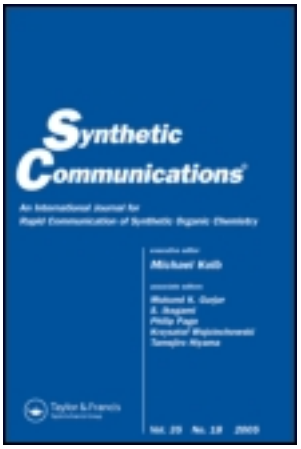

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Brønsted Acidic Ionic Liquids: New, Efficient, and Green Promoter System for the Synthesis of 4(3H)-Quinazolinones

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BRØNSTED ACIDIC IONIC LIQUIDS: NEW, EFFICIENT, AND GREEN PROMOTER SYSTEM FOR THE SYNTHESIS OF 4(3H)-QUINAZOLINONES

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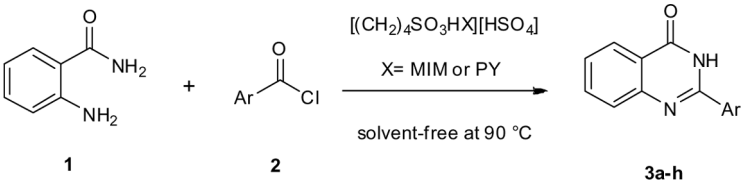
GRAPHICAL ABSTRACT



Abstract *A simple, inexpensive, and efficient new synthesis of 4(3H)-quinazolinones from the reaction of 2-aminobenzamide with aroyl chlorides in the presence of two new halogen-free Brønsted acidic ionic liquids, 3-methyl-1-(4-sulfonic acid)butylimidazolium hydrogen sulfate [$(CH_2)_4SO_3HMIM][HSO_4$] and 1-(4-sulfonic acid) butylpyridinium hydrogen sulfate [$(CH_2)_4SO_3HPY][HSO_4$], green and reusable catalysts, with excellent product yields under solvent-free conditions is reported. The products could be separated simply from the catalyst, and the catalyst could be recycled without noticeably decreasing the catalytic activity.*

Keywords 2-Aminobenzamide; aroyl chlorides; Brønsted acidic ionic liquids; 4(3H)-quinazolinones

INTRODUCTION

4(3H)-Quinazolinones are an important class of fused heterocycles with an array of biological activities such as inhibition of humane erythrocyte purine nucleoside phosphorylase[1] and poly(ADP-ribose) polymerase,[2] treatment of diabetes and obesity,[3] and antagonist,[4] antitumor,[5] anti-inflammatory,[6] insecticidal, and antimicrobial activity.[7] They are also important building blocks in the total synthesis of

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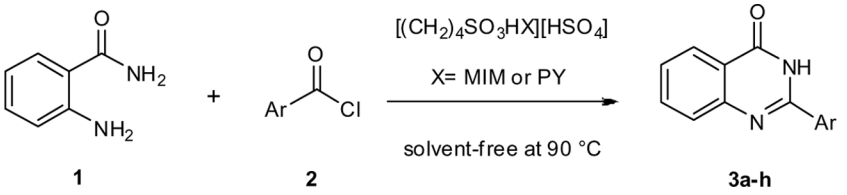


Scheme 1. Synthesis of 4(3H)-quinazolinones.

natural products[8] and are the constituents of some isolated naturally occurring alkaloids.[9] A small number of quinazolinones have been reported as potent chemotherapeutic agents in the treatment of tuberculosis.[10] The antihyperlipidemic activities of these compounds were also investigated.[11] There are several methods for the synthesis of 4(3H)-quinazolinones using I_2/KI,[12] $NaHSO_3$,[13] *P*-toluenesulfunic acid/2,3-dichloro-5,6-dicyanobenzoquinonce (DDQ),[14] $CuCl_2$,[15] $FeCl_3$,[16] $Ga(OTf)_3$,[17] $Bi(TFA)_3$-[nbp]),[18] $Sc(OTf)_3$,[19] H-Y zeolites,[20] and Preyssler nanoparticles[21] as catalysts. Though these methodologies are quite useful, most of the methods encounter some limitations, such as expensive catalysts, longer reaction times, and harsh reaction conditions. Therefore, the development of simple, efficient, clean, high-yielding, and environmentally friendly approaches using new catalysts for the synthesis of these compounds is an important task for organic chemists.

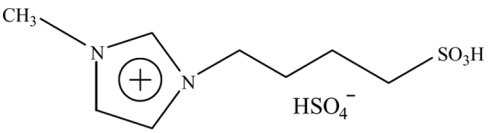
Ionic liquids (ILs), recognized as environmentally benign media, have been widely applied in many reactions as catalysts or dual catalyst–solvents because of their low vapor pressure, reusability, and high thermal and chemical stability.[22,23] The introduction of Brønsted acidic functional groups into cations or anions of the ILs, especially the SO_3H-functional groups, obviously enhanced their acidities and water solubilities.[24–27] Therefore, Brønsted acidic ILs can be used as highly efficient acid catalysts. Moreover, their polar nature makes them useful under solvent-free conditions. In fact, the use of Brønsted acidic ILs as catalysts is an area of ongoing activity. However, development and exploration of these catalysts are currently in the preliminary stages.

In continuation of our previous works on the applications of reusable acid catalysts in the synthesis of organic compounds,[28–31] herein we report a simple method for the green synthesis of 4(3H)-quinazolinones from reaction of 2-aminobenzamide with aroyl chlorides in the presence of Brønsted acidic ILs at 90 °C under solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

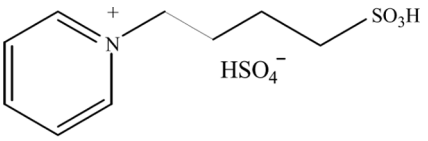
For our investigations, two Brønsted acidic ILs, 3-methyl-1-(4-sulfonic acid)-butylimidazolium hydrogen sulfate $[(CH_2)_4SO_3HMIM][HSO_4]$ (IL_1) and 1-(4-sulfonic acid)butylpyridinium hydrogen sulfate $[(CH_2)_4SO_3HPY][HSO_4]$ (IL_2), were prepared according to the 12 literature procedure.[32,33]

Initially to optimize the reaction conditions, the reaction of 2-aminobenzamide with 4-chlorobenzoyl chloride was used as a model reaction. Therefore, a mixture of 2-aminobenzamide (5 mmol) and benzoyl chloride (5 mmol) was heated on an oil



$[(CH_2)_4SO_3HMIM][HSO_4]$

Figure 1. Brønsted acidic IL_1 structure.



$[(CH_2)_4SO_3HPY][HSO_4]$

Figure 2. Brønsted acidic IL_2 structure.

bath at 90 °C under various reaction conditions. In the absence of the catalysts, the product **3c** was obtained in a trace amount after 15 min, whereas in a presence of a catalytic amount of the catalysts (2 mol%), the product **3c** was formed in a very short period of time with excellent yield.

Also, the reaction was carried out in various solvents and also under solvent-free conditions (Table 1). As shown in Table 1 for IL_1, in comparison to conventional methods the yield of the reaction under solvent-free conditions is greater and the reaction time is shorter. Also, the yield increased as the reaction temperature was raised, and at 90 °C the product **3c** was obtained in excellent yield. In the other studies, all the reactions were carried out at 90 °C in the presence of 2 mol% of the ILs under solvent-free conditions.

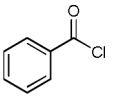
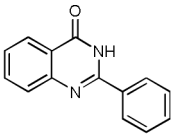
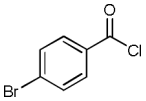
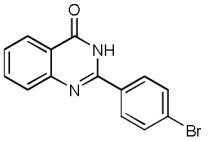
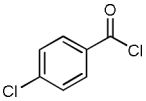
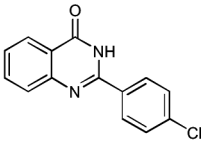
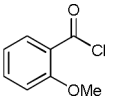
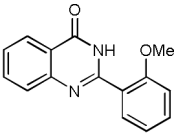
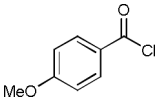
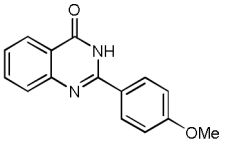
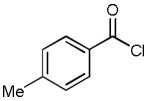
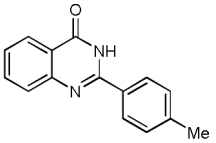
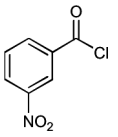
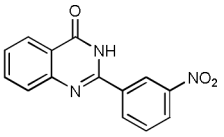
To evaluate the generality of this model reaction, we prepared a range of 4(3H)-quinazolinones under the optimized reaction conditions. In all cases, the expected products were obtained in excellent yields in very short reaction times. The results are shown in Table 2.

Table 1. Synthesis of compound **3c** in the presence of $[(CH_2)_4SO_3HMIM][HSO_4]$ (2 mol%) in different solvents at reflux temperature (for entry 6 at 90 °C)

Entry	Solvent	Time (min)	Yield (%)[a]
1	EtOH	5	80
2	CH_2Cl_2	8	74
3	THF	8	68
4	CH_3CN	12	64
5	H_2O	12	55
6	Solvent-free	1	94

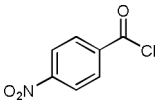
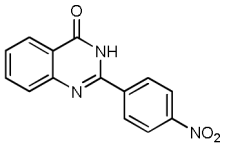
[a]Isolated yields.

Table 2. Synthesis of 4(3H) quinazolinones **3a–h** in the presence of IL_1 and IL_2 (2 mol%) under solvent-free conditions at 90 °C

Entry	Aroyl chloride	Products[a]	Time (min) (IL_1/IL_2)	Yield (%)[b] (IL_1/IL_2)	Mp (°C)
1		 **3a**	1/2	94/92	235–237[12]
2		 **3b**	1/<1	96/94	316–318[12]
3		 **3c**	1/<1	96/95	306–307[12]
4		 **3d**	2/4	88/85	209–211[12]
5		 **3e**	2/3	90/88	248–249[12]
6		 **3f**	2/4	96/96	242–244[12]
7		 **3g**	1/1	98/96	353–351[12]

(*Continued*)

Table 2. Continued

Entry	Aroyl chloride	Products[a]	Time (min) (IL_1/IL_2)	Yield (%)[b] (IL_1/IL_2)	Mp (°C)
8		 **3h**	1/1	90/88	362–364[12]

[a]All the products were known and characterized by ^{1}H NMR and IR spectral data and by comparison with authentic samples.[12]
[b]Isolated yields.

CONCLUSION

In conclusion, we have reported a new catalytic method for the synthesis of 4(3H)-quinazolinones from the reaction of 2-aminobenzamide with aroyl chlorides in the presence of Brønsted acidic ILs as efficient, reusable, and eco-friendly homogeneous catalysts. The catalysts can be reused after a simple workup, with a gradual decline of their activity being observed. High yields, short reaction times, simplicity of operation, and easy workup are some advantages of this protocol.

EXPERIMENTAL

All chemicals were commercially available and used without further purification. The Brønsted acidic ILs were synthesized according to the literature. Melting points were recorded on an Electrothermal type 9100 melting-point apparatus. The infrared (IR) spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR spectra (100 and 500 MHz) were recorded on Bruker AC100 and Bruker DRX500 spectrometers.

Typical Procedure for the Prepration of Brønsted Acidic Ionic Liquid $[(CH_2)_4SO_3HMIM][HSO_4]$ (IL_1)

A mixture of 1-methylimidazole (0.2 mol) and 1,4-butane sultone (0.2 mol) was charged into a 150-mL conical flask. The mixture was stirred at room temperature for 4 days until it became solid. The white solid zwitterion was washed repeatedly with ether, filtered to remove nonionic residues, and dried in vacuum. Then, a stoichiometric amount of concentrated sulfuric acid (98%, 10.9 mL) was added dropwise to the white solid zwitterion slowly at 0 °C. The mixture was stirred at 80 °C for 6 h. The product was washed with diethyl ether and dried in vacuo at 50 °C for 2 h to get the viscous clear ILs.

Brønsted acidic ionic liquid $[(CH_2)_4SO_3HPY][HSO_4]$ (IL_2) was prepared with a similar procedure.

General Procedure for the Synthesis of 4(3H)-Quinazolinones from the Reaction of 2-Aminobenzamide with Aroyl Chlorides Using Brønsted Acidic Ionic Liquid

To a mixture of 2-aminobenzamide (5 mmol) and aroyl chlorides (5 mmol), 2 mol% IL was added. The reaction mixture was heated on the oil bath at 90 °C for a few minunets. The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction, the mixture was poured into ice-cold water and stirred thoroughly, which resulted in precipitation of the desired product. The precipitated solid was filtered and washed with ethanol and water. The pure product was obtained by recrystallization from ethanol. The structure of the products was confirmed by ^{1}H NMR, IR spectra, and comparison with authentic samples prepared by reported methods.[12]

Recycling the Catalysts

All of these catalysts are soluble in water and therefore could be recycled from the filtrate. Catalysts were recovered by evaporation of the water, washed with diethyl ether, dried at 50 °C under vacuum for 1 h, and reused in another reaction without appreciable reduction in the catalytic activity. Such procedure applied for **3c** in the presence of IL_1 in a second run resulted in 94% yield.

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