

Investigation of the Effect of Different Ionic Liquids on the Mannich Reaction of Paraformaldehyde, Secondary Amines and Naphthols

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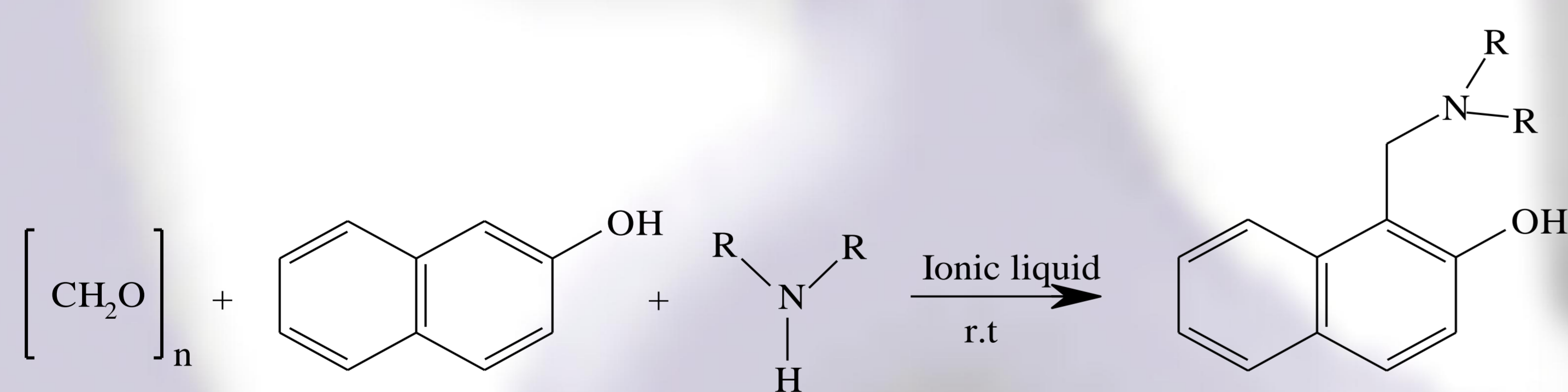
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1. Introduction

The *Mannich* reaction is one of the most important C-C bond formation methods in organic synthesis, and its products (*Mannich* bases) are of considerable importance in industry, natural products chemistry, and pharmacy. Various substrates have been used as the CH-acidic component in *Mannich* reactions, such as ketones, β -ketoesters, malonates, and nitro compounds. Also, electron-rich aromatics have been aminoalkylated in *Mannich* reactions to give useful building blocks for the synthesis of pharmaceuticals, pesticides, and natural products [1].

In the past decade, ionic liquids attract much interest in the context of green synthesis. Use of ionic liquids as catalysts and solvents for *Mannich* reaction has been reported in recent years, due to their unique properties, including negligible vapor pressure and high thermal and chemical stability, high conductivity and low volatility [2,3].

We now wish to describe our preliminary results on an efficient three-component and one-pot method for aminomethylation of electron-rich aromatic compounds using paraformaldehyde, secondary amines and an electron-rich aromatic compound such as α - or β -naphthol, at room temperature in ionic liquids with good to high yields and short reaction time (**Scheme 1**).



Scheme 1. Three component reaction between paraformaldehyde, secondary amines and naphthols.

2. Results

A mixture of 1.0 mmol naphthol, 1.0 mmol paraformaldehyde and 1.0 mmol secondary amine and about 0.5 cc of an ionic liquid as catalyst and solvent were mixed and the mixture was stirred at room temperature for 1 hour. The progress of the reaction was monitored with TLC, then diethyl ether or ethyl acetate (5 mL) were added for 3-4 times. The organic phase was separated, washed with water, dried over $MgSO_4$, and the solvent was removed using a rotary evaporator. The crude product was further purified by recrystallization and was characterized by comparison of IR and melting point.

In the primary experiments, different ionic liquids such as octyl methyl imidazolium tetra fluoro borate, butyl methyl imidazolium tetra fluoro borate, ethyl methyl imidazolium tetra fluoro borate and butyl dimethyl imidazolium tetra fluoro borate were studied for *Mannich* reaction of paraformaldehyde, pyrrolidine and β -naphthol at room temperature. Among the others, [omim] BF_4 was found to be the most efficient ionic liquid for this reaction. The product can be separated easily from the reaction system, and the ionic liquid can be reused.

With knowing the best condition for this reaction, we have prepared different *Mannich* bases in Table 1 with good to high yields.

Table 1. Some examples of the three component reaction between paraformaldehyde, secondary amines and naphthols in presence of [omim] BF_4 .

Naphthol	Aldehyde	Amine	Product	Time/h	Yield %
	$[CH_2O]_n$			1	85
	$[CH_2O]_n$			1.5	60
	$[CH_2O]_n$			1	> 50

3. Discussions and conclusion

In conclusion, a mild, one-pot and fast aminomethylation of β -naphthol or α -naphthol with secondary amines at rt and in presence of ionic liquids has been achieved in good to high yields. The reaction time was 1–1.5 h.

4. References:

- [1] Ali Sharifi, Mojtaba Mirzaei, and M. Reza Naimi-Jamal, *Monatshefte fur Chemie* **2001**, 132, 875-880.
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- [3] Z. Guoying, J. Tao, G. Haixiang, L., Buxing, H., Jun, H., Donghai, S., *Green Chem.* **2004**, 6, 75.