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ORIGINAL PAPER

Effective water mediated green synthesis of polysubstituted quinolines without energy expenditure

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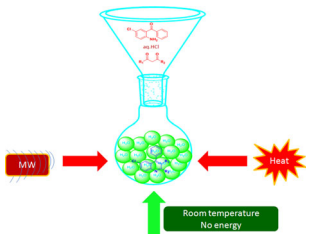
Abstract This study explores a green methodology for the synthesis of polysubstituted quinolines through Friedländer annulation using water as a solvent. To evaluate the viability of this methodology, results obtained were compared with methods involving the usage of energy, such as mechanical stirring, heating, microwave irradiation, and solvent free heating reaction. To demonstrate the efficiency and consistency of this method, a bulk batch reaction has been performed using this protocol and many quinoline derivatives have been synthesised and characterised by ^{1}H, ^{13}C NMR, melting range, and HR-MS.

Graphical abstract



Keywords Microwave · Friedländer annulation · Green chemistry

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Introduction

Quinoline derivatives have wide range of applications from medicine [1] to materials [2, 3]. Most of the polysubstituted quinolines were synthesised by Friedländer annulation. A large number of modifications have been carried out in the Friedländer synthesis [4], though the modifications and developments are keep going in the same field, every seconds are peeling out old skin and getting new of its own. After the discovery of Friedländer quinoline synthesis, numerous strategies have been developed to synthesise quinoline by changing starting precursors, catalysts, reaction conditions, using different energy sources (conventional heating [5] and microwave irradiation [6]).

Generally, Friedländer reactions were performed either in the presence of base as a catalyst or high temperature reflux in solvent in the absence of catalyst. Initially, Kempter and co-workers modified the Friedländer annulation using hydrochlorides of *o*-aminoarylketones and they reported that acids are more favourable catalysts than the bases [4]. Subsequently, scientists were invaded to use acid catalyst for the synthesis of quinoline. In recent years, many literatures can be found on simplifying Friedländer annulation using Lewis acids [7, 8], metal salts [9–12], metal nano particles [13, 14], Lewis acid surfactant combined catalyst [15], iodine [16], chitosan-SO_3H [17], propylphosphonic anhydride (T_3P) [18, 19], hydrochloric acid (HCl) [20], sulfuric acid (H_2SO_4) [21], trifluoroacetic acid (TFA) [22], *p*-toluenesulfonic acid [23]. Unfortunately, these techniques suffer from harsh reaction conditions, unfavourable for large scale, expensive catalyst usage, inadequate catalyst reusability, power consumption, hazardous reagents, organic solvents, and waste disposal.

It is essential to develop a method for the synthesis of polysubstituted quinolines in bulk scale. When considering

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the kilogram level of transformation, the process should be inexpensive, reproducible, lesser power conceptive, good yield and less wastage productive, less hazardous, benign, involving mild reaction condition and benign solvent usage [24], but there is no perfect green solvent for all type of reactions [25]. Water is an innocuous solvent [26], and hence mostly used in green synthesis [27]. The present work made an attempt to simplify the Friedländer annulation and established a methodology without any energy expenditure in the presence of aqueous hydrochloric acid in water medium at room temperature. We have chosen green solvents (water) and have carried out the experiments and evaluated the efficiency of the solvent towards synthesis of quinolines by Friedländer annulations without energy expenditure. The newly developed procedure has been applied to prepare various reported polysubstituted quinoline derivatives and extended to unreported derivatives as well.

Results and discussion

Initially, we carried out the synthesis of quinoline derivatives with trifluoroacetic acid, sulfuric acid, and hydrochloric acid as a catalyst in water at room temperature (RT) without shaking, stirring, heating, microwave irradiation, or sonication. Trifluoroacetic acid and sulfuric acid have shown comparable results with hydrochloric acid, but trifluoroacetic acid and sulfuric acid are corrosive and are not benign. Hence, we specifically focused on hydrochloric acid and used it as a catalyst.

We performed reactions at room temperature by treating 2-amino-5-chlorobenzophenone, acetylacetone, hydrochloric acid in water with different ratio of precursors. In water, 2-amino-5-chlorobenzophenone was not consumed completely in absence of hydrochloric acid in 1:1:1 ratio. To fix the exact ratio of starting intermediate, we performed reaction in water with different proportion of reactants. When we increased the amount of diketone from 1.5 to 2.0 equivalents with fixed proportion of hydrochloric acid there was no change in conversion then, we increased the hydrochloric acid proportion from 1.0 to 3.0 equivalents and observed that the yield was increased to 45 % but reaction was not completed. When the amount of diketone was increased to 2.2 equivalents then the reaction was found to be completed. Finally, 1:2.2:3 (2-amino-5-chlorobenzophenone, acetylacetone, hydrochloric acid) equivalent ratio gave the maximum yield with completion of reaction. Results were furnished in Table 1.

Subsequently, the optimised reaction conditions was extended to various electron donating and electron releasing group substituted *o*-aminoarylketone, aromatic diketone, aliphatic diketone, chlorodiketone, aliphatic ketoester, aliphatic cyclic ketone, cyclic diketone, aryldiketone, *N*-methylpiperidone, *N*,*N*-dimethylacetamide to get the corresponding quinoline derivative and to prove the generality of the reaction.

The lesser yield may be attributed with the heterogeneity of reaction mixture. Due to this heterogeneity, water mediated reactions required additionally one more equivalent diketone. The additional equivalent of a diketone may complete the reaction by increasing the availability of diketone and the proximity of starting material. The water mediated reaction has not resulted in the formation of few compounds (**5**, **6**, **8**, **9**, **10**, **24**). It might be due to inadequate solubility of solid diketones. These reactions to afford compounds **5**, **6**, **8**, **9**, **10**, **24** were not found to proceed in different proportion of water and methanol mixture (50:50, 25:75) also. Though water mediated process requires an additional equivalent of starting material, it can be regarded as a benign process using green solvent without the need of distillation. The work up was done simply by adding the

Table 1 Optimisation of reaction conditions

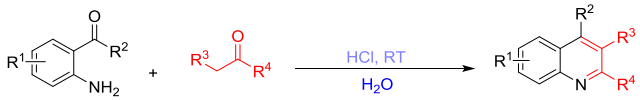
Entry	HCl/eq.	Diketone/eq.	Solvent	Time/h	Yield/%
1	–	1.0	MeOH	24	No product
2	1.0	1.0	Water	24	Traces
3	1.0	1.5	Water	24	26[b]
4	1.0	2.0	Water	24	29[b]
5	1.5	2.0	Water	24	52[b]
6	2.0	2.0	Water	24	67[b]
7	2.5	2.0	Water	24	73[b]
8	3.0	2.0	Water	24	75[b]
9	3.0	2.2	Water	16	90[a]

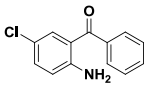
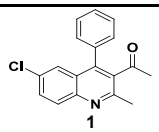
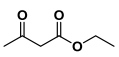
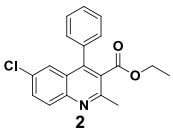
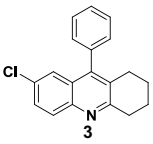
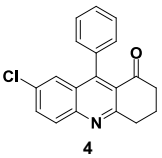
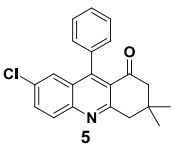
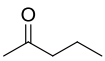
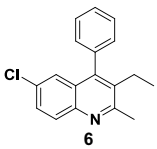
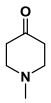
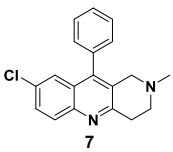
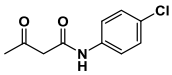
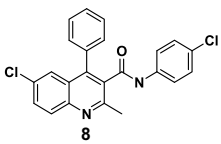
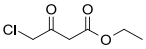
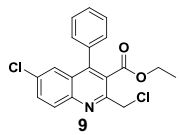
Reaction conditions: HCl and diketone have been taken with respect to 1 eq of *o*-aminoketone

[a] *o*-Aminoketone 100 % conversion

[b] *o*-Aminoketone not 100 % conversion

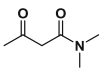
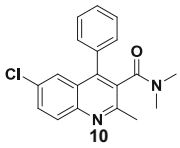
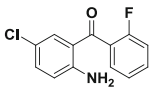
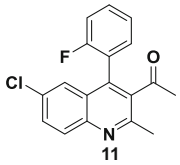
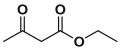
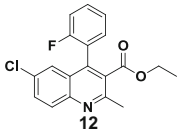
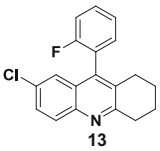
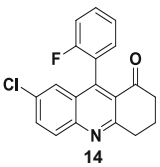
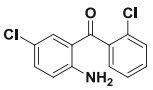
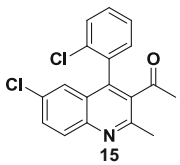
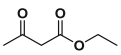
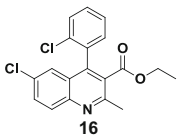
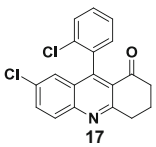
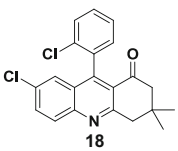
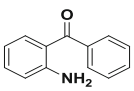
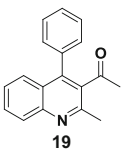
Table 2 Yield and reaction time of water mediated quinoline synthesis in the presence of HCl at RT



Entry	*o*-Aminoaryl-ketone	Diketone	Product	Time / h	Yield	M.p./°C (Lit.)
1			 **1**	16	90	221–223 (151–154 [21])
2			 **2**	19	78	98–100 (102–105 [21])
3			 **3**	5	86	225-227 (225-227 [6])
4			 **4**	14	85	228–232 (185–189 [22])
5			 **5**	24	–	
6			 **6**	24	–	
7			 **7**	5 days	73	140–143
8			 **8**	24	–	
9			 **9**	24	–	106–108 (105–106 [9])

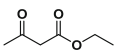
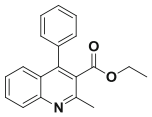
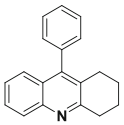
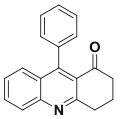
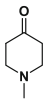
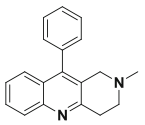
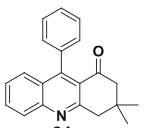
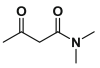
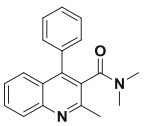
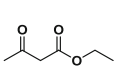
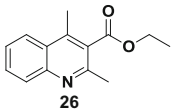
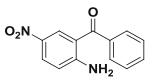
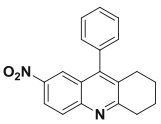
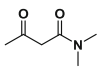
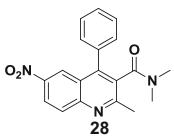
solution of $NaHCO_3$ (pH around 9–10) into the reaction mixture. After the addition of $NaHCO_3$ solution, the solid obtained was filtered and washed with water to afford the product. It may applicable for cost effective preparation of some quinoline derivatives. Yield and reaction time were furnished in Table 2.

Table 2 continued

Entry	*o*-Aminoaryl-ketone	Diketone	Product	Time/h	Yield	M.p./°C (Lit.)
10			 **10**	24	63	222–225
11			 **11**	14	79	122–126 (140–142 [20])
12			 **12**	16	81	120–122 (120–121 [20])
13			 **13**	6	84	168–171 (172–174 [20])
14			 **14**	5	82	216–220 (170–172 [20])
15			 **15**	16	79	129–131
16			 **16**	14	80	102–106
17			 **17**	12	83	180–183
18			 **18**	24	–	
19			 **19**	19	84	170–176 (168–170 [9])

To prove the nonenergy expenditure nature of this process, we have done same experiments under different external force like mechanical stirring, heating, microwave irradiation, and solvent free heating condition then compared the results with non-energy expenditure method (Fig. 1). When we carried out reaction under stirring with

Table 2 continued

Entry	*o*-Aminoaryl-ketone	Diketone	Product	Time/h	Yield	M.p./°C (Lit.)
20			 **20**	19	84	109–110 (96–100 [9])
21			 **21**	5	89	140–142 (138 [28])
22			 **22**	5	84	153–154 (158 [14])
23			 **23**	11 days	82	98-100
24			 **24**	24	–	
25			 **25**	18	68	232–236
26			 **26**	12	74	Oil
27			 **27**	14	78	155–160
28			 **28**	16	67	158–161

different RPM (rotation per minute) no change in the reaction time and yield was observed in both solvents. When reaction mass was heterogeneous, reactants will be static to make collision it requires external force like stirring or shaking. In the homogenous mixture, due to molecular rotations and vibrations, collision will take place effortlessly without external force. This may be the reason why there was no difference in yield and reaction time in the processes with and without the energy expenditure. Same reactions were performed under conventional heating and microwave irradiation. Conventional heating (90 °C) acquired 5 h. Under microwave irradiation (340 W) reaction was completed within 10 min.

Isolation of product was simply by filtration and washing with $NaHCO_3$ and water. No column chromatography was used for the product purification. Compound **26** is a liquid in nature; we used diethyl ether for extraction. To exhibit the consistency of the process, we performed 50 g

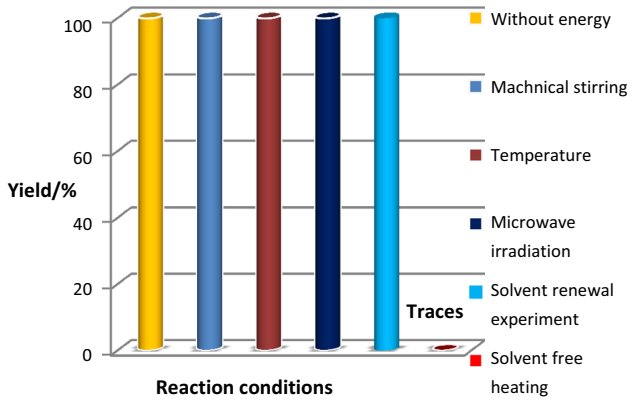


Fig. 1 Comparison of non-energy expenditure process with energy required process

(21.6 mmol 2-amino-5-chlorobenzophenone, 47.52 mmol of acetylacetone, 64.8 cm^3 of hydrochloric acid) batch size reaction in a 1 dm^3 beaker without agitation kept the reaction mixture for appropriate time (Scheme 1). Reaction mixture was slowly added into a 200 cm^3 of 20 % sodium bicarbonate solution, solid obtained was filtered and washed with 200 cm^3 water and then with 33 cm^3 of diethyl ether.

We performed experiments using 1 eq of *o*-aminoketone, 6 eq of diketone in solvent free heating condition (120 °C). Reactions were not completed and only a few combinations of reactants shown the traces product formation in TLC (**1**, **2**, **19**, **20**).

Conclusions

This work explored green methodology for the synthesis of quinoline derivatives. The advantage of this method is cost effectiveness and benign process since it involves water as a solvent and no energy expenditure. Also, this work was a successful method for the preparation of polysubstituted quinolines in large scale to confirm the efficiency of the method. Pure compounds were obtained without the use of noxious organic solvents (no column chromatography was performed). This green methodology was evaluated by comparing with the processes involving energy expenditure, such as stirring, heating, microwave irradiation, and solvent free heating reaction. Using these protocols successfully, 22 compounds were synthesised and characterised.

Experimental

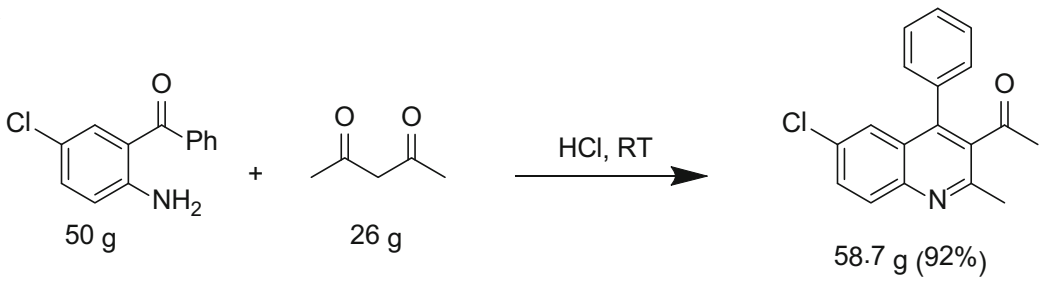
All chemicals and regents were used for experiments which are commercially available and used without further purification. Reactions were monitored by TLC. NMR spectra were recorded on Bruker Avance 400 MHz spectrometer, with TMS as an internal standard. Chemical shift values were expressed in parts per million (ppm). Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; bs broad singlet. The melting range of synthesised compounds was determined by Elchem Microprocessor based DT apparatus using an open capillary tubes and are calibrated with benzoic acid.

General synthesis of polysubstituted quinolines

HCl (10 N, 3.0 cm^3) was added to 10 mmol of aminoarylketone and 15 cm^3 of distilled water followed by 22 mmol of diketone; the reaction mixture was allowed to be placed at room temperature for appropriate time without agitation. The completion of reaction was confirmed by TLC. Reaction mixture was basified with 10 cm^3 20 % $NaHCO_3$ and the solid was filtered and washed with 20 cm^3 water followed by 1.5 cm^3 diethyl ether, then dried over air.

8-Chloro-2-methyl-10-phenyl-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridine (**7**, $C_{19}H_{17}ClN_2$)
Pale yellow crystal; m.p.: 140–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.32$ (s, 3H), 2.78 (t, 2H), 3.32 (t, 2H), 7.23–7.14 (m, 3H), 7.50–715 (m, 4H), 7.88 (d, $J = 9.2$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 33.8$, 46.1, 52.8, 56.7, 124.6, 126.8, 127.1, 128.4, 128.8, 128.9, 129.7, 130.1, 131.5, 135.2, 144.2, 145.1, 156.3 ppm.

Scheme 1



6-Chloro-N,N,2-trimethyl-4-phenylquinoline-3-carboxamide (**10**, $C_{19}H_{17}ClN_2O$)
White crystal; m.p.: 222–225 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.58$ (s, 3H), 2.85 (s, 3H), 3.15 (s, 3H), 7.38 (m, 1H), 7.65–7.56 (m, 4H), 7.77 (d, $J = 2.4$ Hz, 1H), 7.94–7.91 (m, 1H), 9.04 (d, $J = 8.8$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.0$, 34.4, 37.7, 123.8, 125.9, 127.0, 128.5, 128.6, 129.4, 129.6, 130.9, 131.8, 131.9, 135.0, 136.4, 137.0, 151.5, 154.4, 164.1 ppm.

2-Methyl-10-phenyl-1,2,3,4-tetrahydrobenzo[b][1,6]naphthyridine (**23**, $C_{19}H_{18}N_2$)
Brown crystal; m.p.: 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.39$ (s,3H), 2.86 (q, 2H), 3.34 (t, 2H), 3.41 (s, 2H), 7.34–7.23 (m, 3H), 7.64–7.48 (m, 4H), 8.03 (d, $J = 8.4$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 33.8$, 46.1, 52.9, 56.9, 125.6, 125.8, 126.4, 128.1, 128.5, 128.7, 128.7, 128.9, 136.0, 144.9, 146.8, 155.9 ppm.

N,N,2-Trimethyl-4-phenylquinoline-3-carboxamide (**25**, $C_{19}H_{18}N_2O$)
Orange crystal; m.p.: 231–236 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.58$ (s, 3H), 2.85 (s, 3H), 3.17 (s, 3H), 7.37 (d, $J = 7.2$ Hz, 1H), 7.60–7.58 (m, 4H), 7.84–7.73 (m, 2H), 8.04–8.00 (m, 1H), 9.07 (d, $J = 8.8$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.8$, 34.4, 37.7, 122.1, 126.1, 127.1, 128.3, 128.8, 129.4, 129.4, 129.8, 130.6, 130.8, 132.5, 152.6, 154.0, 164.5 ppm.

N,N,2-Trimethyl-6-nitro-4-phenylquinoline-3-carboxamide (**28**, $C_{19}H_{17}N_3O_3$)
Off-white solid; m.p.: 158–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.63$ (s, 3H), 2.73 (s, 3H), 2.73 (s, 3H), 7.60–7.37 (m, 6H), 7.97 (d, $J = 2.4$ Hz, 1H), 7.99 (d, $J = 2.4$ Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.0$, 33.3, 37.1, 124.8, 126.3, 127.5, 128.3, 128.6, 128.8, 129.2, 129.4, 130.9, 132.0, 132.3, 133.2, 141.6, 146.0, 154.8, 165.5 ppm.

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