

One-pot mannich base synthesis using dehydro acetic acid and protic ionic liquids

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ABSTRACT

Three-component Mannich reaction of ketones, aromatic aldehydes and aromatic amines was catalyzed by four Bronsted acidic ionic liquids comprising of iodide and borate at room temperature. Ionic liquid have been used as catalyst and solvent to produce some Mannich bases in high yield (75%) and shorter reaction time (20 minutes). Work up has been facilitated by simple extraction with water to recover ionic liquid for recycling up to four times without any significant loss in activity.

Key words: Dehydroacetic acid, Mannich Reaction

INTRODUCTION

Multicomponent reactions have been proven to be an economic and facile approach for building of complex molecules in one synthetic step. A remarkable diversity can be achieved by varying the starting materials. Such appealing reactions offer an elegant course for synthesis of carbon-carbon and carbon-hetero atom linkages with high atom economy, simple methodology and high selectivity in one-pot procedure [1]. Mannich reaction is a fundamental method for a formation of β -amino carbonyl compounds of synthetic intermediates for natural product synthesis (alkaloids and polyketides) and in pharmaceutical industry [2]. The conventional catalysts for the synthesis of classical

Mannich bases are mainly organic and mineral acids such as acetic acid [3], proline [4], p-dodecylbenzenesulfonic acid [5] and lewis acids [6]. In contribution to green chemistry, many studies reported on employing traditional volatile and flammable solvents to benign alternatives such as non-volatile solvent, supercritical system, aqueous media or solventless conditions. In this context, Mannich type reactions have also been reported in water [10]. In current years, ionic liquids (ILs) have been used as an environmentally benign solvents, efficient catalysts and a promising substitutes for volatile organic solvents and traditionally used acid/ base catalysts in construction of organic moieties [11, 12]. Use of organic solvents in reaction mixture usually leads to serious safety issues such as volatility, flammability and toxicity [12, 13]. The use of ionic liquids as reaction media offers a convenient solution to both solvent emission and catalytic recycling problems [10]. Beside high activity and selectivity, these versatile liquids are center of interest as they possess unique properties such as flexibility, high stability in air and water, easy separation and purification processes, reusability, non-volatility, non-flammability, noncorrosive nature, controlled immiscibility, low toxicity, low vapour pressure, low viscosities, high thermal and chemical stabilities [14-16]. Recently work on Mannich reaction is being carried out using ionic liquids.

METHODOLOGY

Chemicals All the reacting molecules used such as Dehydroacetic acid [3-Acetyl-4-hydroxy-6-methyltetrahydro-2H-pyran-2-one], aromatic amines, aromatic aldehydes, methyl imidazole with 1,3-propane sultone and 1,4-butane sultone were purchased from Sigma Aldrich and used without any purification procedure. Melting points of the Mannich bases were determined in open capillaries and are uncorrected.

Synthesis of ionic liquids: The task specific ionic liquids have been synthesized by using an analogous method as reported in literature [17-18] with slight modifications. 1,3-propane sultone and 1,4-butane sultone were reacted

with *N*-methylimidazole in equimolar ratio affording the respective zwitterions that were then converted to ILs by acidification with two protic acids. The corresponding ILs was used further without any purification.

Mannich reaction: A typical procedure Dehydroacetic acid (10 mmol), benzaldehyde (10 mmol), aniline (10 mmol) and 5 mmol of catalyst were taken in round bottom flask at 25°C. The completion of reaction was determined using TLC. For work up, some amount of water was added and extraction with ethyl acetate was done. The excess solvent was evaporated via rotary evaporator to afford solid product which was recrystallized from acetonitrile and dried under vacuum until constant weight was obtained. At the end, the aqueous layer containing IL was vacuum dried at 70 °C to reuse ionic liquid for future use.

RESULTS AND DISCUSSIONS

The ionic liquids were synthesized by the reaction of methyl imidazole with 1,3-propane sultone and 1,4-butane sultone for preparation of Mannich bases. Spectral analysis confirmed the structure of synthesized ILs. these synthesized ILs were used to catalyze Mannich reaction using dehydroacetic acid (10 mmol), benzaldehyde (10 mmol) and aniline (10 mmol) as model substrates at room temperature. The reaction mixture gradually turned to highly viscous material within 30 minutes. The reaction work up was done by addition of a small amount of water followed by extraction with ethyl acetate and finally evaporation of organic solvent. For purification, the synthesized Mannich bases were recrystallized from acetonitrile and the aqueous layer was further dried for recycling ionic liquid. Among the four protic ILs 75% of Mannich base was obtained as highest yield by 1-methyl-3-(3-sulfopropyl)-imidazolium borate ([mimps]HBO) in 20 minutes [Table 1].

Table1: Effect of ionic liquid on yield of Mannich base^a

Entry	Catalyst	SolventUsed	ReactionTime (min)	Isolated Yield (%)
01	-	-, EtOH ^{b,c,d}	10	NR ^{a,b,c,d}
02	[mimps]I	-, EtOH ^{b,c,d}	120	NR ^{a,b,c,d}
03	[mimbs]I	-, EtOH ^{b,c,d}	120	NR ^{a,b,c,d}
04	[mimps]HBO	-	20	75
05	[mimbs]HBO	-	30	69

^aReaction conditions: Dehydroacetic acid(10mmol), benzaldehyde (10mmol), aniline(10mmol), catalyst (5mmol) r.t.

^byield in presence of solvent | ^cyield obtained at 60°C | ^dyield obtained at 80°C

Table2: Effect of amount of ionic liquid on Mannich reaction

Sr. No	IonicLiquid (mmol)	ReactionTime (min)	IsolatedYield(%)
01	0	24 h	0
02	1	30	71
03	3	30	66
04	5	30	75
05	7	30	74
06	9	30	75

Table3: Effect of ionic liquid/solvent on Mannich reaction^a

Entry	Ionic Liquid / Solvent	Isolated Yield	Entry
01	[mimps]HBO	75	01
02	[mimps]HBO/H ₂ O	71	02
03	[mimps]HBO/C ₂ H ₅ OH	69	03
04	[mimps]HBO/CH ₂ Cl ₂	63	04
05	[mimps]HBO/C ₆ H ₆	42	05

^aReaction conditions: cyclohexanone (10mmol), benzaldehyde (10mmol), aniline (10mmol), [mimps]HBO (5mmol)r.t.

For determining the amount of IL used, the reaction of Dehydro acetic acid(10mmol), benzaldehyde(10mmol), aniline (10mmol) was catalysed under variable amounts of [mimps] HBO at room temperature. It was found that the yields of the Mannich base was increased with the increase in the amount of [mimps] HBO (Table2), where 5mmol was found as an optimal amount. This observation might be rationalized on basis of pKa, which depicts that their action is catalysed by conjugate bases (Γ and B (OH)₄⁻) of the protic acids(HI and H₃BO₃).

Mannich reaction was also conducted in polar and non-polar organic solvents to check the effect of solvent on the yield of product for the estimation of the best reaction conditions. Here in the action of cyclohexanone, benzaldehyde and aniline was selected as standard reaction. It was found that their action in which no solvent was used gave the highest yield of 75% among the solvents selected showing that the ionic liquid may act as dual-reagent without need of any external solvent (Table3).

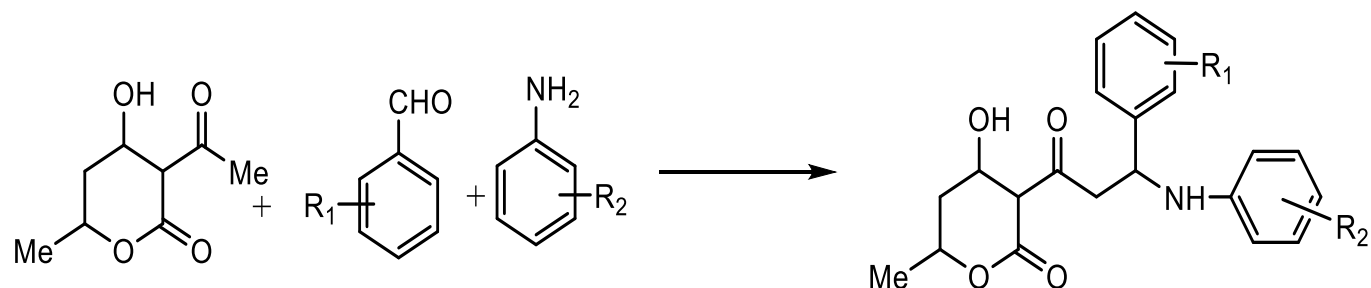


Table 4. Preparation of Mannich base using [mimps] HBO as catalyst

Sr.No	R ₁	R ₂	Product	Yield	Mp(°C)
01	H	H		75	114-115
02	CH ₃	H		73	150-151
03	OCH ₃	H		75	178-179
04	NO ₂	H		74	141-153
05	Cl	H		75	130 -132

CONCLUSION

Present methodology deals with a useful and effective way for synthesis of Mannich bases at room temperature in short reaction duration (20minutes) and good yield (75%)using ILs as dual reagents. There portedsynthetic method can be expected as an environmentally green procedure that might give valuable organic transformations by substituting conventional volatile, toxic and flammable organic solvents with ILs. Simplex perimental and work up conditions along with reusability of IL can contribute a new method of green chemistry concept.

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