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PII: S0040-4039(14)00659-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.04.047
Reference: TETL 44509

To appear in: *Tetrahedron Letters*

Received Date: 18 March 2014
Revised Date: 10 April 2014
Accepted Date: 14 April 2014

Please cite this article as: Amarasekara, A.S., Hasan, M.A., 1-(1-Alkylsulfonic)-3-methylimidazolium chloride Brönsted acidic ionic liquid catalyzed Skraup synthesis of quinolines under microwave heating, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.04.047

1-(1-Alkylsulfonic)-3-methylimidazolium chloride Brönsted acidic ionic liquid catalyzed Skraup synthesis of quinolines under microwave heating

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Abstract: 1-(1-alkylsulfonic)-3-methylimidazolium chloride Brönsted acidic ionic liquids are shown as excellent catalysts and reaction mediums for Skraup synthesis of quinolines under microwave conditions without the use of nitrobenzene as an oxidant and metal catalysts.

Keywords: Skraup synthesis, quinolines, acidic ionic liquid, microwave

1. Introduction

Quinolines are an important class of heterocyclic compounds as this ring system occurs in many natural products and biologically active compounds[1]. There are several classical named reactions that can be used to assemble the quinoline structural core, such as; Skraup[2,3,4,5], Doebner–Miller[6,5], Friedlander[7], Combes[8], Conrad–Limpach[9] and Pfitzinger[10] reaction. Generally these reactions involve a cyclo-condensation of aniline or aniline derivative with a carbonyl compound, followed by an aromatization with dehydration/oxidation reactions. The only exception is the Skraup reaction where glycerol is used as one of the starting materials; in this process the carbonyl compound acrolein is believed to be generated in situ by the dehydration glycerol. The use of glycerol, which is the main byproduct in the rapidly developing biodiesel industry as one of the starting materials is an attractive feature in the Skraup reaction and is in align with current interest in developing technologies for the utilization of renewable feedstocks for the preparation of useful chemicals and intermediates. Classical quinoline synthesis involves a heating of a mixture of aniline, glycerol, and sulfuric acid with an oxidizing agent like nitrobenzene, arsenic acid, ferric oxide or vanadic acid to 120-130 °C for several hours[11,12]. There are a number of drawbacks in the original method such as harsh reaction conditions requiring high temperature, highly acidic conditions, violent reactions in large scale operations, use of toxic substances like arsenic oxide, tedious isolation from complex reaction mixtures to poor yields. Later reports have shown that addition of boric acid or acetic acid can be used to control the violent reactions in Skraup synthesis, however in many cases an equivalent amount of oxidizing agent such as nitrobenzene is required to produce the quinoline product[3].

There are a few recent attempts to improve the glycerol based quinoline synthesis by heating under microwave conditions[13,14,15,16]. In one example Găină *et.al.* reported the use of microwave heating for the synthesis of 7-amino-8-methylquinoline by Skraup synthesis[15]. In this experiment, a mixture of 2,6-diaminotoluene, glycerol and excess of arsenic (V) oxide as an oxidant were subjected to microwave heating in concentrated sulfuric acid to produce 7-amino-8-methylquinoline in 32% yield.

Ionic liquids are an emerging class of materials; first recognized as non-volatile reaction mediums, but in recent years branched in to variety of applications such as catalysts, gas adsorbents, and chromatography stationary phases. The sulfonic acid group functionalized ionic liquids are a special class in ionic liquid arena; these new molecular architectures can combine acid properties and ionic liquid characteristics into a single material and often used as highly effective acid catalysts under mild conditions[17,18,19]. The enhanced catalytic activity of the acidic ionic liquid systems are frequently attributed to their ability to bind with substrates by polar interactions such as hydrogen bonds[20]. Our interests in the applications of sulfonic acid group functionalized Brönsted acidic ionic liquids (BAILs) in dehydration of carbohydrates and biomass processing[21,22,23,24,25,26] has led us to explore the acidic ionic liquid catalyzed dehydration of glycerol to acrolein and application in the Skraup quinoline synthesis.

Imidazolium cation based sulfonic acid group functionalized ionic liquids were selected for the study due to their distinct ability to dehydrate carbohydrates under mild conditions[27,20]. The Brönsted acidic ionic liquids **1a,b** used in this study were prepared by condensation of methyl imidazole with 1,3-propane or 1,4-butane sultone and acidification of the zwitterion with concentrated HCl as shown in figure 1[21]. The general reaction of using Brönsted acidic ionic liquids **1a,b** as catalysts as well as solvents for the Skraup quinoline synthesis is shown in figure 2. In our preliminary investigations we have attempted to substitute Brönsted acidic ionic liquids for sulfuric acid under thermal and microwave (MW) heating conditions. Where we have studied mixtures of aniline (**2a**), glycerol (**3**), BAIL (**1a**), and nitrobenzene in 1: 3: 1.5: 1.1 molar ratios, as shown in entries 1, and 2 of table 1. In the first experiment, conventional thermal reaction was tested by heating the mixture in an oil bath at 120 °C, for 6 h (entry 1). This reaction produced only 10% yield of quinoline. Next microwave heating was tested on second reaction mixture of similar composition. The microwave heating for 100 s (five 20 s MW exposures with 5 s cooling intervals between pulses) produced 71% yield of quinoline as shown in the second entry in table 1. The ^{1}H NMR analysis of the crude reaction mixture showed that all the nitrobenzene used remains unaffected, suggesting that either nitrobenzene is not required for the oxidation step or acting as a catalyst in the reaction. In the next experiment we have omitted nitrobenzene in order to identify the role of nitrobenzene, and used a mixture of aniline, glycerol, and BAIL in 1: 3: 1.5 molar ratio, as shown in entry 3 of table 1. Interestingly, this reaction produced 74% yield of quinoline showing that it is not necessary to use nitrobenzene or other oxidant for the oxidation step in the Skraup quinoline synthesis when BAIL is used in place of sulfuric acid and under microwave heating conditions. We believe that oxygen from air acts as the oxidant under the current reaction conditions.

In the next step we have explored the possibility of reducing the amount of BAIL catalyst used for the reaction. In this experiment only a 0.1 equivalent of BAIL was used in comparison to aniline as shown in entry 4. However, this reaction failed to turn out a high yield of quinoline as in the previous experiment, produced only 12% yield of quinoline and most of the glycerol remained unreacted. This low catalyst loading experiment demonstrated that it is necessary to use equivalent amounts of BAIL to act as a catalyst as well as the solvent medium for the glycerol to acrolein dehydration step.

In order to prove the general applicability of the reaction on substituted anilines we have tested the method on two other aromatic amines *p*-toluidine (**2b**) and *o*-chloroaniline (**2c**) using BAIL catalyst **1a** as shown in entries 5 and 6. These reactions also produced corresponding quinolines 6-methylquinoline (**4b**) and 8-chloroquinoline (**4c**) in good yields and the products were identified by comparison of ^{1}H and ^{13}C NMR spectra with published data[28,29,30]. The analogous Brönsted acidic ionic liquid 1-(1-butylsulfonic)-3-methylimidazolium chloride (**1b**) was also tested in the Skraup quinoline synthesis for the preparation of quinolines **4a-c** using general quinoline synthesis procedure (see the supporting information) and the results of these experiments are shown in entries 7-9 in table 1. We are currently working on recovering the ionic liquid from the aqueous phase after separation of the product and reusing in the Skraup synthesis. A comparison of ^{1}H NMR spectra of the ionic liquid recovered with the fresh ionic liquid showed that no decomposition occurs under the microwave reaction conditions used.

In conclusion we have shown that 1-(1-alkylsulfonic)-3-methylimidazolium chloride Brönsted acidic ionic liquids are excellent catalysts and reaction mediums for Skraup synthesis of quinolines, where acrolein is generated in situ by dehydration of glycerol under microwave conditions. There are a number of advantages of using 1-(1-alkylsulfonic)-3-methylimidazolium chloride Brönsted acidic ionic liquids as reaction mediums and catalysts in the Skraup synthesis. This include; shorter reaction time, better yields, ease of isolation of the quinoline product and most importantly elimination of the use nitrobenzene or other oxidizing agents and additional metal catalysts.

Acknowledgments

We thank NSF grants CBET-0929970, CBET-1336469, HRD-1036593, and USDA grant CBG-2010-38821-21569 for financial support.

Table 1. Product yields and reaction conditions used in the Brönsted acidic ionic liquid catalyzed Skraup synthesis of quinolines

Entry	Ar-NH_2	BAIL	Ar-NH_2:glycerol:BAIL, Conditions	Product, Yield %
1	**2a**	**1a**	1: 3: 1.5, with 1.1 equivalent of nitrobenzene, oil-bath heating 120 °C, 6 h	**4a**, 10%
2	**2a**	**1a**	1: 3: 1.5, with 1.1 equivalent of nitrobenzene, MW for 100 s	**4a**, 71%
3	**2a**	**1a**	1: 3: 1.5, MW for 100 s	**4a**, 74%
4	**2a**	**1a**	1: 3: 0.1, MW for 100 s	**4a,** 12%
5	**2b**	**1a**	1: 3: 1.5, MW for 100 s	**4b**, 78%
6	**2c**	**1a**	1: 3: 1.5, MW for 100 s	**4c**, 70%
7	**2a**	**1b**	1: 3: 1.5, MW for 100 s	**4a**, 73%
8	**2b**	**1b**	1: 3: 1.5, MW for 100 s	**4b**, 76%
9	**2c**	**1b**	1: 3: 1.5, MW for 100 s	**4c**, 67%

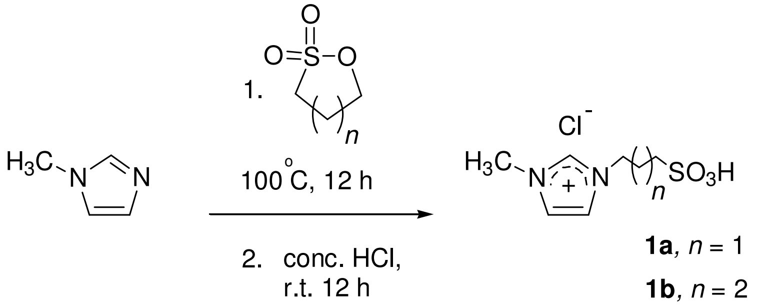

Figure 1. Synthesis of Brönsted acidic ionic liquids (**1a,b**)

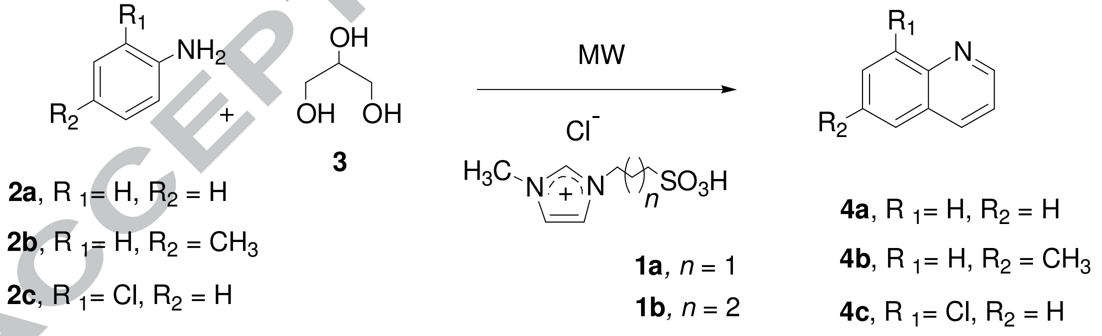

Figure 2. Brönsted acidic ionic liquid (**1a,b**) catalyzed synthesis of quinolines (**4a-c**)

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