Efficient and Rapid Stereoselective Synthesis of *trans*-4,5-Diaminocyclopent-2-enones by Acidic Ionic Liquid under Solvent-free Conditions

D. Ramesh, T. Srikanth Reddy, M. Narasimhulu, S. Rajaram, N. Suryakiran, K. Chinni Mahesh, and Y. Venkateswarlu*
Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500007, India

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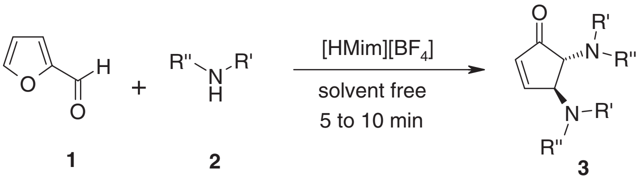
Acidic ionic liquid 1-methylimidazolium tetrafluoroborate $[HMim]^+[BF_4]^-$, was successfully employed as a reusable catalyst for the reaction of furfural and secondary amines to yield 4,5-diaminocyclopent-2-enones exclusively as trans diastereomer in the absence of solvent. The inherent Brønsted acidity and high polarity of ionic liquid resulted in the significant enhancement in the reaction rate.

The synthesis and selective functionalization of cyclopentenones have been a focus in recent years. Recently, (−)-agelastatin A, an architecturally unusual antineoplastic alkaloid has been isolated from the axinellid sponge *Agelas dendromorpha* by Pietra and co-workers.[1] The retrosynthesis analysis of (−)-agelastatin A leads to an embedded *trans*-diaminocyclopentane motif.[2] A literature search revealed that amines **2** react with furfural (**1**) in 2:1 ratio in the presence of protic acids to give highly colored Stenhouse salts.[3]

Lewis and Mulquiney reported in low yield the formation of *trans*-4,5-diaminocyclopent-2-enones (**3**) and substantially high yield of thermodynamically stable 2,4-diaminocyclopent-2-enone from the reaction of furfural (**1**) and amines **2** under harsh conditions i.e. refluxing in methanol in the presence of hydrochloric acid.[4] Recently, Li and Batey developed a method for exclusive formation of **3** using $Sc(OTf)_3$ and $Dy(OTf)_3$.[5]

However, many of these reported methods suffer from one or more disadvantages, such as long reaction time, strictly anhydrous conditions, expensive reagents, or harsh reaction conditions. In addition, reported methods used highly polar organic solvents leading to complex isolation and recovery procedures. Therefore we sought to develop a more efficient and convenient method for synthesis of **3**, which avoids these drawbacks. In recent years ionic liquids have attracted extensive interest as excellent alternatives to organic solvents, due to their favorable properties, such as reusability, non inflammability, no measurable vapor pressure, low cost, high thermal stability, ease of handling and ability to solvate a broad spectrum of organic substrates that has widened the horizon of their applicability.[6] As a result, ILs are considered as promising alternative solvents for organic reactions.[7] Brønsted ILs have been recently reported to serve as both reaction medium and catalyst in many transformations.[8] In that, $[HMim]^+[BF_4]^-$ has been exploited as an efficient Brønsted acid promoter IL in various organic transformations.[9] There are no previous reports on the reaction of furfural with secondary amines using IL.

In this report (Scheme 1) we describe a rapid and efficient method for synthesis of **3**, compared to most of the existing protocols, in which this method does not need solvent because $[HMim]^+[BF_4]^-$ IL plays the dual role of catalyst and reaction medium, and does not need anhydrous conditions. In continuation of our studies on the development of new protocols under solvent-free conditions and recyclable reaction medium,[10] we wish to report here the use of $[HMim]^+[BF_4]^-$ IL as catalyst and solvent.



Scheme 1.

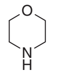
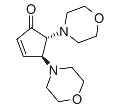
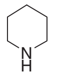
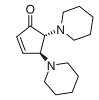
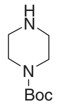
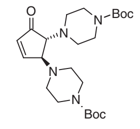
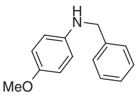
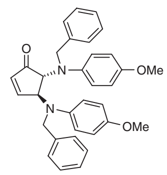
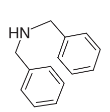
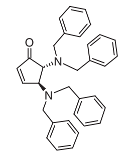
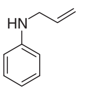
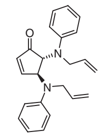
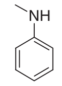
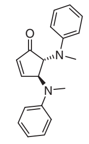
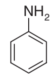
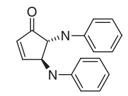
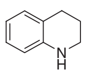
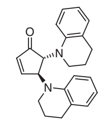
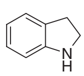
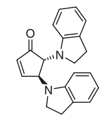
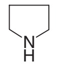
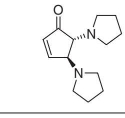
Initially we studied the reaction of furfural with morpholine using 10 mol % of various Lewis acids such as $La(NO_3)_3$, I_2, $BiCl_3$, and $Bi(NO_3)_3$ with 4 Å MS in acetonitrile at room temperature for 10 h to form corresponding **3** in 40, 18, 86, and 95% yields respectively. Also we studied the reaction without catalyst and also with the IL tetrapropylammonium L-proline carboxylate [TPA][L-Pro] IL[10a] to yield **3** in 10% at room temperature for 20 h (Table 1). However, when we used $[HMim]^+[BF_4]^-$ IL, the reaction was completed in 5 min under solvent-free conditions in 98% yield with complete trans selectivity, at room temperature. Encouraged by the reaction, furfural was allowed to react with various other secondary amines (Table 2, Entries 1–11). The reaction of furfural with the amines such as dibenzylamine (Table 2, Entry 5), *N*-methylaniline (Table 2, Entry 7), tetrahydroquinoline (Table 2, Entry 9), and indoline (Table 2, Entry 10) has been completed in 5 min with excellent yields. Further, Boc group was not effected during the reaction (Table 2, Entry 3) under acidic conditions of IL $[HMim]^+[BF_4]^-$. The reusability of IL is always an advantage for viable commercial processes. We have checked the reusability of the IL in the reaction of furfural with morpholine for four runs and find the product formation in 98, 97, 97, and 95% respectively. The formation of trans diastereomer was established from the coupling constant $J = 3$ Hz between H-4 and H-5 in the ^{1}H NMR spectrum.[5,11,12]

Table 1. Reaction of furfural (**1**) with morpholine using various catalysts

Entry	Catalyst	Time	Solvent	Yield[a] /%
1	$La(NO_3)_3$	10 h	Acetonitrile	40
2	I_2	10 h	Acetonitrile	18
3	$BiCl_3$	10 h	Acetonitrile	86
4	$Bi(NO_3)_3$	10 h	Acetonitrile	95
5	No catalyst	20 h	Acetonitrile	10
6	[TPA][Pro] IL	20 h	No solvent	10
7	$[HMim]^+[BF_4]^-$ IL	5 min	No solvent	98

[a] Isolated yields after chromatographic purification.

Table 2. Reaction of furfural (**1**) with various secondary amines using $[HMim]^+[BF_4]^-$ IL under solvent-free conditions

Entry	Substrate	Product	Time /min	Yield /%[a]
1			5	98
2			10	92
3			10	83
4			10	85
5			5	98
6			10	76
7			5	92
8			10	78
9			5	94
10			5	98
11			10	90

[a]Isolated yields after chromatographic purification.

In conclusion, we have described a fast and efficient synthesis of *trans*-4,5-diaminocyclopent-2-enones (**3**) in IL $[HMim]^+[BF_4]^-$ as catalyst as well as reusable reaction medium. In addition to simplicity and solvent-free conditions this method provides excellent yields of **3** exclusively trans selectivity in short reaction times (5–10 min), which makes it is a useful and important addition to the existing methods.

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11 **General experimental procedure**: To a mixture of furfural (**1**) (1 mmol) and morpholine (2 mmol), $[HMim]^+[BF_4]^-$ IL (1 mL) was added, the reaction mixture was allowed to stir for the appropriate time (Table 2) at room temperature. The progress of the reaction monitored by TLC ($R_f = 0.5$, $MeOH:CH_2Cl_2$ in 0.5:9.5). After completion of the reaction water (5 mL) was added and the product was extracted into ethyl acetate (3 × 10 mL). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure to give crude product, which was purified by silica gel column chromatography eluting with ethyl acetate in hexane to get pure 4,5-diaminocyclopent-2-enones. The water layer was evaporated to dryness under reduced pressure and the ionic liquid was reused for the next four runs.

12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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