A simple, efficient and solvent-free reaction for the synthesis of quinolones using caesium iodide

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A series of quinoline derivatives has been synthesised from the reactions of 2-aminoacetophenone and 2-aminobenzophenone with different ketones in the presence of caesium iodide under solvent-free and thermal conditions. This method has the advantages of good yields, a clean reaction, simple methodology, short reaction times, easy work-up and green conditions.

Keywords: quinolones, caesium iodide, solvent-free, simple methodology, easy work-up, Friedländer synthesis

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] and antitumour agents like camptothecin[4] also contain quinoline nuclei. The benzo[5,6]pyrrolizino[1,2-*b*]quinoline system, which displays potent *in vitro* cytotoxic activity against MCF7 cells, is synthesised using the Friedländer quinoline synthesis as a key step.[3] Recently quinolines have also been shown to be potential agents for the treatment of erectile dysfunction as they exhibit 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 catalysed by both acids and bases, but the acids are more effective. Brønsted acids like hydrochloric acid, sulfuric acid, *p*-toluenesulfonic acid, citric acid and phosphoric acid have been widely used to effect the Friedländer condensation.[6–8] 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 side reactions. Lewis acids such as $ZnCl_2$,[9] $AuCl_3.3H_2O$,[10] $SnCl_2.2H_2O$,[11] $Bi(OTf)_3$,[12] LiOTf[13] and I_2[14] are also found to be effective in the Friedländer condensation, but the use of environmentally toxic $ZnCl_2$ and expensive $AuCl_3$ limits their application.

In order to avoid the toxic and chronic effects of organic solvents, the solvent-free microwave-assisted synthesis of quinolones was reported by Ranu *et al.*[15] and Song *et al.*[16] but these microwave-assisted syntheses are not suitable for large scale production. Since quinoline derivatives are increasingly useful and important in drugs and pharmaceuticals, the development of a simple, eco-benign and high-yielding protocol is desirable.

Recently we reported the efficiency of caesium iodide as a convenient catalyst for the synthesis of *N*-substituted azepines under aqueous conditions. These one-pot three-component cyclisations were carried out by the reaction of aromatic amines, 2,5-dimethoxytetrahydrofuran and dimethyl/diethyl acetylenedicarboxylates in high yield at ambient temperature.[17]

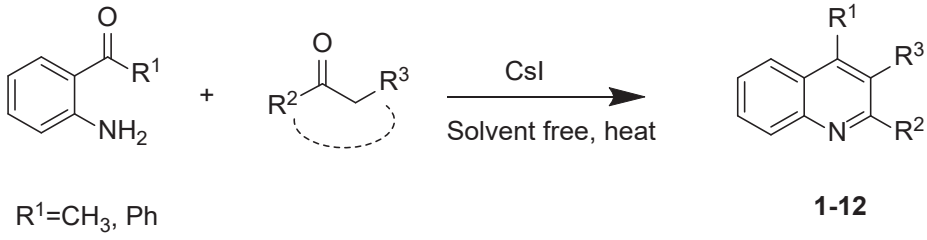
Here we report a simple, efficient and solvent-free synthesis of quinolines by using caesium iodide under thermal conditions. Thus the treatment of *o*-amino-substituted aromatic ketones with dicarbonyl compounds in the presence of caesium iodide leads to the formation of various 2,3,4-trisubstituted quinolines (Scheme 1) in excellent yields and in short reaction times.

Results and discussion

For the reaction between 2-aminoacetophenone and dimedone, to minimise the formation of byproducts and to achieve good yields of the desired product **1**, the reaction was optimised by varying the amount of CsI catalyst (Table 1). The yields of the product with 3, 5, 10 and 15 mol% of catalyst are 73%, 80%, 95% and 78%, respectively (Table 1, entries 2–5). The same reaction when performed without catalyst for 5 h gave a low yield of product **1**. When the catalyst was increased to 20 mol%, the product yield decreased to 70% (Table 1, entry 6). Therefore, it was found that the use of 10 mol% of the catalyst was optimum.

To further optimise the reaction conditions, we conducted the Friedländer condensation of 2-aminobenzophenone with ethyl acetoacetate to the form desired quinoline **10** in the presence of catalyst (10 mol%) in different solvents such as CH_2Cl_2, EtOH, MeOH, CH_3CN and $CHCl_3$ (Table 2, entries 1–5). Reaction in $CHCl_3$ and dichloromethane (DCM) gave low product yields even after 16 h (Table 2, entries 1 and 2) and the yields were moderate in the case of methanol, acetonitrile and ethanol under reflux (Table 2, entries 3–5). The best results were obtained when the reaction was carried out in solvent-free conditions at 100 °C for 30 min in the presence of catalyst (Table 2, entry 6). Therefore, solvent-free conditions were selected for the reaction.

Our investigations clarified that the best results can be obtained when the reaction was performed in the absence of solvent at 100 °C using 10 mol% of CsI as catalyst. The results of the reaction between 2-aminoacetophenone and 2-aminobenzophenone with various carbonyl compounds in



Scheme 1

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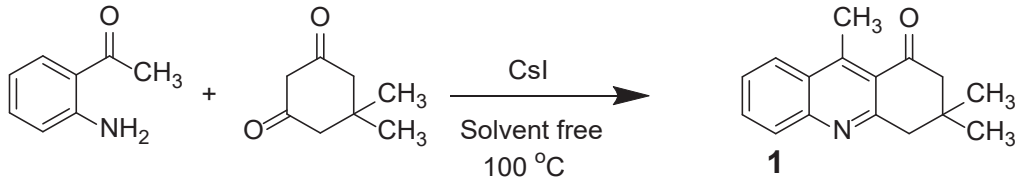
Table 1 Effect of amount of catalyst on the synthesis of compound **1**

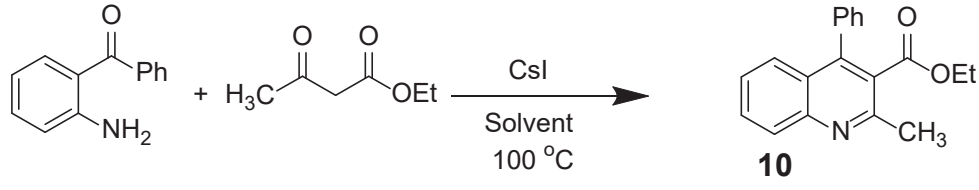


Entry	Catalyst/mol%	Time/h	Yield/%[a,b]
1	–	5	43
2	3	2	73
3	5	1	80
4	10	0.5	95
5	15	1	78
6	20	1.5	70

[a]Isolated yield of product **1**.

[b]Reaction conditions: 2-aminoacetophenone (1.2 mmol), dimedone (1.0 mmol) in the presence of CsI catalyst under solvent-free conditions.

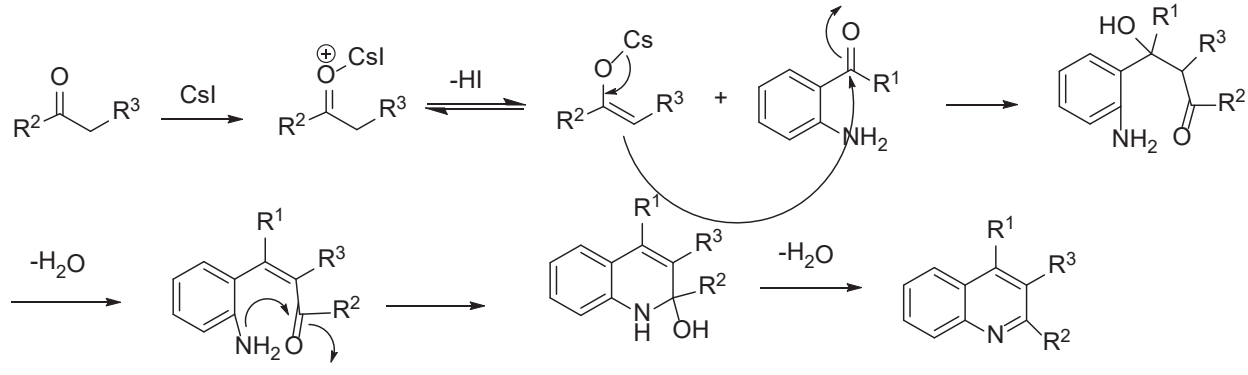
Table 2 Effect of solvent on the reaction times and yields of compound **10**[a]



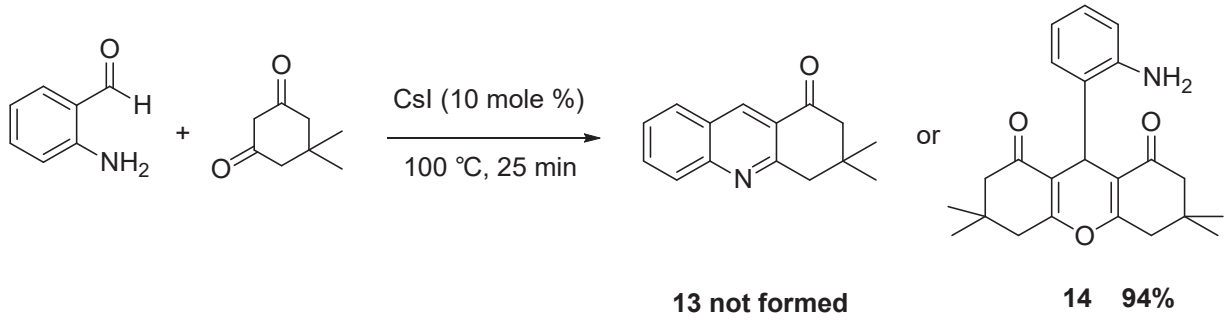
Entry	Solvent	Temperature/°C	Time/h	Yield/%[b]
1	CH_2Cl_2	38	16	30
2	$CHCl_3$	60	16	27
3	CH_3CN	82	16	78
4	MeOH	63	16	62
5	EtOH	78	16	73
6	–	100	1	93

[a]Reaction conditions: 2-aminobenzophenone (1.2 mmol), ethyl acetoacetate (1.0 mmol) in the presence of CsI catalyst (0.1 mmol) under reflux in various solvents.

[b]Isolated yield of product **10**.

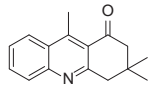
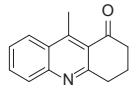
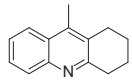
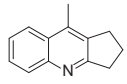
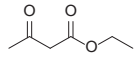
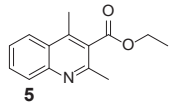
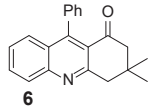
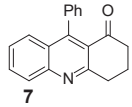
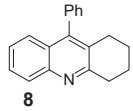
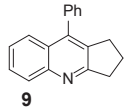
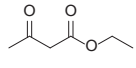
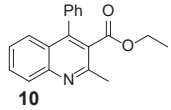
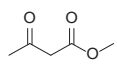
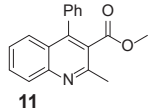
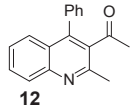


Scheme 2 Proposed mechanism.



Scheme 3

Table 3 Synthesis of quinoline derivatives in the presence of CsI[a]

Entry	R^1	Ketone	Product	Time/min	Yield/%[b]
1	CH_3		 **1**	30	93
2	CH_3		 **2**	35	96
3	CH_3		 **3**	45	88
4	CH_3		 **4**	55	85
5	CH_3		 **5**	60	74
6	Ph		 **6**	45	89
7	Ph		 **7**	40	93
8	Ph		 **8**	50	84
9	Ph		 **9**	70	80
10	Ph		 **10**	60	93
11	Ph		 **11**	50	79
12	Ph		 **12**	50	80

[a]Reaction conditions: 2-aminoacetophenone or 2-aminobenzophenone (1.2 mmol), α-methylene carbonyl compound (1.0 mmol) in the presence of CsI catalyst (0.1 mmol) under solvent-free conditions at 100 °C.

[b]Isolated yield of products.

the presence of caesium iodide under solvent-free conditions at 100 °C are shown in Table 3.

According to Table 3, a series of polyfunctionalised quinolines were easily prepared in excellent yields by a Friedländer reaction of *o*-aminoaryl ketones with α-methylene ketones using caesium iodide as a catalyst under solvent-free conditions. In these reactions, among α-methylene carbonyl compounds, dimedone and 1,3-cyclohexanedione gave better isolated yields. In the case of cyclic ketones, acridine derivatives were obtained in high yields. Acylic dicarbonyl compounds also gave 2,3,4-trisubstituted quinolones in high yields.

The suggested mechanism of the CsI catalysed transformation is shown in Scheme 2. Caesium iodide is suggested to catalyse efficiently enol formation, dehydration and final condensation.

We decided to attempt to prepare acridinone **13** by reaction of 2-aminobenzaldehyde with dimedone under optimised reaction conditions. (Scheme 3). Unexpectedly, xanthene derivative **14** was formed in 94% yield instead of compound **13**.

Experimental

Chemicals and apparatus

All solvents, reagents and compounds were purchased from Merck and Fluka. FTIR spectra were recorded on an AVATAR-370-FTIR Thermo Nicolet. Mass spectra were recorded on a Varian Mat CH-7 instrument at 70 eV. Reactions were monitored by TLC using silica gel plates and the products were identified by comparison of their spectra and physical data with those of the authentic samples. Melting points were measured on an Electrothermal 9100 apparatus. NMR spectra were recorded on an ASPECT 3000 Avance Brucker-400 MHz spectrometer. All chemical shifts in NMR experiments are reported as ppm and were referenced to residual solvent.

Synthesis of quinolines **1**–**12** *and xanthene* **14***; general procedure*

Typically, 2-aminoacetophenone or 2-aminobenzophenone (1.2 mmol) with an enolisable ketone (1 mmol) was uniformly mixed with CsI (20 mg, 10 mol%) at 100 °C. After reaction completion, as indicated by TLC, the reaction mixture was cooled, diluted with CH_3CN (5 mL) and filtered. The filtrate was concentrated and the product was recrystallised or purified by column chromatography (for spectroscopic characterisation) on silica gel using ethyl acetate/*n*-hexane as eluent.

*3,3,9-Trimethyl-3,4-dihydroacridin-1(2*H*)-one* (**1**): Yield 93%; m.p. 95 °C (lit.[18] not reported); IR (KBr, cm^{-1}): 2962, 2955, 2921, 2864, 2845, 1681, 1672, 1560, 1215, 762; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.23 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.78 (dt, *J* = 6.9, 1.2 Hz, 1H), 7.58 (dt, *J* = 6.9, 1.2 Hz, 1H), 3.19 (s, 2H, CH_2), 3.08 (s, 3H, CH_3), 2.68 (s, 2H, CH_2), 1.15 (s, 6H, $2CH_3$); MS (*m/z*): 239 (M^+), 237, 222, 209, 194, 182, 153, 139, 115, 71.

*9-Methyl-3,4-dihydroacridin-1(2*H*)-one* (**2**): Yield 96%; m.p. 63–64 °C (lit.[19] 64–66 °C); IR (KBr, cm^{-1}): 3061, 2944, 2871, 1677, 1603, 1563, 1374, 855; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.20 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.77 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.57 (dt, *J* = 8.0, 1.2 Hz, 1H), 3.27 (t, *J* = 6.9 Hz, 2H), 3.04 (s, 3H), 2.8 (t, *J* = 6.4 Hz, 2H), 2.20 (quint, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl3): δ 197.9, 162.2, 151.6, 148.4, 137.5, 131.8, 129.9, 128.1, 128.0, 127.5, 40.6, 34.4, 22.7, 21.5; MS (*m/z*): 211 (M^+), 209, 182, 166, 139, 126, 85, 71.

9-Methyl-1,2,3,4-tetrahydroacridine (**3**): Yield 88%, m.p. 74–75 °C (lit.[19] 76–77 °C); IR (KBr, cm^{-1}): 2930, 2859, 1638, 1581, 1451, 1380, 750; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.69 (t, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 3.27 (m, 2H), 2.9 (m, 2H), 2.64 (s, 3H), 1.98 (m, 4H); MS (*m/z*): 197 (M^+), 182, 167, 153, 128, 115, 77.

*9-Methyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline* (**4**): Yield 85%; m.p: 57–58 °C (lit.[19] 58–60 °C); IR (KBr, cm^{-1}): 3227, 2982, 1593, 1377, 1212; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.2 Hz,

1H), 3.18 (t, *J* = 7.6 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.59 (s, 3H), 2.21 (quint, *J* = 7.6 Hz, 2H); MS (*m/z*): 182 (M^+), 167, 154, 127, 83, 71.

3,3-Dimethyl-9-phenyl-3,4-dihydroacridin-1(2H)-one (**6**): Yield: 89%; m.p. 189–190 °C (lit.[20] 191 °C); IR (KBr, cm^{-1}): 3068, 3035, 2949, 2937, 2892, 2864, 1687, 1605, 1560, 1484, 1220, 772, 697; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.78 (dt, *J* = 6.8, 1.6 Hz, 1H), 7.47–7.55 (m, 4H), 7.43 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.2 (dd, *J* = 7.2, 1.6 Hz, 2H), 3.29 (s, 2H, CH_2), 2.59 (s, 2H, CH_2), 1.18 (s, 6H, $2CH_3$); MS (*m/z*): 301 (M^+), 299, 270, 244, 216, 196, 85, 71.

9-Phenyl-3,4-dihydroacridin-1(2H)-one (**7**): Yield: 93%; m.p. 153–155 °C (lit.[21] 153–156 °C); IR (KBr, cm^{-1}): 3043, 2948, 2876, 1689, 1555, 1486, 764, 703; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.79 (dt, *J* = 6.4, 1.6 Hz, 1H), 7.50–7.55 (m, 3H), 7.48 (dd, *J* = 6.4, 1.6 Hz, 1H), 7.42 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.20 (dd, *J* = 6.8, 1.6 Hz, 1H), 3.40 (t, *J* = 6.8 Hz, 2H), 2.73 (t, *J* = 6.8 Hz, 2H), 2.28 (quint, *J* = 6.8 Hz, 2H); MS (*m/z*): 273 (M^+), 270, 242, 215, 200, 188, 175, 150, 135, 108, 85, 71.

9-Phenyl-2,3-dihydro-1H-cyclopenta[b]quinoline (**9**): Yield: 80%; m.p. 132–133 °C (lit.[22] 132–134 °C); IR (KBr, cm^{-1}): 3057, 3029, 2962, 2918, 1568, 1487, 1432, 1384, 1341, 1310, 764; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.09 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.61–7.68 (m, 2H), 7.51–7.57 (m, 2H), 7.49 (tt, *J* = 8.0, 1.2 Hz, 1H), 7.35–7.42 (m, 3H), 3.26 (t, *J* = 7.6 Hz, 2H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.18 (quint, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl3): δ 167.4, 148.0, 142.6, 136.8, 133.6, 129.3, 128.8, 128.5, 128.2, 127.9, 126.2, 125.6, 125.4, 35.2, 30.3, 23.5; MS (*m/z*): 245 (M^+), 243, 215, 201, 188, 168, 167, 138, 120, 108.

9-(2-Aminophenyl)-3,3,6,6-tetramethyl-3,4,5,6,7,9-hexahydro-1H-xanthene-1,8(2H)-dione (**14**): Yield: 94%; m.p. 190–191 °C; IR (KBr, cm^{-1})**:** 3197, 2949, 2925, 2868, 1643, 1593, 755; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.47 (bs, NH2), 7.15 (dt, *J* = 7.0, 1.2 Hz, 1H), 6.59–7.05 (m, 3H), 4.66 (s, 1H), 2.60 (d, *J* = 7.0 Hz, 1H), 2.47 (d, *J* = 7.0 Hz, 1H), 2.3–2.4 (m, 4H), 1.99 (d, *J* = 7.0 Hz, 1H), 1.94 (d, *J* =7.0 Hz, 1H), 1.12 (s, 3H), 1.03 (s, 3H), 0.99 (s, 6H); MS (*m/z*): 365 (M^+), 364, 280, 265, 226, 210, 171, 149, 134, 107, 83, 78. Anal. calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83; found: C, 75.34; H, 7.38; N, 3.71%.

The melting points of the other products were: **8**, 135–137 °C (lit.[22] 136–138 °C; **10**; 99–102 °C (lit.[22] 100–102 °C); **11**, 86–97 °C (lit.[22] 86–88 °C); **12**, 109–110 °C (lit.[22] 108–110 °**C**) and compound **5** was an oil (lit.[19] oil).

Conclusion

In conclusion, a one-pot, mild, efficient, and environmentally benign protocol has been developed for the synthesis of quinoline derivatives catalysed by caesium iodide in high yields.

Compared to previously reported methods, moreover, the mild reaction conditions, easy work-up, clean reaction profiles, lower catalyst loading and cost efficiency render this approach as an interesting alternative.

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