Communication

Synthesis of Polysubstituted Quinolines Using Cyanuric Chloride as a Catalyst under Aqueous Conditions

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A mild, eco-friendly and efficient route for the synthesis of quinolines and polycyclic quinolines via Friedländer annulation using cyanuric chloride as a catalyst under aqueous conditions is described.

Keywords: Quinolines; Polycyclic quinolines; Friedländer annulation; Cyanuric chloride.

INTRODUCTION

The chemical industry is a major contributor to environmental pollution due to the ubiquitous use of several hazardous organic solvents, flammables, carcinogens, explosives, etc. The development of non-hazardous alternatives is not only due to the increased regulatory pressure focusing on organic solvents but the great importance with respect to green chemistry.[1] Organic reactions in water as solvent have many advantages from both economic and environmental point of view.[2] Although water is inexpensive, non-toxic and non-flammable, it is frequently overlooked as a solvent for organic reactions. Most of catalysts and reagents are either deactivated or decomposed in water and in general organic compounds are insoluble in water. Therefore, carrying out organic reactions in water poses one of the fundamental challenges to organic chemists.

The synthesis of quinoline derivatives has been considered of great interest to organic chemists owning to its wide range of biological and pharmaceutical properties such as anti-malarial, anti-inflammatory, anti-asthmatic, anti-bacterial, anti-hypertensive and tyrosine kinase inhibiting agents.[3] In addition, quinolines are valuable synthones used for the preparation of nano- and meso-structures with enhanced electronic and photonic properties.[4] Consequently, various methods were developed for the synthesis of quinoline derivatives. The Friedländer annulation has been catalyzed by both acids and bases. Under base catalyzed conditions 2-aminobenzophenone fails to react with simple ketones such as cyclohexanone or β-ketoesters.[5] Brønsted acids like hydrochloric acid, sulphuric acid, *p*-toluene sulphonic acid, phosphoric acids are widely used as catalysts for this conversion.[6] However, many of these classical methods require high temperatures, longer reaction times, drastic conditions, and low yields. Therefore, new catalytic systems are continuously explored. As a result, recently Lewis acids such as $Ag_3PW_{12}O_{40}$, $Y(OTf)_3$, $FeCl_3$ or $Mg(ClO_4)_2$, $NaAuCl_4.2H_2O$, $SnCl_2$ or $ZnCl_2$, $Bi(OTf)_3$, NaF, $SnCl_2.2H_2O$, $CeCl_3.7H_2O$, $ZnCl_2$, and I_2 have been used in presence of organic solvent for the synthesis of quinolines.[7a-k] Also, microwave irradiations have been used for the synthesis of these compounds.[8a-c] However, there have been no reports on the use of cyanuric chloride for Friedländer quinoline synthesis.

RESULTS AND DISCUSSION

In earlier reports we showed the efficacy of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine, TCT) for various transformations.[9] In continuation of our research work in the development of synthetic methods using cyanuric chloride, we report herein, the efficient application of this reagent for Friedländer annulation followed by cyclodehydration of ketones under aqueous conditions.

Initially, we optimized the amount of cyanuric chloride as a catalyst required for the reaction of 2-aminobenzophenone (1 mmol) and dimedone (1 mmole). When this reaction is carried out without catalyst (Table 1, entry 1) even trace mount of the product did not formed. When the amount of catalyst used is less than 16 mol%, low to moderate yield of quinoline is obtained (Table 1, entries 2-5). With 16 mol% of the catalyst, the corresponding quinoline

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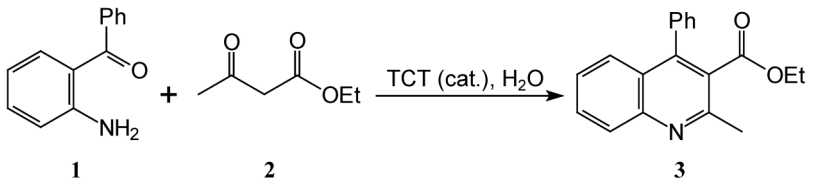
Scheme I



1 **2** **3**

Table 1. Catalytic study of cyanuric chloride for the synthesis of quinoline **3c** under aqueous medium at room temperature

Entry	Cyanuric chloride (mol %)	Time (h)	Yield[a] (%)
1	--	50	--
2	2	50	05
3	4	48	15
4	8	40	30
5	12	40	45
6	16	30	78
7	20	20	96
8	20	22	88[b]
9	24	19	96
10	30	18	96

[a] Isolated yields.
[b] The reaction was carried out with 2-aminobenzophenol (100 mmol), dimidone (100 mmol) by using 20 mol% cyanuric chloride and 100 mL water.

was obtained in good yield (Table 1, entry 6). While the use of 20 mol% catalyst leads to the excellent yield of the product (Table 1, entry 7) whereas the yield of the product did not improve even after using excess amount of the catalyst (Table 1, entries 9, 10).

Using the best conditions reported in Table 1, we then continued to study the reaction by using variety of 2-aminoaryl and α-methylene ketones respectively. The results were summarized in Table 2 indicating that both cyclic and acyclic ketones underwent smooth reaction with 2-aminoaryl ketones to give high yields of products. The present protocol is highly effective for substituted 2-aminoaryl ketones such as 2-aminobenzophenone and 2-amino-5-chlorobenzophenone. In general, the yields of the quinoline dervetives were high. It is noteworthy to mention that the method is clean and free form side reactions which normally observed under basic conditions.

Comparison of effect of cyanuric chloride catalyst with reported catalysts is shown in Table 3. As compared to recently reported method,[10] involving the use of heavy metal ion and stringent conditions under aqueous medium the present protocol is superior as no heavy metal ion is used in this protocol. In some methods[7d,7f,7i] costly heavy metal ions with low catalyst loading are used. However, these methods suffer from disadvantages like use of hazardous and toxic organic solvents and poor yields of the products.

The advantages of the present protocol are: (i) use of inexpensive catalyst (ii) use of water as a green solvent (iii) mild reaction conditions (iv) method works well on 100 mmol scale therefore, this protocol may be applicable on large scale synthesis of these bioactive molecules (Table 1, entry 8) (v) purification of the product using column chromatography is not required.

In conclusion, we believe that the present methodology compared to many of the reported methods offers a simple and efficient route for the synthesis of poly-substituted quinolines under aqueous medium at room temperature. Mild conditions, simple work-up procedure, pure products and excellent yields make an alternative contribution to the existing methodologies.

EXPERIMENTAL SECTION

All Chemicals were of analytical grade and purchased from Aldrich and Fluka companies. ^{1}H NMR spectra were recorded on 300 MHz (Varian Mercury) instrument using $CDCl_3$ as a solvent and TMS as an internal standard. IR spectra were recorded on Bomem MB 104 IR spectrometer. Melting points are not corrected. Chemical shifts are given in ppm and *J* values are quoted in Hz.

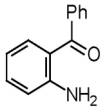
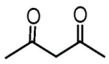
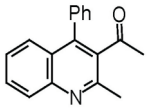
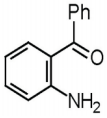
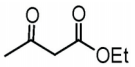
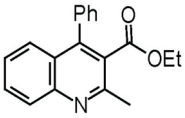
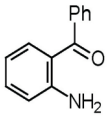
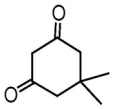
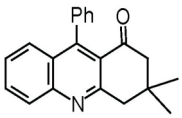
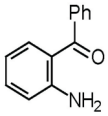
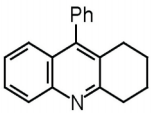
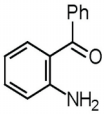
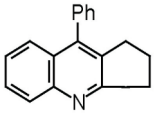
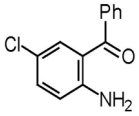
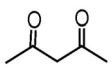
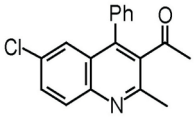
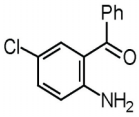
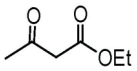
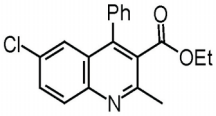
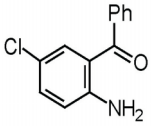
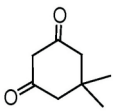
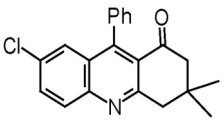
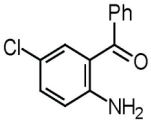
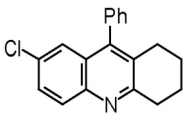
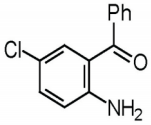
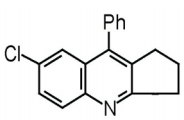
General experimental procedure

A mixture of 2-aminoaryl ketone (1.0 mmol), α-methylene ketone (1 mmol) cyanuric chloride (20 mol%) and water (1.0 mL) was stirred at room temperature for the specified time (Table 2). After completion of the reaction (TLC), the resulting suspension was neutralized with 2N NaOH. The crude solid was separated by filtration under suction and washed with water to get practically pure white or slightly yellow powder.

Spectral data of the compounds

3a: Yellow solid; m.p. 112 °C; IR (KBr): 3029, 2962,

Table 2. Synthesis of poly-substituted quinolines using cyanuric chloride as a catalyst under aqueous conditions

Entry	Substrate (1)	Substrate (2)	Product (3)	Time (h)	Yield[a] (%)
a				18	93
b				16	95
c				20	96
d				17	90
e				17.30	88
f				16	93
g				12.30	95
h				14.30	94
i				16	91
j				17	85

[a] Yields pure isolated products

1707, 1615, 1572, 1480, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.81 (s, 3H), 2.01 (s, 3H), 7.10-7.15 (m, 2H), 7.20 (t, *J* = 8.4 Hz, 1H), 7.25-7.29 (m, 3H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.35 (t, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3, 29.2, 31.4, 124.5, 125.6, 126.0, 128.1, 128.4, 129.5, 134.7, 147.0, 153.0, 205.6; Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.78; N, 5.36. Found: C, 82.70; H, 5.81; N, 5.32.

3b: Yellow solid; m.p. 97 °C; IR (KBr): 3028, 2960, 1701, 1610, 1563, 1482, 907 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.10 (t, *J* = 7.4 Hz, 3H), 2.91 (s, 3H), 4.11 (q, *J* = 7.4 Hz, 2H), 7.42-7.47 (m, 6H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.70 (t, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 15.4, 23.6, 61.4, 123.8, 125.7,

Table 3. Comparison of cyanuric chloride catalyst against reported catalysts

Entry	Catalyst	Loading (mol %)	Reaction Conditions	Time	Yield (%)	Ref.
1	*p*-TsOH	100	M.W./Oil bath 100 °C	3-10 min	86-96	[8a]
2	$NaAuCl_4.2H_2O$	2.5	EtOH/40-60 °C	6 h	54-93	[7d]
3	$CeCl_3.7H_2O$	25	CH_3CN/r.t.	1.5-5 h	65-95	[7i]
4	Diphenyl Phosphate	150	Neat/110 °C	4 min	53-78	[8c]
5	$ZnCl_2$, $SnCl_2$	150	EtOH/70 °C	3 h	70-94	[7e]
6	Ionic liquid	100	100 °C	3.3-6.0 h	88-96	[11]
7	$Zr(DS)_4$	10	H_2O-EtOH/Reflux	3.15 h	50-98	[10]
8	Cyanuric chloride	20	H_2O/r.t.	12.30-20 h	85-96	

126.1, 127.9, 129.2, 29.8, 141.2, 147, 154.2, 168.9; Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.32; H, 5.88; N, 4.80. Found: C, 78.30; H, 5.89; N, 4.78.

3c: Yellow solid; m.p. 193 °C; IR (KBr): 3054, 1712, 1603, 1575, 1209, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.21 (s, 6H), 2.26 (s, 2H), 2.39 (s, 2H), 7.22 (d, *J* = 8.7, 2H), 7.47-7.49 (m, 2H), 7.5 (t, *J* = 7.2 Hz, 1H), 7.74-7.76 (m, 4H); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 28.18, 31.99, 48.25, 54.02, 126.24, 127.26, 127.91, 127.98, 128.44, 131.27, 137.46, 148.91, 150.71, 160.94, 197.48; Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 5.30. Found: C, 83.66; H, 6.37; N, 5.27.

3d: Yellow solid; m.p. 143 °C; IR (KBr): 3057, 2935, 1608, 1577, 1480, 1212, 708 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.81-1.90 (m, 2H), 1.97-2.12 (m, 2H), 2.70 (t, *J* = 7.0 Hz, 2H), 3.23 (t, *J* = 7.2 Hz, 2H), 7.30-7.39 (m, 3H), 7.52-7.68 (m, 5H), 8.10 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 22.64, 22.76, 27.74, 33.99, 125.09, 125.47, 126.40, 127.44, 128.01, 128.32, 128.85, 136.88, 146.13, 158.71; Anal. Calcd for $C_{19}H_{17}N$: C, 87.99; H, 6.60; N, 5.40. Found: C, 87.96; H, 6.61; N, 5.41.

3e: White solid; m.p. 136 °C; IR (KBr): 3060, 2958, 1606, 1487, 826, 716 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.12 (m, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 3.19 (t, *J* = 7.0 Hz, 2H), 7.27-7.35 (m, 3H), 7.49-7.67 (m, 5H), 8.01 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 14.6, 22.7, 29.4, 34.8, 123.1, 125, 126.9, 127.8, 128.9, 133.7, 137.8, 147.2, 166.7; Anal. Calcd for $C_{18}H_{15}N$: C, 88.12; H, 6.16; N, 5.70. Found: C, 88.10; H, 6.18; N, 5.67.

3f: Yellow solid; m.p. 153 °C; IR (KBr): 3032, 2961, 1702, 1608, 1569, 1483, 909, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.90 (s, 3H), 2.61 (s, 3H), 7.30-7.33 (m, 2H), 7.50-7.60 (m, 5H), 7.91 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 31.6, 124.7, 125.8, 128.8, 129.1, 129.8, 130.8, 132.3, 134.5, 135.4, 142.9, 145.8, 153.8, 204.9; Anal. Calcd for $C_{18}H_{14}ClNO$: C, 73.09; H, 4.77; N, 4.73. Found: C, 73.07; H, 4.75; N, 4.75.

3g: Yellow solid; m.p. 125-127 °C; IR (KBr): 3060, 2980, 1720, 1600, 1221, 909, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.21 (t, *J* = 7.4 Hz, 3H), 2.83 (s, 3H), 4.13-4.17 (q, *J* = 7.1 Hz, 2H), 7.31-7.62 (m, 7H), 8.01 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (200 MHz, DMSO, d_6): δ = 13.31, 23.21, 61.14, 124.41, 125.21, 127.66, 128.47, 128.89, 128.99, 130.84, 130.97, 131.33, 134.13, 144.67, 145.46, 154.53, 167.06; Anal. Calcd for $C_{19}H_{16}ClNO_2$: C, 70.04; H, 4.94; N, 4.29. Found: C, 70.03; H, 4.91; N, 4.30.

3h: Yellow solid; m.p. 238-240 °C; IR (KBr): 3062, 2985, 1712, 1603, 1578, 1210, 735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.22 (s, 6H), 2.28 (s, 2H), 2.41 (s, 2H), 7.35-7.38 (m, 2H), 7.55-7.65 (m, 5H), 8.01 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 28.19, 31.99, 48.27, 54.04, 124.8, 125.8, 128.8, 129.1, 129.8, 130.8, 132.3, 134.5, 135.4, 142.9, 145.8, 153.8, 204.9; Anal. Calcd for $C_{21}H_{18}ClNO$: C, 75.10; H, 5.40; N, 4.17. Found: C, 75.07; H, 5.42; N, 4.18.

3i: Yellow solid; m.p. 158-160 °C; IR (KBr): 3060, 2945, 1606, 1575, 1480, 1215, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.49 (m, 2H), 1.57 (m, 2H), 2.54 (t, *J* = 6.5 Hz, 2H), 3.30 (t, *J* = 7.1 Hz, 2H), 7.32-7.34 (m, 2H), 7.59-7.70 (m, 5H), 7.98 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23, 28.2, 34.3, 124.6, 127.5, 128.2, 128.9, 129.1, 129.3, 129.5, 130.2, 131.3, 136.5, 144.8, 145.8, 159.6; Anal. Calcd for $C_{19}H_{16}ClN$: C, 77.67; H, 5.48; N, 4.76. Found: C, 77.64; H, 5.50; N, 4.73.

3j: White solid; m.p. 150-152 °C; IR (KBr): 3060, 2958, 1606, 1486, 715 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.12 (m, 2H), 2.90 (t, *J* = 7.4 Hz, 2H), 3.20 (t, *J* = 7.2 Hz, 2H), 7.30-7.36 (m, 2H), 7.55-7.59 (m, 5H), 8.01 (d, *J* = 8.6

Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3, 30.2, 35, 124.4, 126.9, 128.2, 128.6, 129, 130.3, 131.2, 134.3, 135.9, 141.8, 146.3, 167.7; Anal. Calcd for $C_{18}H_{14}NCl$: C, 77.27; H, 5.04; N, 5.00. Found: C, 77.23; H, 5.05; N, 4.97.

ACKNOWLEDGEMENT

More P. E. thanks UGC, New Delhi and Chairman, Agricultural Development Trust, Baramati for sanctioning Study leave.

Received June 19, 2008.

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