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A novel synthesis of 1-aryl tetrazoles promoted by employing the synergy of the combined use of DMSO and an ionic liquid as the solvent system at ambient temperature

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ABSTRACT

The synergy of the combined use of DMSO and an ionic liquid viz. $(bbim)^+Br^-$ has brought about a mild, convenient, efficient, and rapid protocol for the synthesis of 1-substituted-1*H*-1,2,3,4-tetrazoles via the condensation of amines, triethyl orthoformate, and sodium azide at ambient temperature in excellent isolated yields (85–90%). The inherent Bronsted acidity of ionic liquid and high polarity of both IL and DMSO resulted in a significant enhancement in the reaction rate.

1. Introduction

The chemistry of heterocycles has acquired immense importance in recent years. Tetrazoles represent an important class of heterocycles which exhibit a wide range of applications in medicinal as well as synthetic chemistry.[1] The tetrazole ring as an analog and metabolically stable substitute of a carboxy group is extensively used in molecular design and in the synthesis of modified amino acids and peptidomimetics.[2] Since the acidity of tetrazole group corresponds closely with that of carboxylic acid, replacement of C-terminal amino acid residue with a tetrazole analog often preserves or improves the biological activity of the parent peptides. Alzheimer's β-secretase (BACE1) inhibitor KMI-420 and its α-isomer are potent drug molecules that possess tetrazole sub-units.[3] This nitrogen-rich ring system is used in propellants,[4] explosives,[5] and pharmaceuticals.[6] Furthermore, tetrazole moieties are important synthons in synthetic organic chemistry.[7]

Although many synthetic protocols for 1-aryl tetrazoles have been reported since the last mid-century, there is still a need for the generation of more efficient processes for the synthesis of 1-aryl tetrazoles. The routes to 1-substituted tetrazoles include acid-catalyzed cycloaddition between hydrozoic acid and isocyanides,[8] 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,[9] and PCl_5 and yttribium triflate-catalyzed cyclization from an amine, triethylorthoformate, and sodium azide in volatile organic solvents.[10]

Each of these methods has one or more of the following drawbacks. For instance, the use of 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 made use of volatile 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 on both a laboratory and industrial scale.

The use of room temperature ionic liquids (ILs) as solvents for chemical reactions offers several advantages from the environmental perspective.[11,12] In this context, in recent times, room temperature ionic liquids (RTILs), especially those based on the 1,3-dialkylimidazolium salts, have shown great promise as an attractive alternative to conventional solvents. They possess the unique advantages of high thermal stability, negligible vapor pressure, immiscibility with a number of organic solvents, and recyclability.[13] In many cases, the products are weakly soluble in the ionic phase so that the products can be easily separated by simple

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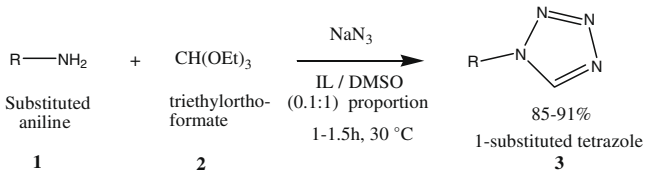


Scheme 1.

extraction. Srinivasan and co-workers[14] have recently reported the synthesis of 1-substituted tetrazoles in monobutylimidazolium ionic liquid.

Very recently we have investigated the synergy of the combined use of ionic liquid and DMSO in the proportion 0.1:1 to synthesize a variety of esters in remarkably short reaction times from acyl or alky halides by their reaction with sodium carboxylates in the above-mentioned mixed solvent medium in the absence of any added catalyst under ambient conditions. In individual solvents, there was no reaction of phenacyl bromide with sodium benzoate under ambient conditions in DMSO, whereas that in the IL took 16 h for completion under similar conditions. Using the above solvent mixture conditions DMSO/IL (1:0.1 proportion), the reaction was completed in just 15 min (paper communicated to Synth. Commun.).

In continuation of our research devoted to the combined use of ionic liquid and DMSO in 0.1:1 proportion, we extended the investigation of this system toward the synthesis of 1-substituted tetrazoles by a one-pot condensation of sodium azide, substituted amines, and triethyl orthoformate to afford 1-substituted-*1H*-1,2,3,4-tetrazoles in excellent isolated yields in remarkably short reaction times without any added catalyst (Scheme 1).

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, methyl, methoxy, and aliphatic benzylamine easily underwent condensation with triethyl orthoformate and sodium azide to give 1-aryl-*1H*-1,2,3,4-tetrazoles in 1–1.5 h with excellent isolated yields. The results are summarized in Table 1. Whereas the unsubstituted aniline reaction was completed in just 20 min, in the presence of electron-withdrawing or electron-donating groups in reactant, the reaction was completed within 1–1.5 h. It may be postulated that the inherent Bronsted acidity of the ionic liquid plays an important role in the breakdown of triethyl orthoformate, DMSO by virtue of its inherent properties activates the azide anion as a 'naked anion' due to its non-solvation effects and also high polarity of combined

Table 1
Synthesis of 1-substituted-*1H*-1,2,3,4-tetrazoles

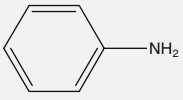
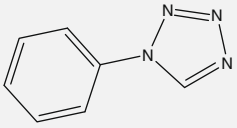
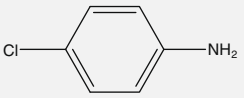
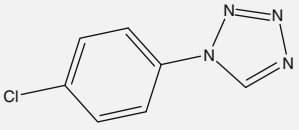
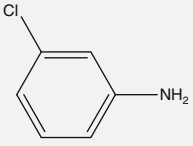
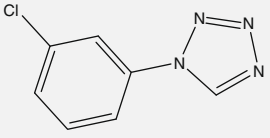
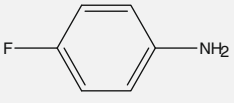
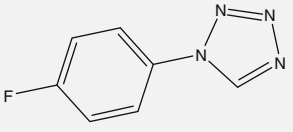
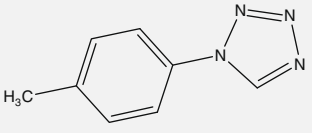
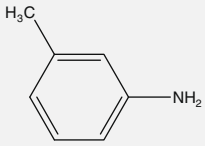
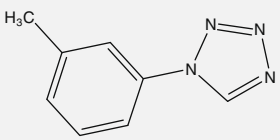
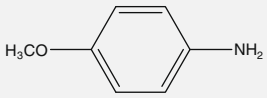
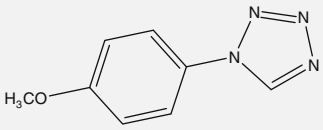
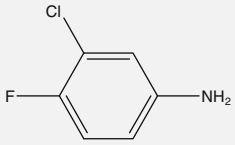
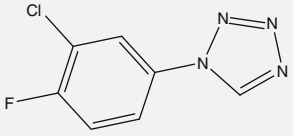
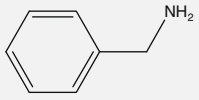
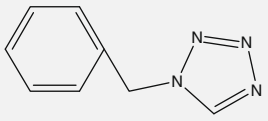
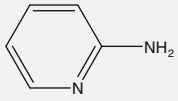
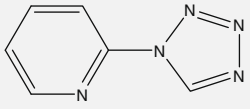
Entry	Substrate	Product	Compd No.	Time (min)	Yield[a] (%)
1			**3a**	20	86
2			**3b**	80	88
3			**3c**	75	90
4			**3d**	75	85
5			**3e**	80	88

Table 1 (*continued*)

Entry	Substrate	Product	Compd No.	Time (min)	Yield[a] (%)
6			**3f**	80	89
7			**3g**	90	85
8			**3h**	85	90
9			**3i**	90	86
10			**3j**	80	85

[a] Isolated yields; TLC single spot.

solvents serves to solubilize sodium azide and facilitates the [3+2] cycloaddition.

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 solvents such as 2-methoxyethanol, DMF, and methanol required very harsh reaction conditions such as refluxing for 6–24 h. Compared to the reported methods, our method is convenient, safe, and can be performed under ambient conditions with easy isolation procedures by drowning the reaction mixture into ice water.

The [3+2] cycloaddition between hydrazoic acid and cyanide derivatives is well known and is one of the most efficient routes. Unfortunately, hydrazoic acid is highly explosive. Practically, the use of sodium azide would be convenient even though the [3+2] cycloaddition energy barrier is significantly lower when used with hydrazoic acid than with azide. To overcome this energy limitation, synthesis has 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 1 equiv of NaN_3, since the IL promotes this reaction by virtue of its inherent Bronsted acidity and both IL and DMSO provide high polarity in addition to their function as a reaction medium, thus obviating the necessity of using any additional catalyst.

The synergy of combined use of IL and DMSO is evident from the observation that the reaction did not proceed at all either in DMSO or in $[bbim]^+Br^-$ individually under similar conditions. The IL could be recovered from the aqueous filtrate by subjecting it to dehydration and removal of DMSO. The IR of this recovered IL was identical to the synthetic $(bbim)Br^-$ used in the process.

In conclusion, we have developed a mild, convenient, and efficient protocol for the synthesis of 1-substituted-*1H*-1,2,3,4-tetrazoles via the condensation of amines, triethyl orthoformate, and sodium azide using an IL and DMSO (0.1:1 proportions) as a solvent as well as a promoter. The process gave rise to excellent isolated yields of 1-substituted-*1H*-1,2,3,4-tetrazoles in 1–1.5 h under ambient reaction conditions in shorter reaction times than hitherto reported under ambient conditions.

2. Typical procedure for 1-phenyl-*1H*-1,2,3,4-tetrazole in IL+DMSO (0.1:1)

The IL $[bbim]^+Br^-$ is synthesized as per the procedure reported by us.[17]

A mixture of aniline (5.3 mmol), triethyl orthoformate (6.4 mmol), and sodium azide (5.3 mmol) in $[bbim]^+Br$ and DMSO in 0.1:1 (0.5 g:5 g) proportions was stirred at ambient reaction conditions. The progress of the reaction was monitored by TLC

with an elluant mixture of *n*-hexane and ethyl acetate (4.5:0.5). After completion, the reaction mixture was added to crushed ice. The precipitated product was filtered, washed with water, and dried. The product was pure enough (single spot on TLC) for all practical purposes. However, for characterization purposes it was further purified by column chromatography.[18]

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18. Selected data for compounds**3a**, **3b, 3g, 3i** are given:
Compound **3a**: pale yellow solid; mp 64–65 °C (lit.[10] 64–65 °C); IR ($CHCl_3$): 1598, 1506, 1465, 1401, 1215, 1091, 1075, 1042, 998; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.51–7.75 (m, 5H, ArH), 9.02 (s, 1H, tetrazole H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 121.1, 129.9, 130.1, 133.7, 140.5; Anal. Calcd for $C_7H_6N_4$: C, 57.53; H, 4.14; N, 38.34. Found: C, 57.23; H, 3.98; N, 38.12.
Compound **3b**: White solid; mp 154–156 °C (lit.[10] 155–156 °C); IR ($CHCl_3$): 1653, 1505, 1460, 1425, 1215, 1088, 1034, 996; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.55–7.62(m, 2H, ArH), 7.66–7.73 (m, 2H, ArH), 9.02 (s, 1H, tetrazole H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 122.4, 130.4, 136.0, 140.4; Anal. Calcd for $C_7H_5N_4Cl$: C, 46.55; H, 2.79; N, 31.02. Found: C, 46.28; H, 2.59; N, 30.91.
Compound **3g.** White needles; mp 117–118 °C (lit.[10] 116–117 °C); IR ($CHCl_3$): 2954, 1611, 1594, 1521, 1465, 1215, 1182, 1092, 1043, 996; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.89 (s, 3H, OCH_3), 7.05–7.10 (dd, 2H, *J* = 7.06 and 2.10 Hz, 2H, ArH), 7.58–7.63 (dd, *J* = 7.06 and 2.10 Hz, 2H, ArH), 8.93 (s, 1H, tetrazole H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 55.6, 115.0, 122.8, 126.7, 140.6, 160.5; Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.19; H, 4.37; N, 31.65.
Compound **3i**. White solid; mp 59–60 °C (lit.[10] 58–59 °C); IR ($CHCl_3$): 2950, 2845, 1530, 1476, 1436, 1244, 1163, 1104; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.60 (s, 2H, CH_2), 7.28–7.44 (m, 5H, ArH), 8.52 (s, 1H, tetrazole H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 52.0, 128.2, 129.2, 129.3, 132.8, 142.4; Anal. Calcd for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 59.67; H, 4.89; N, 34.67.