Sulfonic Acid Functionalized Ionic Liquid in Combinatorial Approach, a Recyclable and Water Tolerant-Acidic Catalyst for One-Pot Friedlander Quinoline Synthesis[||]

Jafar Akbari,[†] Akbar Heydari,*[,†] Hamid Reza Kalhor,[‡] and Sirus Azizian Kohan[§]

Chemistry Department, Tarbiat Modares University, P.O. Box 14155, 4938 Tehran, Iran, Biochemistry Department, Tarbiat Modares University, Tehran, Iran, Molecular and Medical Pharmacology Department and The Crump Institute, UCLA School of Medicine, Los Angeles, California 90024

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SO_3H-functionalized ionic liquid was successfully applied as a water tolerant-acidic catalyst for the one-pot domino approach quinoline synthesis in aqueous medium. Various types of quinolines from 2-aminoaryl ketones and β-ketoesters/ketones were prepared in 85−98% yields using the catalytic system of SO_3H-functionalized ionic liquid/H_2O. The ionic liquids was synthesized in a combinatorial fashion. The quinoline products could be conveniently separated from the reaction mixture by filtration, indicating that the whole process was performed in water and exemplifying a green chemistry. More importantly, the catalyst could be easily recycled for five times without loss of much activity. The catalytic system, reported here, possesses advantages of both homogeneous and heterogeneous catalysts.

1. Introduction

Quinolines are very important compounds partially because of their pharmacological properties which include wide applications in medicinal chemistry; notable among them are antimalarial drugs, anti-inflammatory agents, antiasthamatic, antibacterial, antihypertensive, and tyrosine kinase inhibiting agents.[1−3] In addition, quinolines have been used for the preparation of nano and mesostructures with enhanced electronic and photonic properties.[4] Despite quinoline usage in pharmaceutical and other industries, comparatively few methods for their preparation have been reported. Although other methods such as Skraup, Doebner von Miller, and Combes procedures for the preparation of quinolines have been reported,[5,6] the Friedlander annulation is one of the simplest and most straightforward methods for the synthesis of poly substituted quinolines. This method has attracted considerable attention from the view point of combinatorial chemistry.[7] The Friedlander synthesis is an acid or base catalyzed condensation followed by a cyclodehydration between 2-aminoaryl ketone and a second carbonyl compound including a reactive methylene group. Generally, this reaction is carried out by refluxing an aqueous or an alcoholic solution of reactants in the presence of a base at high temperature.[8] Under thermal or base catalysis conditions, *O*-aminobenzophenone does not react with simple ketones such as cyclohexanone and β-keto esters.[9] In addition, modified methods employing $ZnCl_2$, phosphoric acid, $Bi(OTf)_3$, silver phosphotungstate, sodium fluoride, $AuCl_3$, $Zr(NO_3)_4$, $Y(OTf)_3$, and CAN(Cerium(IV) Ammonium Nitrate) have been reported for the synthesis of quinolines.[10] However, many of these procedures have significant drawbacks including low yields, long reaction times, harsh reaction conditions, difficulties in workup, and the use of stoichiometric amounts of catalysts. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the workup and cannot be recovered. Recently, Srinivasan et al. have reported a stoichiomethric amount of $[HBIm][BF_4]$ promoted quinoline synthesis.[11] However, these ionic liquids are sensitive to moisture and are unstable in water,[12] and a stoichiomethric amount of ionic liquids is required. Consequently, the development of water stable acidic catalyst for quinoline synthesis is quite desirable.

One of the main principles of green chemistry is to develop cost-effective and environmentally benign catalytic systems which have become one of the main themes of contemporary synthetic chemistry.[13] Ionic liquids have been considered as eco-friendly alternatives to volatile organic media because of their negligible vapor pressure and nonflammable nature.[14] One of the most remarkable feature of ionic liquids is that the yields can be optimized by changing the anions or the cations. Additionally, the incorporation of functional groups can render a particular capability to the ionic liquids, enhancing their function, which may lead to increase reusability and stability of ionic liquids compared with the unfunctionalized counterparts. Moreover, specific functional groups can also be incorporated for task-specific purposes.[13] Recently, sulfonic acid functionalized ionic liquids were used as solvent−catalyst for several organic reactions such as esterifications, Aldol condensation, Pinacole reaction, aromatic nitration, Biginelli reaction, and Fisher indole synthesis.[15] The use of such task specific ionic liquids (TSILs) as

[||] Dedicated to the memory of Fereidoon Ektheraei.

* To whom correspondence should be addressed. E-mail: akbar.heydari@gmx.de. Fax: (+98) 2182883455.

[†] Chemistry Department, Tarbiat Modares University.

[‡] Biochemistry Department, Tarbiat Modares University.

[§] UCLA School of Medicine.

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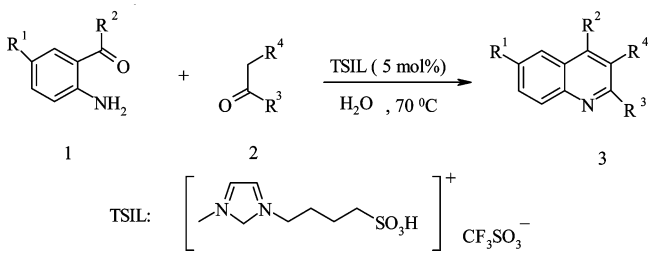
Scheme 1. TSIL Catalyzed Friedlander Reaction



catalysts is an area of current investigations and as aforementioned, these TSILs may further expand the application of ionic liquids in chemistry. These ILs are miscible in water, and their homogeneous system is readily separated from the reaction product, combining advantages of both homogeneous and heterogeneous catalysis. In continuation of our interest in ionic liquid mediated chemical and biochemical transformations,[16] we herein report the one pot domino approach for the synthesis of quinoline derivatives in Friedlander manner using TSIL as a catalyst (Scheme 1). In this reaction, the catalyst plays a dual role; it ensures an effective condensation and cyclization of 2-aminoaryl ketone with second carbonyl group and it also promotes the aromatization to the final product. The approach is shown in Scheme 1. This would be a novel application of SO_3-H functionalized ionic liquid acting as a catalyst for the Friedlander quinoline synthesis.

2. Results and Discussion

Initially, we performed the reaction of 2-aminobenzophenone with ethyl acetoacetate to examine the potential of the TSIL as catalyst in water as a solvent in room temperature. The reaction turned out to be clean and simple, giving the Friedlander condensation products in good to excellent yields. Subsequently, we applied the condition to a variety of 2-aminoaryl ketones and β-ketoesters (Table 1, entries 1, 2, 3, 9, 12). In addition, various 1, 3-diketones reacted with 2-aminoaryl ketones to give the corresponding quinolines (Table 1, entries 4, 5, 6, 10, 11, 13). In the subsequent step, we directed our study to use simple cyclic ketones and it became apparent that the reactions proceed slower than the other compounds (entries 7, 8).

To investigate the effect of solvent, we examined the possibility to run the reaction in the presence of water. Interestingly, no product in the absence of water was observed. Indeed, it has been previously shown that the water content certainly has an effect on the activity of the TSIL.[17] Moreover, the role of water seems to be well-known in the Friedlander reaction.[18] Although the reaction seems to occur in the concentrated organic phase constituting the reagents, the presence of water could assist the reaction to proceed causing the precipitation of the product. Finally, the water tolerant acidic catalyst could be used as homogeneous catalyst because of its good solubility in water and at the end of the reaction the product can be precipitated and subsequently, the catalyst may be recycled from water. The reusability of TSIL was assessed by conducting Friedlander reaction of 2-aminobenzophenon and ethylacetoacetate over five successive cycles without any pretreatment of the TSIL. The results, shown in Table 2 indicate no significant loss of activity of the TSIL. The recycled catalyst was characterized with ^1H and ^{13}CNMR spectroscopies to confirm that its structure is the same as that of the original fresh catalyst.

3. Conclusion

In summary, we have demonstrated an efficient procedure for the synthesis of quinolines, using sulfonic acid functionalized ionic liquid as homogeneous and reusable catalyst. Although the reaction was accomplished in the homogeneous model, isolation of the desired products as well as ionic liquids could be achieved via a simple filtration, and the TSIL could be reused. The catalytic system possesses properties of both homogeneous and heterogeneous catalysis. The advantages of this functionalized ionic liquid are that it can be readily synthesized and the TSIL can be used as an efficient catalyst as well as easily being recycled without any decrease in catalytic activity. Moreover, this methodology offers significant improvements in regard to the yield of products and emphasizes the green chemistry aspects by avoiding toxic catalysts and solvents.

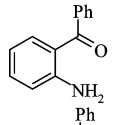
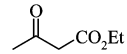
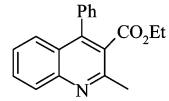
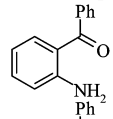
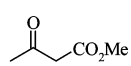
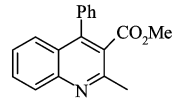
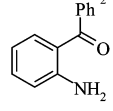
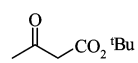
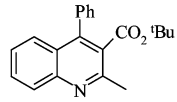
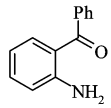
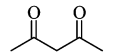
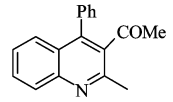
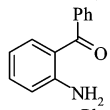
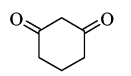
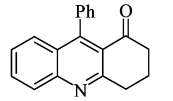
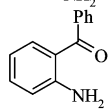
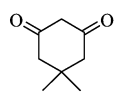
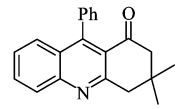
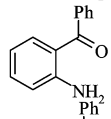
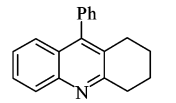
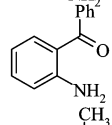
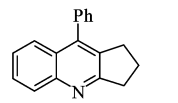
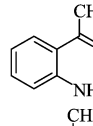
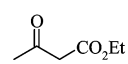
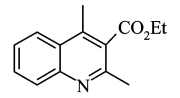
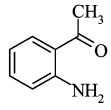
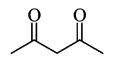
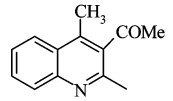
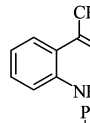
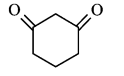
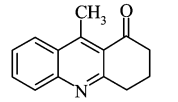
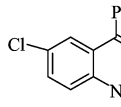
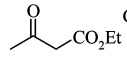
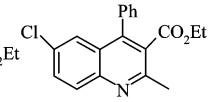
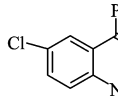
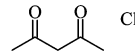
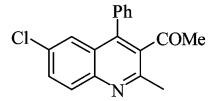
Experimental Section

Preparation of ionic liquids: The synthesis of this ionic liquid has been carried out using a similar method reported in the literature.[14c] The method involves the reaction of neutral nucleophiles *N*-methyl imidazole with 1,4-butane sultone in equimolar ratio to afford the zwitterions that are further converted into ionic liquid by acidification with Trifilic acid in a combinatorial approach. The ionic liquid was formed quantitatively and in high purity as assessed by NMR.[15]

General Procedure for One-Pot Synthesis of Quinolines. TSIL (0.018 gr, 0.1 mmol) was added to a mixture of 2-aminoaryl ketones (2 mmol) and β-ketoester/1,3-diketone/cyclic ketone (2 mmol) in water (1 mL) at 70 °C. The mixture was stirred until completion of the reaction, as indicated by TLC. The ionic liquid was separated from the reaction mixture by extraction with water. The ionic liquid being soluble in water comes in the water layer. The products were separated by filtration and vacuum-dried. The product was identified using NMR in $CDCl_3$. The ionic liquid in the filtrate was separated from the unreacted starting materials by extracting the filtrate with ether. Then, the water layer containing ionic liquid was vacuum-dried at 70 °C for 5 h to remove water, and the ionic liquid was reused.

Physical and Spectral Data for Selected Products. entry 1: Mp 105−106 °C. IR (neat) 3061.6, 2981.5, 1725.9, 1564.2, 1402.3, 1231.0, 1066.1 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 0.97 (t, J = 7.2 Hz, 3H), 2.82 (s, 3H), 4.10 (q, J = 7.2 Hz, 2H), 7.37−7.42 (m, 2H), 7.45−7.54 (m, 4H), 7.62 (dd, J = 8.4, 1.0 Hz, 1H), 7.75 (td, J = 8.3, 1.5 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.1, 24.3, 61.8, 125.5, 126.8, 126.9, 127.8, 128.7, 128.9, 129.3, 129.8, 130.7, 136.1, 146.7, 148.1, 155.0, 168.9; **entry 7:** Mp 131−132°. IR (neat) 3059.7, 2958.1, 1611.7, 1573.0, 1492.9, 1385.8, 1211.4, 1026.2 cm^{-1}. C. ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.64−1.66

Table 1. Synthesis of Quinoline Derivatives Catalyzed by TSIL in Water[a]

entry	Compound 1	Compound 2	product	Time(h)	Yield (%)	condition
1				1	98	A
2				1	96	A
3				3	94	A
4				1	98	A
5				5	90	B
6				5	88	B
7				8	85	B,C
8				8	85	B,C
9				1	96	A
10				1	94	A
11				3	88	B
12				2	94	A
13				1	92	A

[a] Conditions: (A): 5 mol % TSIL, 70 °C; (B) 5 mol % TSIL, 90 °C; (C) 5 mol % TSIL, 90 °C, 1.5 equiv of 2 was used.

Table 2. Catalyst Recycling of TSIL for Quinoline Synthesis

entry	cycle	product yield
1	fresh	98
2	first recycle	98
3	second recycle	98
4	third recycle	96
5	fourth recycle	96
6	fifth recycle	96

(m, 2H), 1.88−1.89 (m, 4H), 2.70−2.75 (m, 2H), 3.31−3.33 (m, 2H), 7.24−7.38 (m, 4H), 7.48−7.65 (m, 4H), 8.06 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 27.5, 28.9, 31.1, 32.4, 40.6, 126.0, 126.8, 127.3, 128.0, 128.6, 128.9, 129.0, 129.9, 134.2, 138.1, 145.9, 146.2, 165.2.134.0, 137.1, 143.0, 148.4, 167.9; **entry 8:** Mp 148−149 °C. IR (neat) 3059.7, 2923.2, 1580.3, 1488.2, 1398.3, 1196.3, 1028.7 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.78−1.86 (m, 2H), 1.94−2.04 (m, 2H), 2.63 (t, J = 6.3 Hz, 2H), 3.23 (t, J = 6.6 Hz, 2H), 7.24−7.35 (m, 4H), 7.49−7.66 (m, 4H), 8.05 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 23.3, 23.4, 28.5, 34.7, 125.8, 126.2, 127.1, 128.1, 128.8, 129.0, 129.5, 137.6, 146.7, 146.9, 159.

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Supporting Information Available. Spectral data for all of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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