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Efficient and rapid synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles in the acidic ionic liquid 1-*n*-butylimidazolium tetrafluoroborate

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Abstract—An efficient synthesis leading directly to 1-substituted-1*H*-1,2,3,4-tetrazoles from easily available amines and sodium azide in stoichiometric proportions using a room-temperature ionic liquid, namely, 1-*n*-butylimidazolium tetrafluoroborate in excellent yields is described. The inherent Brønsted acidity and high polarity of the IL results in a significant enhancement in the reaction rate.

Tetrazoles are an increasingly popular functionality with wide ranging applications.[1] This functional group has roles in coordination chemistry as a ligand, in medicinal chemistry as a metabolically stable surrogate for a carboxylic acid group,[2] and in various materials science applications including propellants[3] and explosives.[4] Furthermore, tetrazole moieties are important synthons in synthetic organic chemistry.[5] Although many 5-substituted tetrazoles are known, there is still a dearth of efficient processes for the synthesis of 1-substituted tetrazoles. The routes to 1-substituted tetrazoles include acid-catalyzed cycloaddition between hydrazoic acid and isocyanides,[6] acid-catalyzed cycloaddition between isocyanides and trimethyl azide,[7] acetic acid or trifluoroacetic acid catalyzed cyclization between primary amines, or their salts, with an orthocarboxylic acid ester and sodium azide,[8] and PCl_5 and ytterbium triflate catalyzed cyclizations from an amine, triethyl orthoformate, and sodium azide in highly polar solvents.[9]

Each of these methods has one or more of the following drawbacks: expensive and toxic metal catalysts, harsh reaction conditions, refluxing for a prolonged period of time, tedious work-ups, and the presence of hydrazoic acid, which is highly toxic and explosive as well as volatile. The few methods that seek to avoid hydrazoic acid liberation during the reaction, by avoiding acidic conditions require a very large excess of sodium azide. In addition, all of the known methods use highly polar organic solvents, leading to complex isolation and recovery procedures. Therefore, we sought to develop a more efficient and convenient method that avoids these drawbacks and could be used both on a laboratory and industrial scale.

In recent times, ionic liquids have attracted increasing interest in the context of green synthesis. Although ionic liquids were initially introduced as alternative green reaction media because of their unique chemical and physical properties of nonvolatility, nonflammability, thermal stability, and controlled miscibility,[10] today they have marched far beyond this border, showing their significant role in controlling reaction as catalysts. The first successful use of an ionic liquid, dialkylimidazolium chloroaluminate, as a catalyst in Friedel–Crafts acylations was reported in 1986.[11] However, moisture sensitivity and decomposition of this chloroaluminate salt under normal atmospheric conditions are two major drawbacks to its practical use. Thus, a number of ionic liquids have been developed subsequently by replacement of chloroaluminate with anionic species such as tetrafluoroborate and hexafluorophosphate,[10c] and applied to chemical transformations. Butylimidazolium salt ILs have already been demonstrated as efficient catalysts and solvents for organic transformations.[12]

Keywords: 1-Substituted-1*H*-1,2,3,4-tetrazoles; Ionic liquid; Substituted amine; Triethyl orthoformate; Sodium azide.
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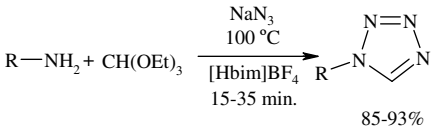


Scheme 1.

As part of an ongoing project concerned with the development of protocols for the preparation of biologically active heterocycles from common intermediates using room-temperature ionic liquids (RTILs), we herein report a one-pot condensation of sodium azide, substituted amines and triethyl orthoformate in 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) at 100 °C to afford 1-substituted-1*H*-1,2,3,4-tetrazoles in excellent isolated yields without any added catalyst (Scheme 1).

Ionic liquids (ILs) based on 1,3-di-*n*-butylimidazolium salts [bbim]X and 1-*n*-butylimidazolium salts [Hbim]X with varying basicity of anions were tested as solvents and promoters for the typical reaction of 4-isopropylaniline with triethyl orthoformate and sodium azide without any added catalyst to afford 1-(4-isopropylphenyl)-1*H*-1,2,3,4-tetrazole.

When we attempted the reaction at lower temperatures, that is, 40–60 °C, there was no product formation as observed by TLC, whereas at 80 °C the reaction proceeded but not to completion even after 8 h. Consequently, the reaction temperature was optimized at 100 °C, which gave the 1-substituted-1*H*-1,2,3,4-tetrazole as the sole product. All further reactions in the various ILs were carried out at 100 °C. No product formation could be observed in the [bbim]X series ILs (up to 12 h) whereas in the [Hbim]X series of the ILs, a facile reaction was observed. Data for the preparation of 1-(4-isopropylphenyl)-1*H*-1,2,3,4-tetrazole **5** in terms of basicity of the anion, Brønsted acidity of the –NH proton and the high polarity of the various ILs with respect to the reaction time for complete conversion are recorded in Table 1.

The efficacy of the ILs to promote this condensation and heterocyclization reaction was correlated to the basicity of the anions of the ILs as well as the polarity of the ILs. It was assumed that the nature of the anion would govern the electrophilicity of the imidazolium cation, which in turn has a bearing on the acidity of the ILs. It was observed that with increasing basicity of the anion (increasing pK_a of the corresponding acid), there was a progressive increase in yield (Table 1). This correlation was also evident when the yield of **5** was compared with the –NH proton chemical shifts of the ILs being indicative of the Brønsted acidities of the [Hbim]X ILs (Table 1). The yield of **5** increased progressively not only with increasing Brønsted acidity of the ILs, as indicated by the increasing downfield shift of the NH proton, but also with increasing polarity of the ILs as indicated by their E_T (30) values.

Table 1. Synthesis of tetrazole **5** in [Hbim]X

ILs	pK_a[a]	–NH proton δ (ppm)	Time[b] (min)	E_T[c] (30) (kcal mol^{-1})	Yield[d] (%)
[Hbim]ClO_4	−11	11.83	210	63.82	81
[Hbim]Br	−9	12.17	120	73.68	86
[Hbim]Cl	−7	12.22	80	73.59	88
[Hbim]BF_4	0.5	14.59	25	74.35	90

[a] The pK_a values of the parent acid of the anions.[13]
[b] The reaction was carried out until completion.
[c] Polarity of ILs determined by Reichardt's dye.[14]
[d] Isolated yield after column chromatography.

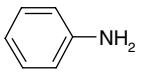
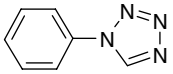
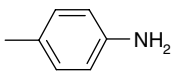
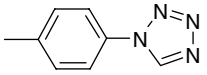
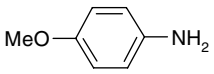
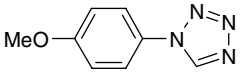
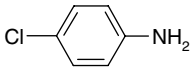
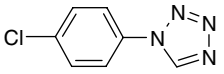
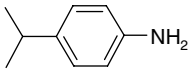
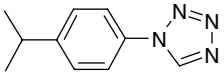
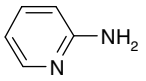
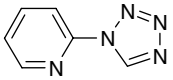
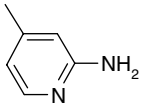
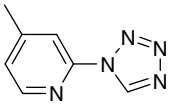
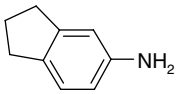
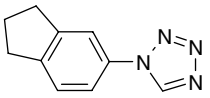
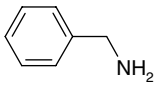
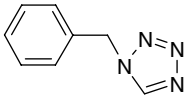
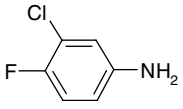
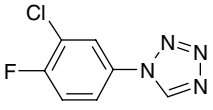
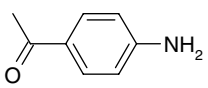
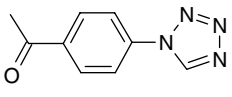
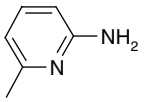
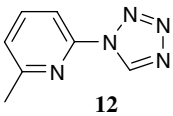
It is evident from these results (Table 1) that the IL [Hbim]BF_4 by virtue of its inherent Brønsted acidity conferred by the most acidic NH hydrogen ($\delta = 14.6$ ppm) and maximum polarity (more polar than 2-methoxyethanol, DMF, and methanol employed so far in the reported methods) among the ILs afforded the best results. It was postulated that the inherent Brønsted acidity of the ionic liquid plays an important role for the breakdown of triethyl orthoformate, and the significantly high polarity of the ionic liquid serves to solublilize sodium azide and facilitates the [3+2] cycloaddition.

A variety of amines such as substituted anilines, heteroaromatic amines, and an aliphatic amine (entry 9) were employed to investigate the scope and generality of this process. The results are recorded in Table 2. It was observed that under similar conditions, a wide range of anilines containing electron withdrawing as well as electron donating groups such as chloro, fluoro, acetyl, methoxy, isopropyl, and methyl and an aliphatic benzylamine easily underwent condensation with triethyl orthoformate and sodium azide to give 1-substituted-1*H*-1,2,3,4-tetrazoles in short reaction times with excellent isolated yields (Table 2).

The methods reported so far for the synthesis of 1-substituted tetrazoles, either in acidic conditions using acids such as hydrochloric, acetic, trifluoroacetic, and sulfuric or in highly polar solvents such as 2-methoxyethanol, DMF, or methanol required very harsh reaction conditions such as refluxing for 6–24 h followed by very tedious work-up procedures involving distillation of high boiling solvents or neutralization followed by distillation under reduced pressure. Compared to the reported methods, our method is convenient, fast, safe, and is easy to work-up.

The [3+2] cycloaddition between hydrazoic acid and cyanide derivatives is well known and one of the most efficient routes. Unfortunately, hydrazoic acid is highly explosive. Practically, the use of sodium azide as substrate in place of hydrazoic acid would be convenient even though, the [3+2] cycloaddition energy barrier is significantly lower with hydrazoic acid than with azide. To overcome this energy limitation, syntheses have been designed either to control the hydrazoic acid formation[15] or to use a large excess of azide ions as sodium azide in the presence of metal catalysts or strong Lewis acids.[16] However, the present methodology needs only one equivalent of NaN_3, since the IL promotes this reaction by virtue of its inherent Brønsted acidity and

Table 2. Synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles in [Hbim]BF_4

Entry	Substrate	Product	Time (min)	Yield[a] (%)
1		 **1**	25	89
2		 **2**	20	88
3		 **3**	20	91
4		 **4**	25	85
5		 **5**	25	90
6		 **6**	20	86
7		 **7**	15	85
8		 **8**	35	93
9		 **9**	30	85
10		 **10**	35	86
11		 **11**	35	87
12		 **12**	15	89

[a] Isolated yield after column chromatography.

high polarity in addition to its function as a reaction medium thus obviating the necessity of using any additional catalyst.

In conclusion, we have developed a mild, convenient, and efficient protocol for the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles via the condensation of amines, triethyl orthoformate, and sodium azide using a RTIL as a recyclable medium as well as a promoter.[17] The process gave rise to excellent isolated yields of 1-substituted-1*H*-1,2,3,4-tetrazoles in short reaction times (15–35 min).

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.050.

References and notes

1. Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, UK, 1996; Vol. 4.
2. Singh, H.; Chawla, A. S.; Kapoor, V. K.; Paul, D.; Malhotra, R. K. *Prog. Med. Chem.* **1980**, *17*, 151.
3. Brown, M. U.S. Patent 3,338,915, 1967; *Chem. Abstr.* **1968**, 87299.
4. (a) Ostrovskii, V. A.; Pevzner, M. S.; Kofmna, T. P.; Shcherbinin, M. B.; Tselinskii, I. V. *Targets Heterocycl. Syst.* **1999**, *3*, 467; (b) Hiskey, M.; Chavez, D. E.; Naud, D. L.; Son, S. F.; Berghout, H. L.; Bome, C. A. *Proc. Int. Pyrotech. Semin.* **2000**, *27*, 3.
5. (a) Burger, A. *Prog. Drug Res.* **1991**, *37*, 287; (b) Schelenz, T.; Schafer, W. *J. Fuel Prakt. Chem.* **2000**, *342*, 91; (c) Ruelke, H.; Friedel, A.; Martin, E.; Kottke, K.; Graefe, I.; Kuehmstedt, H. *Pharmazie* **1991**, 46.
6. (a) Zimmerman, D. M.; Olofson, R. A. *Tetrahedron Lett.* **1969**, *58*, 5081; (b) Fallon, F. G.; Herbst, R. M. *J. Org. Chem.* **1957**, *22*, 933.
7. Jin, T.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 9435.
8. (a) Satoh, Y.; Marcopulos, N. *Tetrahedron Lett.* **1995**, *36*, 1759; (b) Gupta, A. K.; Oh, C. H. *Tetrahedron Lett.* **2004**, *45*, 4113.
9. Su, W.; Hong, Z.; Shan, W.; Zhang, X. *Eur. J. Org. Chem.* **2006**, 2733.
10. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3773; (c) Sheldon, R. *Chem. Commun.* **2001**, 2399; (d) Wilkes, J. S. *Green Chem.* **2002**, *4*, 73; (e) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, *61*, 1015.
11. Boon, J. A.; Levinsky, J. A.; Pflug, J. I.; Wilkes, J. S. *J. Org. Chem.* **1986**, *51*, 480.
12. (a) Palimkar, S. S.; Siddiqui, S. A.; Thomas, D.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2003**, *68*, 9371; (b) Gholap, A. R.; Venkatesan, K.; Thomas, D.; Lahoti, R. J.; Srinivasan, K. V. *Green Chem.* **2004**, *6*, 147; (c) Nadaf, R. N.; Siddiqui, S. A.; Thomas, D.; Lahoti, R. J.; Srinivasan, K. V. *J. Mol. Catal. A: Chem.* **2004**, *240*, 155; (d) Siddiqui, S. A.; Narkhede, U. C.; Palimkar, S. S.; Thomas, D.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron* **2005**, *61*, 3539; (e) Siddiqui, S. A.; Potewar, T. M.; Lahoti, R. J.; Srinivasan, K. V. *Synthesis* **2006**, 2849; (f) Siddiqui, S. A. *Synlett* **2006**, 155, and references cited therein.
13. Perrin, D. D. *Ionization Constant of Inorganic Acids and Bases in Aqueous Solution*, 2nd ed.; Pergamon: Elmsford, New York, 1982.
14. Fletcher, K. A.; Storey, I. A.; Hendricks, A. E.; Pandey, S. *Green Chem.* **2001**, *3*, 210.
15. Sauer, J.; Huisgen, R.; Strum, H. J. *Tetrahedron* **1960**, *11*, 241.
16. Kumar, A.; Narayanan, R.; Shechter, H. *J. Org. Chem.* **1996**, *61*, 4462.
17. *Typical procedure for the synthesis of 1-(4-isopropylphenyl)-1H-1,2,3,4-tetrazole* (**5**): A mixture of 4-isopropylaniline (1 mmol), triethyl orthoformate (1.2 mmol), and sodium azide (1 mmol) in [Hbim]BF_4 (3 mmol) was stirred at 100 °C. The progress of the reaction was monitored by TLC (EtOAc–petroleum ether, 7:13). After completion, the reaction mixture was extracted with a mixture of ethyl acetate–petroleum ether (4:6). The substituted tetrazole extracts into the organic layer leaving behind the ionic liquid as an immiscible phase. The organic layer was separated, dried over sodium sulfate, and the solvent was distilled off under reduced pressure. The isolated product was pure (single spot on TLC) for all practical purposes. It was subjected to further purification by column chromatography (silica gel; EtOAc–petroleum ether, 1:3) to yield the desired 1-(4-isopropylphenyl)-1*H*-1,2,3,4-tetrazole **5** in an excellent yield of 90%. White solid; mp 68–69 °C; IR ($CHCl_3$): 2930, 2872, 1653, 1520, 1464, 1215, 1092, 1038, 998 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29–1.33 (d, $J = 6.95$ Hz, 6H), 2.95–3.09 (m, 1H), 7.42–7.46 (d, $J = 8.49$ Hz, 2H), 7.60–7.64 (d, $J = 8.70$ Hz, 2H), 8.97 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 23.69, 33.78, 121.16, 128.03, 131.50, 140.51, 151.17; Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.97; H, 6.29; N, 29.68; LC–MS: 189.01.
The ionic liquid, 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4), was synthesized as per the method reported by us,[12a] and was successfully recycled and reused three times without any considerable loss in yield.