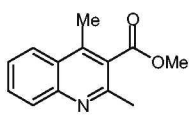
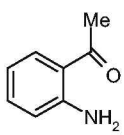
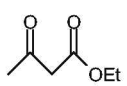
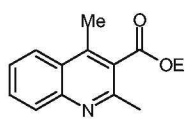
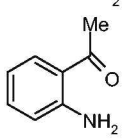
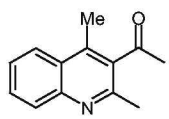
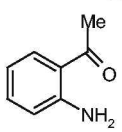
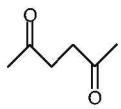
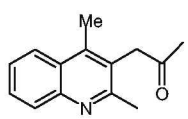
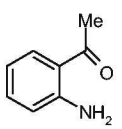
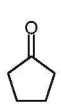
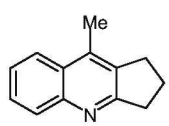
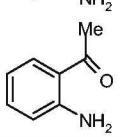
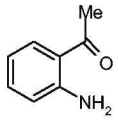
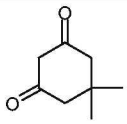
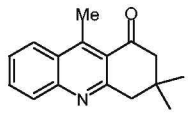
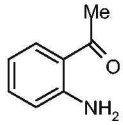
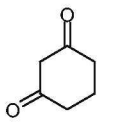
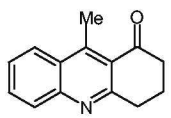
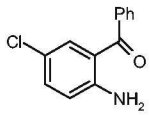
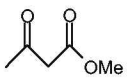
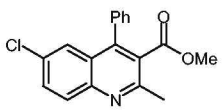
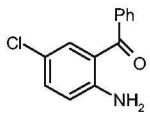
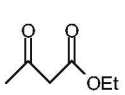
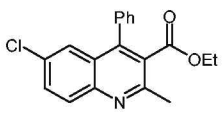
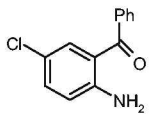
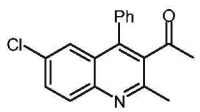
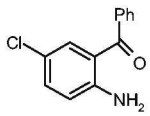
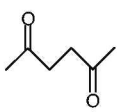
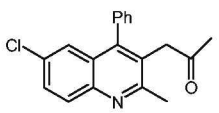
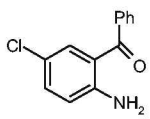
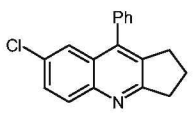
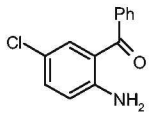
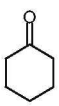
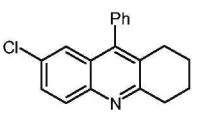
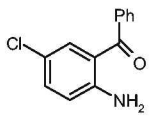
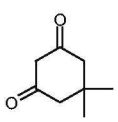
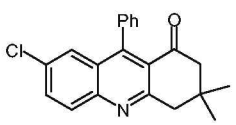
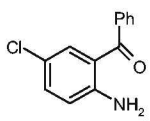
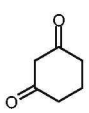
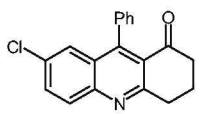
Entry	Aminoaryl ketones (**1**)	α-Methylene carbonyl compounds (**2**)	Quinoline (**3**)	Time/min	Yield*/%	M.p/°C (Lit.)[Ref]
a				35	95	68–69
b				30	97	98 (98–99)[23]
c				40	92	114 (114–116)[23]
d				45	90	115
e				35	94	131 (132–134)[26]
f				40	95	141 (140–142)[23]
g				65	93	192 (190–192)[26]
h				40	92	155 (156–157)[26]
i				25	90	Oil[24]
j				30	91	Oil[24]
k				40	89	Oil[24]
l				45	93	133
m				50	88	61 (60)[24]
n				45	90	78 (78)[24]

Table 1 *continued*

Entry	Aminoaryl ketones (**1**)	α-Methylene carbonyl compounds (**2**)	Quinoline (**3**)	Time/min	Yield*/%)	M.p/°C (Lit.) Ref
o				70	91	105 (105–107)[23]
p				50	87	123
q				35	86	135 (133–135)[25]
r				30	89	108 (109)[24]
s				45	90	150 (151)[24]
t				40	86	129
u				50	85	104 (105)[24]
v				55	84	164 (163)[24]
w				75	91	210 (209–211)[25]
x				45	93	186 (185–189)[25]

*All the products were characterised from their spectral ^{1}H NMR, IR and MS. Isolated and unoptimised yields.

(3d): IR (KBr): 3060, 2974, 2930, 1724, 1560, 1485, 1405, 1295, 1225, 764 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.68–7.11 (m, 9H), 5.58 (s, 2H), 1.93 (s, 6H). Mass (LCMS): *m/e* 262 [M^+ + H].

(3e): IR (KBr): 3070, 2928, 1715, 1615, 1595, 1485, 1405, 1290, 709 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.02 (d, J = 8.0 Hz, 1H, aromatic), 7.53–7.31 (m, 8H, aromatic), 3.22 (t, J = 7.01 Hz, 2H), 2.91 (t, J = 6.56 Hz, 2H), 2.18 (m, 2H). Mass (LCMS): *m/e* 246 [M^+ + H].

(3g): IR (KBr): 3060, 2971, 2932, 1728, 1560, 1495, 1403, 1295, 1228, 766 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.04 (d, J = 8.0 Hz, 1H, aromatic), 7.78–7.66 (m, 1H, aromatic), 7.50–7.38 (m, 5H, aromatic), 7.20–7.06 (m, 2H, aromatic), 3.24 (s, 2H), 2.54 (s, 2H), 1.18 (s, 6H, 2CH_3). Mass (LCMS): *m/e* 302 [M^+ + H].

(3i): IR (KBr): 3070, 2930, 2873, 1725, 1614, 1589, 1214, 1082, 579 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.01 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 8.4 Hz, 1H), 7.02 (t, 1H, J = 8.4 Hz), 3.99 (3H, s), 2.68 (3H, s), 2.62 (3H, s). Mass (LCMS): *m/e* 216 [M^+ + H].

(3l): IR (KBr): 3420, 2924, 2854, 1687, 1597, 1486, 1451, 1281, 1247, 761 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.75 (d, J = 8.0 Hz, 1H, aromatic), 7.58 (t, J = 8.2 Hz, 1H, aromatic), 7.48 (t, 1H, aromatic), 7.23 (d, J = 8.0 Hz, 1H, aromatic), 5.88 (2H, s), 1.96 (6H, s), 1.73 (3H, s). Mass (LCMS): *m/e* 214 [M^+ + H].

(3t): IR (KBr): 3421, 2924, 2855, 1688, 1598, 1486, 1451, 1358, 1281, 1160, 762 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.05 (d, 1H), 7.32–7.72 (m, 7H), 5.80 (s, 2H), 2.66 (s, 3H), 1.94 (s, 3H). Mass

(LCMS): *m/e* 310 [M^+ + H]. Anal. Calcd for $C_{19}H_{16}ClNO$: C, 73.66; H, 5.21; N, 4.52. Found: C, 73.64; H, 5.24; N, 4.54%.

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