Microwave-Assisted Friedel-Crafts Reaction in the Presence of Ionic Liquids

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Introduction

The Friedel-Crafts reaction is one of the most fundamental reactions from synthetic, industrial and pharmacological points of view. This reaction has been widely utilized in the production of pharmaceuticals and fine chemicals. Friedel-Crafts reactions proceed through electrophilic aromatic substitution (EAS) to generate carbon-carbon bonds. In general, this reaction requires a volatile and hazardous halogenated solvent, Lewis acids such as $AlCl_3$, HF or H_2SO4, long reaction time, followed by difficult product recovery and purification. In order to eliminate use of volatile hazardous solvents and shorten reaction times, we have studied microwave assisted Friedel-Crafts reactions using $AlCl_3$-ionic liquid (Al-IL) as the solvent and Lewis acid. Ionic liquids (ILs), known as molten salts, were mainly used in electrochemical studies. In recent years the special physical properties of these salts have introduced them as an ideal non-volatile solvent and catalysts in conventional and microwave assisted organic synthesis. Due to their ionic nature Al-ILs are excellent absorbent of microwave irradiation. Also the mixture of these salts and Lewis acids (e.g. aluminum trichloride) are liquid at room temperature.

The acidity of the Al-IL depends on the ratio of $AlCl_3$ to butyl-3-methyl imidazolium chloride [bmim]Cl. The acid-base properties of this system are described by this equilibrium[1]:

$$2\ AlCl_4^- \rightleftharpoons Al_2Cl_7^- + Cl^-.$$

$Al_2Cl_7^-$ is the Lewis acid and Cl^- the Lewis base. The higher ratio of $AlCl_3$ to [bmim]Cl provides higher concentration of $Al_2Cl_7^-$. This ratio is defined as (N):

$$N = [AlCl_3/ (AlCl_3 + [bmim]Cl)]$$

In a 1:1 ratio of Al to [bmim]Cl (N = 0.5), aluminum is present entirely in the tetrachloroaluminate form (natural melts) and in the 2:1 ratio (N = 0.6), only the heptachloroaluminate form (acidic melts) exists.

In this paper we report use of Al-[bmim]Cl (N = 0.6) in microwave assisted Friedel-Crafts acylation of aromatic compounds. The proposed mechanism for this reaction is the formation of several intermediates including the complex of acid chloride with one or two $AlCl_3$ and formation of benzylium cation[2], which is the key intermediate in these electrophilic aromatic substitutions, followed by release of HCl gas to form the final product.

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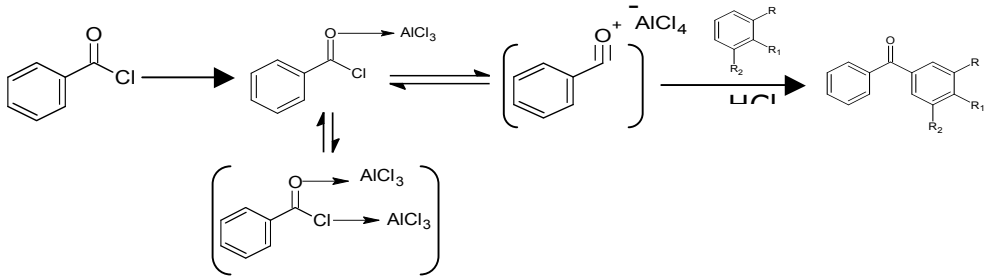
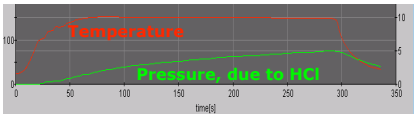


Activated and deactivated aromatic compounds were acylated using benzoyl chloride (Table 1). The formations of product were followed by RP-HPLC, and Ft-IR. In general 1.2 eq. of Al-[bmim]Cl was added to a mixture of 1 eq. of benzoyl chloride and 1.2 eq. of aromatic. These mixtures were heated in a controlled microwave synthesizer for 3 minutes at 150 ºC. The final products were isolated by absorbing the reaction mixture onto silica gel and purifying it by automated flash chromatography using an ethyl acetate/hexane gradient.



The reaction profile of this microwave assisted Friedel-Crafts acylation is shown for 4 mmol scale of benzoyl chloride in a 5 mL microwave vial.

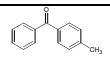
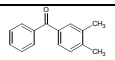
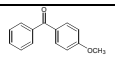
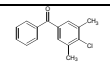
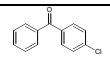
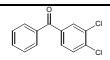
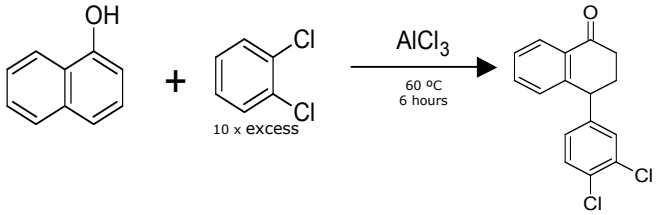
Product	% Isolated Yield	% HPLC Purity
	85.9	94.8
	88.3	95.4
	90.5	87.2
	87.4	89.3
	83.3	91.2
	84.3	88.7

Table 1: The results of Microwave-assisted Friedel-Crafts Acylation of aromatics with benzoyl chloride using Al-[bmim]Cl (N = 0.6) at 150 ºC for 3 minutes.

4-(3',4'-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (8) which is the starting material in the synthesis of the antidepressant medication Zoloft[3], is prepared through Friedel-Crafts alkylation of phenol. The literature reported synthesis of this 1-(2H)-naphthalenone requires 1,2-dichloroethane in 10 times excess as solvent, followed by long reaction time plus multiple steps in the purification process.



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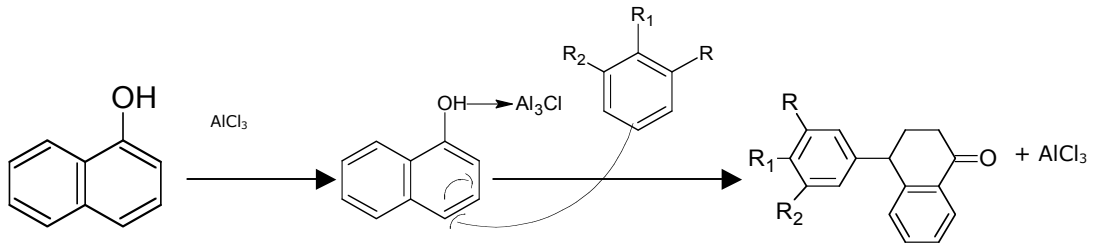
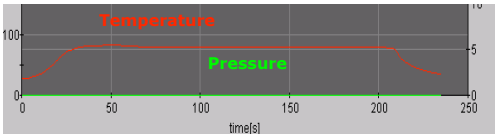
Due to large demand of Zoloft, there is a great need to develop a cost-effective and safe synthetic and purification route for this material. We have studied the effect of microwave irradiation in shortening the reaction time using varieties of aromatic compounds, at different concentrations and temperatures for alkyation of naphthol. In general, a mixture of 1 eq. naphthol to 5-10 eq. substituted aromatic compound and 2.5 eq. of $AlCl_3$, was heated in microwave for 3-8 minutes at 80-150 ºC. In all the cases the isolated yields of desired product were less than 25%. When these reactions were tried in heterogeneous condition using only 1.2 eq. of substituted aromatic to 1-naphthol and 2 eq. of $AlCl_3$ desired product was formed in 90.71 % yield. These results confirm the fact that the rate of Friedel-Crafts alkyaltion of phenol is very slow; and the concentration of 1-naphthalenole and $AlCl_3$ plays the key role in the yield of product. This reaction was repeated using 1.5 eq. Al-[bmim]Cl (N = 0.65) as solvent and catalyst. The desired naphthalenone was formed in 96.6% yield. The proposed mechanism for this reaction is the formation of complex between $AlCl_3$ and oxygen of naphthol followed by electrophilic aromatic substitution and proton transfer.





The reaction profile of the microwave assisted Friedel-Crafts alkylation for the use of Al-[bmim]Cl (N = 0.65) is shown for 3.6 mmole of naphthol in a 5 mL microwave vial.

The heterogeneous reaction mixture of these reaction appeared as a yellow solid. After heating in the microwave for 3 minutes at 80 ºC, reaction mixture turned to a green to dark brown liquid.[4]

The product was isolated without any liquid-liquid extraction. Simply the reaction mixture was pre-absorbed onto silica and transferred on top of a silica cartridge followed by flash chromatography, using ethyl acetate hexane as the mobile phase.[5]

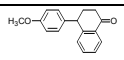
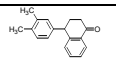
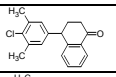
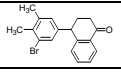
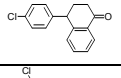
Product	% Isolated Yield	% HPLC Purity
	73.6	89.9
	78.3	90.3
	69.5	92.5
	78.4	85.8
	83.3	91.2
	84.3	88.7

Table 2. The results of Microwave-assisted Friedel-Crafts alkylation using 1.2 eq. of substituted aromatic to 1 eq. of 1-naphthol and 2 eq. of $AlCl_3$ at 80 ºC for 3 minutes.

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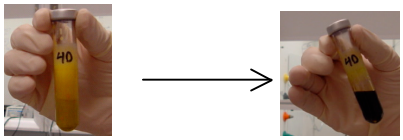
Conclusion

We have established that ionic liquids prepared from $AlCl_3$ and [bmim]Cl with different Lewis acid strength can be used as a catalyst and a solvent in the microwave assisted Friedel-Crafts acylation and alkyation of phenol. Use of these salts in microwave assisted syntheses eliminated the need to use a volatile and hazardous halogenated solvent and also shortened the reaction times from hours to minutes. Also we have shown by absorbing the reaction mixture onto silica, followed by normal phase flash chromatography products can be isolated without any liquid-liquid extraction in short time and high yield and purity.

References:

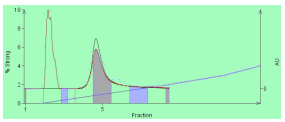
1. Boon, J.A., Levisky, J., Pflug, L., Wilks, J.S., *J. Org. Chem.* 1986, 51, 480-483.
2. Csihony, S, Mehdi, H. Homonny, Z., Vértes, A., Farkas, Ö., Horváth, I. T., *J. Chem. Soc., Dalton Trans.*, 2003, 680-685.
3. Quallich, G., CHIRALITY, 2005, 17:S120-S126.

4.

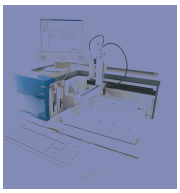


Before After

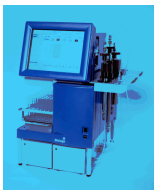
5.



Flash Chromatography Separation of Compound 8



Emrys™ Liberator Microwave System



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