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An efficient synthesis of quinolines via Friedländer reaction: New reusable catalyst $(\text{UO}_2(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O})$

Mahmood Kamali

Kharazmi University, Faculty of Chemistry, 49-Mofetteh Ave. Tehran, Iran

ABSTRACT

2-Aminoaryl ketones underwent condensation with a variety of α -methylene ketones to afford 2,3,4-trisubstituted quinolines. Such quinolines were obtained by using $\text{UO}_2(\text{CH}_3\text{COO})_2 \cdot 2\text{H}_2\text{O}$ as a new catalyst in ethanol as solvent under reflux condition. The advantages of this method are excellent products yields, short times reaction and easy work up. Also, the reusability of the catalyst has also been evaluated up to four consecutive runs.

Keywords: Friedlander synthesis, quinolines, uranyl acetate dihydrate

INTRODUCTION

Quinoline and their derivatives have attracted much interest for their biological activities such as anti-malarial [1], anti-bacterial [2], anti-inflammatory [3], anti-asthmatic [4], anti-hypertensive [5], anti-platelet activity [1, 6], antagonists [7], analgesic agents [8]. In addition, they have other activities in polymers [9], catalysts [10], corrosion inhibitors [11], preservatives [12], and antifoaming agent in refineries [13].

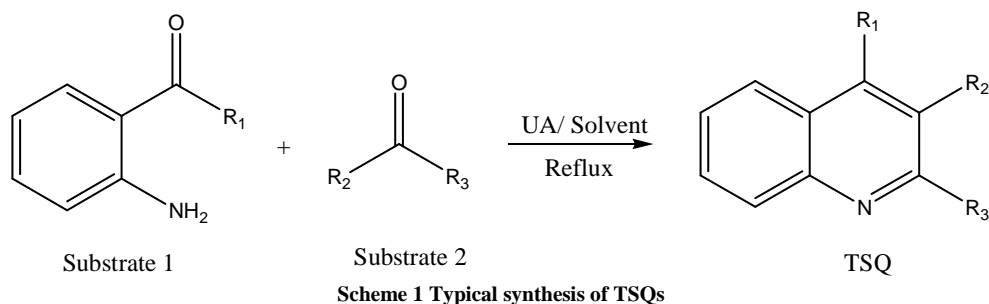
Due to this importance, the development of efficient methodologies for the synthesis of quinolines is in great demand. Some methods via Skraup [14], Doebner–Miller [15], Combes [16], Conrad-Limpach [17], Povarov [18], Camps [19], Niementowski [20] and Friedlander [21] syntheses were developed which provide quinoline derivatives. Friedlander synthesis is one of the most important of these approaches.

German chemist Paul Friedländer reacted 2-aminobenzaldehydes with acetaldehyde to form quinoline derivatives. Some of the modified methods have been reported for this reaction which includes bases such as KOH [22], bicyclic pyrrolidine derivative [23], Brønsted acids such as sulfamic acid [24], ZnCl_2 [25], Trifluoroacetic Acid [26], copper(II) chloride-sulfuric acid [27], hydrochloric acid [28] and p-toluene sulphonic acid [29], Lewis acids such as Neodymium(III) Nitrate Hexahydrate [30], ZnCl_2 - SnCl_2 [31], silica chloride [32], $\text{B}(\text{HSO}_4)_3$ [33], $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ [34], Sodium fluoride [35], iodine [36], $\text{Bi}(\text{OTf})_3$ [37], $\text{Y}(\text{OTf})_3$ [38], SnCl_2 [39] and $\text{NaAuCl}_4 \cdot 2\text{H}_2\text{O}$ [40], or ionic liquid-catalyzed [41] conditions.

In continuation of my investigations on catalytic effect of uranyl acetate (UA) [42,43], here in, I report an efficient synthesis of 2,3,4-trisubstituted quinolones (TSQs) by UA in solvent free condition.

RESULTS AND DISCUSSION

In order to study the efficiency of new methods, the catalytic effect of UA, 2-aminoacetophenone (1), ethylacetoacetate (2) was refluxed in various solvents (H_2O , ethanol, acetone, THF, acetonitrile, chloroform) by using of UA (20 mol%) as typical reaction to give TSQ_1 (Scheme 1 & Table 1). These reactions were shown, the ethanol is the best of solvent.

**Table 1 Effect of solvent on the reaction times and yields**

Entry	Solvent	Time (min)	Yield (%)
1	H ₂ O		40
2	<i>EtOH</i>		89
3	CHCl ₃		47
4	Acetone		56
5	THF		43
6	CH ₃ CN		58

Reaction condition: 2-Amino acetophenone (2.0 mmol), Ethylacetoacetate (2.4mmol) in the presence of catalyst (17 mg) under reflux condition in various solvents.

In order to optimize the reaction conditions, several methods were examined on the same model reaction by conducting the reaction. The reactions were performed in different times and amount of UA. The results from this study are presented in Table 2, whereby the better yields (89%) were obtained when the amount of UA was 2.5 mol% with 3 hours reaction time.

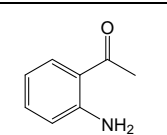
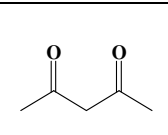
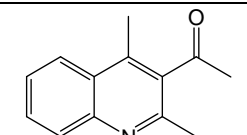
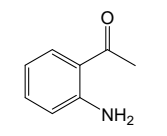
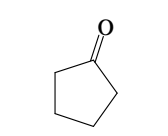
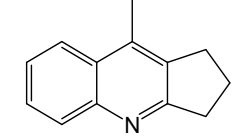
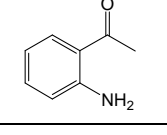
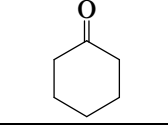
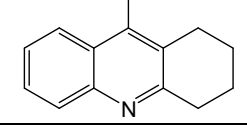
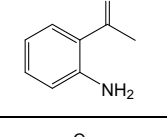
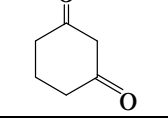
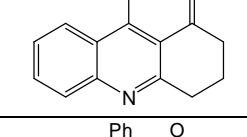
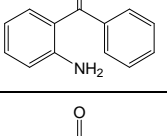
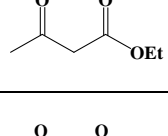
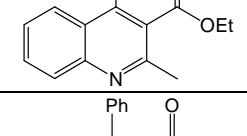
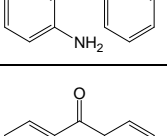
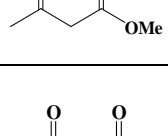
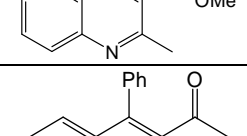
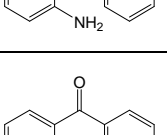
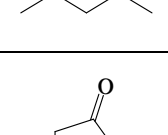
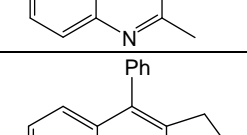
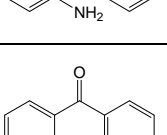
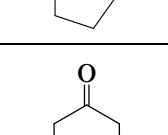
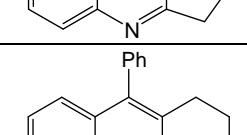
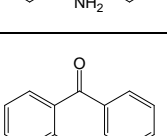
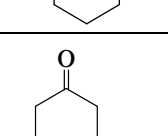
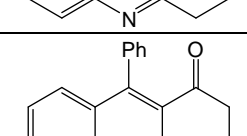
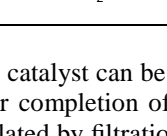
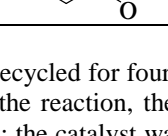
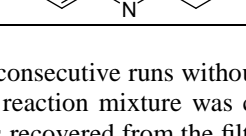
Table2 Synthesis of TSQ₁ under different conditions for optimization of reactions

Temp °C of React.	Catalyst (mol %)	Time (h)	Product Yield (%)
1	20	4	80
2	10	4	83
3	5	4	89
4	2.5	4	89
5	1	4	71
6	2.5	3	89
7	2.5	2	78

The reaction under the optimized reaction conditions was evaluated by carrying out the reactions between 2-aminoacetophenone or 2-aminobenzophenone with a variety of methylene ketones (ethyl acetoacetate, methyl acetoacetate, acetyl acetone, cyclohexanone, cyclopentanone and cyclohexan-1,3-dione,). In all of the cases, the corresponding TSQ derivatives were obtained in acceptable yields and purity. However, the reactions demonstrated that in the case of 2-aminoacetophenone as substrate, the yields of TSQs were generally lower compared, when the reactions were carried out with 2-aminobenzophenone. The results of all these studies are summarized in Table 3.

Table 3 details of quinolines synthesis

Entry	Substrate 1	Substrate 2	Product	Product Yield (%)	mp °C	
					Found	Lit.
1				89	Oil	Oil[44]
2				88	Oil	Oil[44]

3				90	Oil	Oil[44]
4				88	62-63	60-61[45]
5				87	77-79	76-78[45]
6				92	67-69	68[46]
7				91	102-103	100-101[47]
8				91	86-88	87-88[44]
9				92	110-112	112-113 [47]
10				90	140-142	139-141[47]
11				90	139-143	138-141 [46]
12				93	156-158	156-157 [41]

Interestingly, catalyst can be recycled for four consecutive runs without significant loss of activity (Table 4). For this purpose, after completion of the reaction, the reaction mixture was cooled to room temperature. The precipitated solid was isolated by filtration; the catalyst was recovered from the filtrate by evaporation of the ethanol, and reused for the similar reaction.

Table 4 Recycled of UA and SuSA in the synthesis of Biginelli reactions

Catalyst	Runs				
	1	2	3	4	5
Product yield (%)	89	88	85	82	75

Experimental

All reactions were carried out in an efficient hood. The starting materials were purchased from Merck and Fluka chemical companies. Melting points were determined with a Branstead Electrothermal model 9200 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer RX1 Fourier transform infrared spectrometer. The ^1H and ^{13}C NMR spectra were recorded in CDCl_3 or DMSO-d_6 on Bruker Avance 300 MHz spectrometers. Elemental analyses were carried out by a Perkin Elmer 2400 series II CHN/O analyzer.

Synthesis of Ethyl 2,4-dimethylquinoline-3-carboxylate (TSQ₁) as general procedure: In a 50 mL round bottomed flask, 2-aminoacetophenone (2mmol), ethylacetoacetate (2.4mmol) and UA (5mol%) were mixed in ethanol (10 mL), the solution was refluxed for 3 hours (Table 1 & 2). After completion of the reaction, the reaction mixture was cooled to room temperature. The resulting solid was collected by filtration as crude product, which was purified by silica gel column chromatography with cyclohexane and ethyl acetate (9:1) to give the pure product. Oil, FTIR (KBr): 3073, 2941, 1726, 1643, 1575, 1219, 740 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): 1.73 (t, $J = 7$ Hz, 3H), 2.76 (s, 3H), 2.81 (s, 3H), 4.11 (q, $J = 7$ Hz, 2H), 7.23–8.06 (m, 3H), 8.41 (d, $J = 8$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, CDCl_3): 14.5, 15.2, 22.8, 60.3, 122.4, 125.3, 125.9, 126.8, 128.9, 133.3, 141.5, 148.1, 155.3, 167.1 ppm; Anal. Calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.21; H, 6.32; N, 6.21.

CONCLUSION

In conclusion, I have successfully developed a quick, convenient and efficient method for the synthesis of 2,3,4-trisubstituted quinolines. The advantages of method include generality and simplicity of procedure, shorter reaction time, simple workup, reusable catalyst condition, and pure products in excellent yields.

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