A One Step Synthesis Of Polyfunctional Quinoline Using Heterogeneous Silica Chloride As Catalyst Under Sonic Condition

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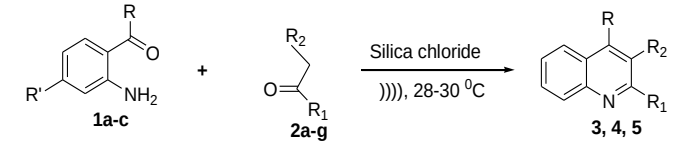
Abstract: A simple, rapid and efficient method for the preparation of polyfunctional quinoline derivatives by the reaction of 2-aminobenzophenone with ketones or 1,3-diketones in the presence of silica chloride under heterogeneous, solvent-free and sonic condition is reported. The significant features of this method are short reaction times, high yields of the products, mild reaction condition, solvent-free reaction, economy, non-toxicity and reusability of the catalyst.

Index Terms: 2-aminoaryl ketones, 1,3-diketones, room temperature reaction, polyfunctional Quinoline, Silica Chloride, solvent-free reaction and Ultrasound.

1 INTRODUCTION

Quinoline rings are of great interest, they represent a major class of heterocycles because of their presence in many pharmacologically significant compounds and in some bioactive natural products like Luotonin A and Camptothecin [1-3]. They have various biological activities like antimalarial, anti-asthmatic, anti-hypertensive, anti- inflammatory and tyrokinase PDGF-RTK inhibiting agents [4-6]. They act as precursors for the preparation of nano-meso structures and polymers that are used for enhancing electronic, optoelectronic or non-linear optical properties along with mechanical properties. Although the classical methods [7] like Miller, Combes, Conrad-Limpach-Knorr, Niementowski and Pfitzinger reactions have been developed for the synthesis of quinoline building blocks, Friedlander annulations reported by Friedländer in the year 1882 [8] is considered to be the most simple and easy approach for the synthesis of poly-substituted quinolines The condensation of 2-aminoaryl aldehydes or ketones and carbonyl compounds containing active methylene functionality under acidic and basic conditions for the synthesis of quinolines is termed as Friedlander annulations. Thermal and basic conditions are unfavourable for the reaction of *o*-aminobenzophenone with cyclohexanone, desooxybenzoin and *β*-ketoesters [9,10]. The most common protocols for the Friedlander reaction are the presence of Lewis acids such as $FeCl_3$, $Mg(ClO_4)_2$, $CuSO_4{\cdot}5H_2O$, $FeSO_4{\cdot}7H_2O$, $SnCl_2$, $AlCl_3$, $Bi(OTf)_3$, $Sc(OTf)_3$, $CeCl_3{\cdot}7H_2O$, silver phosphotungstate, molecular iodine, sodium fluoride and $NaAuCl_4{\cdot}2H_2O$ [11,12]. A few reactions have also been carried out under microwave irradiation. Most of the developed methods suffer from harsh reaction conditions, low yields, high temperature, tedious work-up and the use of stoichiometric and relatively expensive reagents. In continuation of our work on the development of green chemistry protocols [13-16], we herein are reporting of a general and effective one-step procedure for the synthesis of poly substituted quinolines under sonic condition as shown in the **Scheme 1**. Reactions on solid-supports under solvent-free conditions are currently the subject of interest; they provide an attractive and practical means of exploring organic synthesis. The advantages of using these silica supported catalyst instead of their solution phase counterparts in organic synthesis are that they are (a) less toxic and (b) it is easier to prepare and to handle (b) after the completion of reaction these solid catalyst can be separated from the product by a simple filtration, thus the purification protocols including chromatography and liquid-liquid extractions, which are time consuming are not required. (c) the catalyst is cheap hence Large quantity of reagent can be used, thus driving the reaction to completion, hence it is easy to scale up (d) One-pot multiple step/ multi-component reactions are easier to carry out using silica supported catalyst. The silica–supported reagent also have a number of advantages over the polymeric counterparts, such as, (a) Silica neither shrinks nor swells in any solvent and, it does not partially dissolve in any solvent either. (b) It is free flowing and thus easy to weigh out and handle (c) It does not require extensive washing for high recoveries and it won't stick to glassware (c) Most silica bond reagents and scavengers can withstand temperatures of over 200 °C and are suitable for use in microwave synthesizers [17,18]. Sonochemistry is a unique and distinctive chemistry, in which the physical properties of the medium may have a decisive effect on chemical reactivity. The reactions carried out under sonochemical conditions are considered to be a clean and green protocol [19,20]. When sound waves pass through liquid medium, they induce vibrational motion to the medium, the solvent molecules then compress, stretch and oscillate around their mean position due to time-varying pressure, at a point when the intensity of the sonic waves is higher enough to break the intermolecular forces existing between the solvent molecules it breaks down and a cavity is formed. The process of generating cavitational bubble is called acoustic cavitation [8]. The driving force for sonochemical reaction is the formation of cavitation; hence the general requirement for these reactions is that at least one of the reactants should be a liquid. J.-L Luche [8b] has divided the sonochemical reaction into three types based on the chemical effects induced by cavitation they are Homogeneous systems, Heterogeneous systems proceeding *via* ionic intermediates and Heterogeneous reactions which include a radical pathway or a mixed mechanism *i.e.* radical and ionic. Other effects were considered to be were considered to be physical rather than chemical and judged to be 'false' sonochemistry.



1a=2-aminobenzopheneone
1b=2-amino, 4-chloro benzopheneone
1c =2-aminoacetophenone

2a=ethyl acetoacetate
2b=methylacetoacetate
2c=acetylacetone
2d=cyclohexanone
2e=cyclopentanone
2f=cyclohexyl-1,3-dione
2g=dimedone

3 [1a,2a-g]
4 [1b,2a-g]
5 [1c,2a,b,c,d,g]

Scheme 1: synthesis of poly substituted quinoline under sonic condition

2. Materials and Methods

2.1 *Materials and instrument*

Commercially available reagent grade chemicals were used as received. All reactions were followed by TLC on E. Merck silica gel 60 F_{254} plates (UV light). ^{1}H NMR spectra were recorded on a Brucker 400 instrument in $CDCl_3$ with $SiMe_4$ as internal reference. Melting points were obtained manually by open capillary method. Sonication was performed in a SIDILU, Indian make sonic bath operating at 35 KHz (constant frequency) and 120 W. All the reactions were performed in open vessels without any mechanical stirring.

2.2 *Preparation of Catalyst*:

Dry silica gel 10g was placed in 100ml three neck round bottomed flask equipped with a condenser and a calcium chloride guard tube, to this dry CH_2Cl_2 (30 mL) was added. Thionyl chloride 10g was added drop wise over a period of 30min from addition funnel at room temperature, after the completion of addition the stirring was continued, the evolved HCl and SO_2 was quenched by allowing the gas through saturate bicarbonate solution. After stirring for 2h the solvent was evaporated under reduced pressure to give the free flowing silica chloride [21]

2.3 *General Procedure*:

2-Aminoaryl ketones (5 mmol) and β-keto ester (5 mmol) along with silica chloride (100 mg) were taken in a test tube and placed arbitrarily in sonic bath in such a way that the contents in the test tube were lower than the level of the water in the sonic bath. The temperature of the bath was maintained between 25−26 °C by circulating water. In case of solid starting materials, acetonitrile (3 ml) was added to perform the reaction. All the reactions were monitored on TLC, after the completion of the reaction ethyl acetate (10 mL) was added to the reaction mass, the solid catalyst was filtered and washed with ethyl aceta te (5 × 2 mL) and the combined organic layers were dried over Na_2SO_4, and evaporated to get the almost pure solid products.

2.4 *Spectral data*:

3a: ^{1}HMR ($CDCl_3$): δ 7.73–7.70 (m, 1H, ArH), 7.59–7.50 (m, 2H, ArH), 4.08–4.03 (q, 2H, CH_2), 2.79 (s, 3H, CH_3), 0.95-0.94(t, 3H, CH_3). ESI-MS: 314.6 (291 + Na^{23})
3f: ^{1}HMR ($CDCl_3$): δ 7.39–7.18 (m, 10H, ArH), 2.25–2.10 (m, 4H, 2 CH_2), 0.98(s, 3H, CH_3). ESI-MS: 302.1 (301+ H^1)
4a: ESI-MS: 348.3 (325+ Na^{23})
4b: δ 7.72–7.59 (m, 2H, ArH), 7.56–7.49 (m, 2H, ArH), 7.48–7.35(m, 5H, ArH), 3.8(s, 3H, CH_3), 2.79(s, 3H, CH_3)
4c: ESI-MS: 296.3 (295+ H^1)
4g: ESI-MS: 358.3 (335+ + Na^{23})
5a: ^{1}HMR ($CDCl_3$): δ 7.50–7.41 (m, 1H, ArH), 2.50(s, 3H, CH_3), 2.29(s, 3H, CH_3), 2.25(s, 3H, CH_3).
HRMS: 230 (229 + H^1)

At the beginning, the reaction of 2-aminobenzophenone with ethyl acetoacetate in presence of silica chloride (100 mg) at 27 °C was chosen to optimise the reaction conditions, we tested the reaction in various solvents and also under solvent-free condition. To have a better understanding, we carried out the model reaction of 2-aminobenzophenone with ethyl acetoacetate in presence of silica chloride with different solvent under silent condition. The results of these studies are presented in **Table 1**, in comparison to the conventional method, the reaction under sonic condition gave better result, and that polar solvent works better for both silent and sonic condition. To improve the yield, further reactions were carried out under sonic condition using polar solvents and **Table 1** entry 6; clearly indicate solvent free reaction is high yielding.

Table1. Optimization studies under silent and sonic condition.

S.No	Solvents	Silent condition[a]		Sonic condition[b]	
		Time (hr)	Yield (%)[c]	Time (hr)	Yield (%)[c]
1	DCM	7	ND	3	ND
2	Ethanol	5	50	2	50
3	Dioxane	6	45	2	50
4	THF	5	45	2	50
5	Acetonitrile	4	65	1	70
6	Solvent free	4	80	1	80

[a]Silent condition: stirring the starting materials with catalyst (100mg) at the reflux temperature of the respective solvent. [b]Sonic condition: The reactants and the catalyst (100mg) were sonicated at 25-26 °C in the respective solvent. [c]Isolated yield

The reaction condition was further optimised by varying different amounts of catalyst with regard to the model reaction, for this study we took varying quantities of the catalyst like, 50mg, 75mg, 100mg and 200mg of silica chloride without any solvent. With higher quantity of catalyst 200mg the reaction did not happen, this could be due to the formation of thick mass with the acid catalyst and could also be because of the presence very little liquid reactant for the sonication to happen effectively; with lesser quantity of the catalyst the yields were poor. The results of these observations are presented in **Table 2**; from the table it is clear that increasing the time period of the reaction, also did not give any fruitful results. The best suitable condition for the Friedlander annulations is sonicating the 2-Aminoaryl ketones and β-keto ester along with silica chloride (100 mg) at room temperature for a time period not more than 90min.

Table 2: Catalyst load for the reaction

Catalyst quantity (mg)	Sonication time (min)[a]	Yield (%)
50	180	30
75	180	50
100	90	80
200	180	50

[a]Reaction condition as mentioned in experimental section

With the optimised conditions on hand, substituted quinolines were prepared in high yield using substituted 2-aminoaryl ketones with different β-keto esters, all the reactions proceeded smoothly as shown in **Table 3**. The main advantage of the present protocol is that, the catalyst used is a heterogeneous and after the completion of the reaction it was easily removed by filtration. The removed catalyst was washed with organic solvent and dried for about 2h at 100°C, to check the reusability of the reaction, the dried catalyst was used for the model reaction following the same reaction condition and it was found that the catalyst worked twice consecutively, yielding the product up to 70%, then after there was a drastic decrease in the yield indicating that the catalyst cannot be recycled, this could be due to the depletion of chloride ions from the surface of the catalyst.

Table 3: library of molecules synthesised under sonic condition[a]

Quinoline	Time (min)	Yield (%)[b]
3a [1a, 2a]	30	85
3b [1a, 2b]	30	85
3c [1a, 2c]	30	85
3d [1a, 2d]	75	88
3e [1a, 2e]	60	80
3f [1a, 2f]	45	82
3g [1a, 2g]	45	83
4a [1b, 2a]	30	87
4b [1b, 2b]	35	85
4c [1b, 2c]	30	86
4d [1b, 2d]	80	85
4e [1b, 2e]	50	89
4f [1b, 2f]	45	83
4g [1b, 2g]	40	81
5a [1c, 2a]	25	85
5b [1c, 2b]	30	88
5c [1c, 2c]	30	86
5d [1c, 2d]	80	87
5g [1c, 2g]	70	80

[a]Reaction condition as mentioned in experimental section.
[b]Isolated yields, all the compounds are known and the melting point of the synthesized compounds are consistent with the reported values

We also observed that, the effect of ultrasonic irradiation by carrying the reactions with different substrates under sonic condition and without sonication. In all the cases reactions carried out under sonic condition gave better yields. The reason may be the phenomenon of cavitation produced by ultrasound. Because the super-high pressure and temperature generated by the collapse of the acoustic cavitations can never be gained in classical heating, the thermal effects of ultrasonic waves accelerate the reaction rate and enhance the yield. Ultrasound through cavitation phenomenon causes an increase in the mass and heat transfer to the surface by disruption of interfacial boundary layers. This enhanced reaction temperature and reactant contact surface could be the motivating force for the efficient formation of quinolines. Moreover due to the presence of silica chloride, a heterogeneous catalyst, the cavity collapse near the solid surface is non-spherical and drives high-speed jets of liquid to the solid surface which leads to the acceleration of dissolution and heat and mass transfer

3 Conclusion

To summarize, an easy and efficient protocol had been developed under sonic condition for the synthesis of poly substituted quinolines. Shorter reaction duration and easy work up procedure are the added advantage of this method.

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