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A green solvent-free protocol for the synthesis of poly-substituted quinolines using 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl} as an efficient and homogeneous catalyst

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ABSTRACT

An efficient, simple and clean protocol for the synthesis of poly-substituted quinolines from 2-aminoaryl ketones and carbonyl compounds possessing a reactive methylene group in the presence of catalytic amount of Brønsted acidic ionic liquid 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl} is described (Friedländer protocol). Using this protocol, the products are produced in high yields and short reaction times.

KEYWORDS

Poly-substituted quinoline;
2-Aminoaryl ketone;
Carbonyl compound;
Friedländer protocol;
Br∅nsted acidic ionic liquid;
3-Methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl}.

INTRODUCTION

Quinolines are nitrogen containing heterocycles with wide range of medicinal properties which have been used as antimalarial, antiasthmatic, antihypertensive, antibacterial and tyrosine kinase inhibiting agents[1-6]. These compounds have been also applied for the preparation of nano- and mesostructures having enhanced electronic and photonic properties[7]. In addition, poly-substituted quinolines can achieve hierchical self-assembly into a variety of meso and nano structures with enhanced photonic and electronic properties[7-9]. Therefore, development of new efficient protocols for the synthesis of quinoline derivatives is of interest in both medicinal chemistry and synthetic organic chemistry. The most common protocol for the synthesis of quinolines is Friedländer method[10]. Friedländer reaction is acid or base-catalyzed condensation of 2-aminoaryl ketones with carbonyl compounds containing a reactive α-methylene group followed by cyclodehydration[6,10-21]. However, most of the reported protocols for synthesis of quinolines have some disadvantages including long reaction times, low product yields and use of hazardous and expensive catalysts. Moreover, this reaction is usually carried out in harmful organic solvents such as acetonitrile, THF, DMF and DMSO; therefore, workup of the reaction mixture is not only cumbersome but also the green aspect of the reaction is annihilated by using these solvents specially DMF. Consequently, search for finding a simple, green, rapid, inexpensive and efficient procedure for the preparation of these important heterocycles is in demand.

In resent years, investigation of alternatives to toxic and non-green catalysts and reagents has resulted highly growing interest in the application of ionic liquids (ILs) as catalysts and reagents[22-32]. In fact, the user-friendly

and adjustable physico-chemical properties of ILs such as low volatility, non-ûammability, high thermal stability, negligible vapor pressure and ability to dissolve a wide range of materials, have found numerous applications as environmentally benign catalysts and reagents as well as homogenizer of reaction media for organic transformations[22-32]. Among the ILs, Brønsted acidic ionic ones based imidazolium moiety have designed to replace solid acids and traditional mineral liquid acids like sulfuric acid and hydrochloric acid in chemical procedures[27-32]. 3-Methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl} is an interesting Brønsted acidic ionic liquid which we have recently synthesized and applied as an efficient catalyst to promote organic transformations (Figure 1)[28-32].

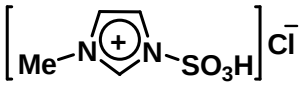


Figure 1 : The structure of [Msim]Cl

Solvent-free organic reactions have been applied as useful protocols in organic synthesis. Solvent-free reactions often lead to shorter reaction times, increased yields and easier workup, in addition to working well in green chemistry protocols, and enhancing the regio- and stereoselectivity of reactions[33-35].

Considering the above points, we report here a new, inexpensive, simple, green and efficient protocol for the preparation of poly-substituted quinolines by Friedländer hetero-annulation between 2-aminoaryl ketones and carbonyl compounds possessing a reactive methylene group catalyzed by 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl}, as a green and imidazolium based ionic liquid with Brønsted acidic property (Scheme 1).

EXPERIMENTAL

All the materials were purchased from Merck, Fluka, Across Organics or Aldrich Chemical Companies. Merck silica gel 60 F254 TLC plates were used for thin layer chromatography (TLC). Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were run on a Bruker Avance DPX FT-NMR spectrometer (δ in ppm).

Procedure for the preparation of ionic liquid [Msim]Cl

A round-bottomed flask (100 mL) was charged with 1-methylimidazole (0.410 g, 5 mmol) in dry CH_2Cl_2 (50 mL), and then chlorosulfonic acid (0.605 g, 5.2 mmol) was added dropwise over a period of 5min at room temperature. After the addition was completed, the reaction mixture was stirred for 20 min, stand for 5min, and the CH_2Cl_2 was decanted. The residue was washed with dry CH_2Cl_2 (3×50 mL) and dried under vacuum to give [Msim]Cl as a viscous colorless oil in 92% yield, 0.912 g[28-31].

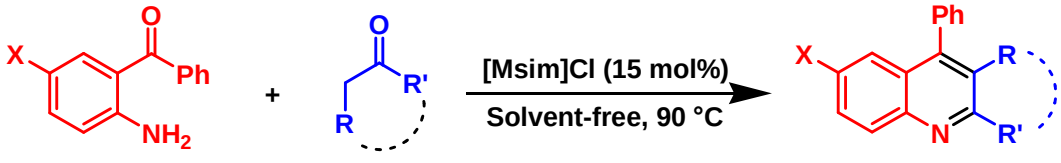
General procedure for the synthesis of poly-substituted quinolines

To a mixture of 2-aminoaryl ketone (1 mmol) and carbonyl compound (1.5 mmol) in a test tube, was added [Msim]Cl (0.03 g, 0.15 mmol), and the resulting mixture was stirred with a small rod at 90 °C for the times reported in TABLE 1. Afterward, the reaction mixture was cooled to room temperature, and H_2O (5 mL) was added to it, and stirred for 3 min to dissolve [Msim]Cl. The crude product (insoluble in water) was filtered and recrystallized from hot ethanol to afford the pure product.

Selected spectral data of the products

7-Chloro-3,3-dimethyl-9-phenyl-3,4-dihydroacridin-1(2*H*)-one (TABLE 1, entry 1)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.15 (s, 6H), 2.56 (m, 2H), 3.25 (s, 2H), 7.14-7.16 (m, 2H), 7.42 (d, *J* = 2.5 Hz, 1H), 7.50-7.51 (m, 3H), 7.66-7.68 (dd, *J* = 2.5, 8.9 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR



X = Cl, H

Scheme 1 : The synthesis of poly-substituted quinolines using [Msim]Cl

($CDCl_3$, 125 MHz): δ 28.4, 32.3, 48.1, 54.3, 124.0, 126.5, 127.9, 128.4, 130.5, 132.3, 136.7, 147.9, 150.1, 162.0, 196.9.

Ethyl 6-chloro-2-methyl-4-phenylquinoline-3-carboxylate (TABLE 1, entry 4)

^{1}HNMR ($CDCl_3$, 500 MHz): δ 0.92 (t, *J* = 7.0 Hz, 3H), 2.75 (s, 3H), 4.02-4.06 (q, *J* = 5.2 Hz, 2H), 7.32 (m, 2H), 7.46-7.51 (m, 4H), 7.60-7.62 (m, 1H), 7.97 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.8, 23.7, 61.6, 124.9, 125.7, 129.1, 129.3, 129.4, 129.5, 131.3, 131.4, 131.8, 134.6, 145.1, 145.9, 155.0, 167.5.

6-Chloro-2-methyl-4-phenylquinolin-3-yl)(phenyl)methanone (TABLE 1, entry 5)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.68 (s, 3H), 7.22 (s, 1H), 7.30-7.35 (m, 5H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.59-7.62 (m, 3H), 7.71-7.73 (dd, *J* = 2.15, 8.9 Hz, 1H), 8.11 (d, *J* = 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.4, 125.4, 126.5, 128.9, 129.0, 129.6, 130.3, 131.0, 131.4, 132.9, 133.6, 134.1, 134.5, 137.3, 145.2, 146.6, 155.5, 197.7.

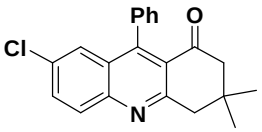
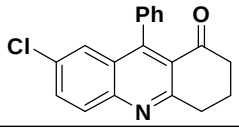
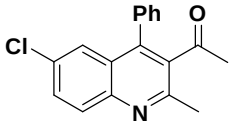
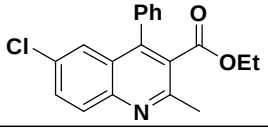
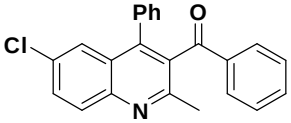
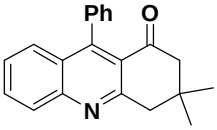
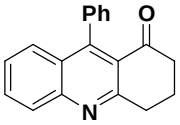
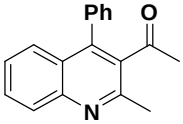
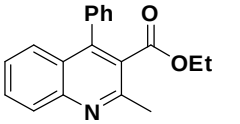
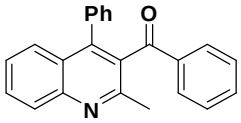
9-Phenyl-3,4-dihydroacridin-1(2*H*)-one (TABLE 1, entry 7)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.62-2.65 (t, *J* = 6.5 Hz, 2H), 3.22 (t, *J* = 6.5 Hz, 2H), 3.75-3.78 (m, 2H), 7.25-7.26 (m, 2H), 7.32 (d, *J* = 2.2 Hz, 1H), 7.51-7.66 (m, 5H), 8.00 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 21.6, 34.6, 40.9, 127.7, 127.5, 127.5, 128.1, 128.2, 128.7, 129.0, 129.1, 132.5, 138.2, 148.7, 150.8, 163.2, 198.3.

RESULTS AND DISCUSSION

To obtain the optimized reaction conditions, the Friedländer hetero-annulation condensation of 2-amino-5-chlorobenzophenone (1 mmol) with dimedone (5,5-dimethylcyclohexane-1,3-dione) (1.5 mmol) was selected as a model reaction (Scheme 1), and its behavior was studied in the presence of different molar ratios of the homogeneous catalyst, 3-methyl-1-sulfonic acid imidazolium chloride {[Msim]Cl} at range of 60-100 °C. The best results were obtained when 15 mol% of the catalyst was employed at 90 °C; in these conditions, the product was produces in 93% within 30 min.

TABLE 1 : The synthesis of poly-substituted quinolines form 2-aminoaryl ketones and carbonyl compounds catalyzed by [Msim]Cl

Entry	Product	Time (min)	Yield[a] (%)	M.p. °C (lit.)
1		30	93	211-212 (211)[20]
2		30	91	186-188 (185)[20]
3		35	89	159-161 (157)[20]
4		40	87	97-99 (99-100)[6]
5		50	84	214-216 (209-211)[19]
6		30	91	192-194 (193-194)[6]
7		30	92	155-157 (151-153)[20]
8		35	90	108-110 (109-110)[6]
9		35	85	102-104 (99)[20]
10		50	87	136-138 (135-138)[6]

[a]**Isolated yield.**

To assess the efficacy and the scope of our protocol, the reaction was examined with different carbonyl compounds and 2-aminoaryl ketones. The results are summarized in TABLE 1. As TABLE 1 indicates, the reaction of 2-amino-5-chlorobenzophenone or 2-aminobenzophenone with various kinds of carbonyl

compounds including cyclic and acyclic β-diketones as well as β-ketoesters proceeded efficiently and the desired products were obtained in high to excellent yields and in short reaction times. Thus, the method is highly efficient and general.

CONCLUSIONS

In conclusion, we have introduced a new method for the preparation of poly-substituted quinolines from 2-aminoaryl ketones and carbonyl compounds possessing a reactive methylene group using catalytic amount of [Msim]Cl as a green Brønsted acidic ionic liquid. The major advantages of this method are high yields, relatively short reaction times, generality, efficiency, low cost, easy preparation of the catalyst, and good agreement with the green chemistry protocols.

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