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Ionic liquid-assisted synthesis of 5-mono- and 1,5-disubstituted tetrazoles

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Interaction of aliphatic, aromatic and heteroaromatic nitriles with NaN_3 or activated nitriles with organic azides in ionic liquids affords the corresponding 5-mono- and 1,5-disubstituted tetrazoles, ionic liquids functioning both as a reaction medium and as a catalyst.

Tetrazole derivatives are of interest as important components of drugs, *e.g.*, antibiotics, antiallergics or hormonal preparations.[1] In addition, these compounds have wide applications in agriculture (as components of herbicides, pesticides, fungicides, plant growth regulators, *etc.*)[1,2] or as components of highly energetic formulations.[3]

Several methodologies were developed to produce different tetrazole types. The simplest synthesis of tetrazoles is based on the [3+2] cycloaddition reaction of nitriles with hydrazoic acid or its derivatives. For example, the interaction of nitriles with NaN_3 or Me_3SiN_3 in the presence of acidic catalysts leads to 5-substituted tetrazoles, while the reaction of nitriles with alkyl azides yields 1,5-disubstituted tetrazoles. The conditions required for reactions with alkyl or aryl cyanides pose the key challenge. A typical synthesis of 5-aryltetrazoles requires a prolonged reactants heating (up to several days) in DMF, toluene or butanol at 100–120 °C in the presence of acidic promoters such as NH_4Cl, $Et_3N{\cdot}HCl$,[4] $Me_2NH{\cdot}HCl$,[5] $BF_3{\cdot}Et_2O$,[6] AcOH[7] or $ZnBr_2$.[8] Pure HN_3 can also be used in the reaction, yet in this case the reaction should be carried out in a sealed tube[9] or in an autoclave.[10] Me_3SiN_3 reacts with ArCN typically in the presence of dibutyltin oxide[11] or trimethylaluminum.[12]

Synthesis of 5-heteryltetrazoles is based on the interaction of HN_3 or NaN_3 with nitriles of heterocyclic carboxylic acids.[13–15] This process can be intensified by microwave irradiation in the presence of NH_4Cl. In this event, the reaction time can be reduced to 10–25 min, however, a violent reaction temperature rise (up to 220 °C within 10 min) results in the partial decomposition of the starting compounds and products.[16] Application of Me_3SiN_3/Bu_2SnO system under microwave irradiation allows the very sophisticated nitriles to be converted into tetrazoles.[17] Synthesis of 5-alkyltetrazoles from alkyl cyanides and NaN_3 proceeds even under harsher conditions compared to 5-aryl- and 5-heteryltetrazoles, *e.g.*, heating in benzene in a sealed tube at 150 °C for 100–120 h is required to convert the alkyl cyanide and HN_3 mixture into 5-alkyltetrazole.[8]

A straightforward synthesis of 1,5-disubstituted tetrazoles from nitriles and organic azides is still unstudied. This reaction is known to run successfully with nitriles having electron-withdrawing groups and proceeds at a rather high temperature (110–145 °C) in a sealed tube.[18,19] Recently,[20] the application of ionic liquids (ILs) (dialkylimidazolium chlorides and bromides) for the microwave-assisted synthesis of substituted tetrazoles in the presence of acetic acid as a catalyst has been reported. However, microwave irradiation results in a high reaction temperature (up to 170 °C) and decomposition of both ILs and initial or final compounds.

This research was devoted to the development of a milder and more general method for the synthesis of both 5-mono- (**1**) and of 1,5-disubstituted (**2**) tetrazoles. Earlier we have found that [3+2] cycloaddition reactions are truly accelerated in ILs.[21,22] So we hoped that this methodology could be developed in the tetrazole synthesis through varying of ILs functioning as a reaction media and as a catalyst. To prepare 5-substituted tetrazoles **1**, aromatic, heteroaromatic and aliphatic nitriles were introduced into the reaction with NaN_3 in readily available and stable to air and moisture dialkylimidazolium ILs with different anions (Scheme 1, Table 1).†

It was found that benzonitrile did not produce 5-phenyltetrazole **1a** by heating with 1.2 equiv. NaN_3 in [bmim][CF_3SO_3] and only longtime heating of the reaction mixture (100 h) in [bmim][PF_6] or [bmim][BF_4] at 100 °C resulted in tetrazole **1a** in 68% or 52% yields, respectively (Table 1, entries 1–3). The best synthetic conditions for 5-phenyltetrazole **1a** proved to be heating of PhCN with 1.2 equiv. of NaN_3 at 100 °C in acidic IL [emim][HSO_4],

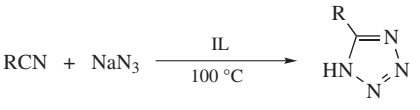
† New compounds exhibited satisfactory elemental analyses. IR spectra were measured on a UR-20 spectrometer; ^1H and ^{13}C NMR spectra were recorded on a Bruker AM300 (300 MHz for ^1H and 75.5 MHz for ^{13}C) spectrometer ($CDCl_3$ and DMSO-d_6 were used as the internal standards). ^{13}C NMR spectra were recorded under proton decoupling conditions. Mass spectra were measured on a Finnigan MAT INCOS-50 instrument. TLC was carried out on Silufol UV-254 plates. Melting points were measured on a Gallenkamp instrument (Sanyo).

† *General procedure for the synthesis of 5-monosubstituted tetrazoles* **1a–f** *in 1-ethyl-3-methylimidazolium hydrogen sulfate [emim][HSO_4].* A mixture of aromatic, heteroaromatic or aliphatic nitrile (5 mmol) and NaN_3 (6 mmol) (for PrCN, 15 mmol was used) in 2 ml of [emim][HSO_4] was stirred at 100 °C in a round bottom flask with the condenser and protection from moisture for the time specified in Table 1. The reaction completion was generally judged by a full conversion of the starting nitrile (TLC monitoring). Then the reaction mixture was cooled to 20 °C and extracted with a mixture of (1) 4 ml ethylacetate + 3 ml hexane (4 times) or (2) 4 ml $MeOBu^t$ + 3 ml CH_2Cl_2 (5 times). The solvents were evaporated *in vacuo* and the final products were characterized by physicochemical methods. The melting points and spectral characteristics of compounds **1a–f** were identical to those described in literature. The IL was reused in the next synthesis after the evaporation of solvent residues.

1a: R_f 0.17 (eluent, $CHCl_3$), yield 0.62 g (85%), mp 215–216 °C (lit.,[8] 215–216 °C).

1b: R_f 0.23 (eluent, $CHCl_3$–acetone, 10:1), yield 0.70 g (96%), mp 239–240 °C (lit.,[15] 239–241 °C).

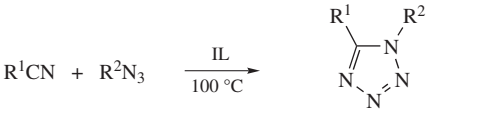
1c: R_f 0.15 (eluent, $CHCl_3$), yield 0.72 g (90%), mp 219–220 °C (lit.,[8] 220 °C).



1a–f

a R = Ph
b R = 3-Py
c R = 4-$NO_2C_6H_4$
d R = Bn
e R = Pr
f R = 4-$MeOC_6H_4$

Scheme 1



2a–c

a R^1 = C(O)Ph, R^2 = Bn
b R^1 = C(O)Ph, R^2 = Bu
c R^1 = C(O)OEt, R^2 = Bn

Scheme 2

Table 1 Synthesis of compounds **1** and **2** in ionic liquids.[a]

Entry	Nitrile	Azide	IL	Product	Time/h	Yield (%)
1	PhCN	NaN_3	[bmim][CF_3SO_3]	**1a**	50	0
2	PhCN	NaN_3	[bmim][PF_6]	**1a**	100	68
3	PhCN	NaN_3	[bmim][BF_4]	**1a**	100	52
4	PhCN	NaN_3	[emim][HSO_4]	**1a**	10	85
5	3-cyanopyridine	NaN_3	[emim][HSO_4]	**1b**	9	96
6	4-$NO_2C_6H_4CN$	NaN_3	[emim][HSO_4]	**1c**	3.5	90
7	BnCN	NaN_3	[emim][HSO_4]	**1d**	5	79
8	PrCN	NaN_3 (3 equiv.)	[emim][HSO_4]	**1e**	80	80
9	4-$MeOC_6H_4CN$	NaN_3	[emim][HSO_4]	**1f**	83	78
10	PhC(O)CN	BnN_3	[bmim][PF_6]	**2a**	85	50
11	PhC(O)CN	BuN_3	[bmim][BF_4]	**2b**	49	72
12	EtOC(O)CN	BnN_3	[bmim][PF_6]	**2c**	44	28
13	EtOC(O)CN	BnN_3	[bmim][BF_4]	**2c**	18	74
14	PhC(O)CN	BnN_3	[emim][HSO_4]	**2a**	102	36
15	PhC(O)CN	BuN_3	[emim][HSO_4]	**2b**	70	56
16	4-$NO_2C_6H_4CN$	NaN_3	[emim][HSO_4] (regenerated)	**1c**	3.5	95(1),[b] 94(2),[b] 100(3)[b]

[a]All reactions were performed at 100 °C. [b]Three cycles of IL regeneration.

which played a part of both a reaction medium and an acidic catalyst (entry 4). These conditions also were the best for the synthesis of 5-(pyridin-3-yl)tetrazole **1b** (entry 5), 5-(4-nitrophenyl)tetrazole **1c** (entry 6) and 5-benzyltetrazole **1d** (entry 7). The interaction of PrCN with NaN_3 in acidic [emim][HSO_4] resulted in 5-propyltetrazole **1e** in 80% yield (entry 8), though a NaN_3 excess (3 equiv.) and longer heating (80 h, 100 °C) were necessary. Longtime heating was also needed for benzonitrile with the electron-donor substituent 4-$MeOC_6H_4CN$ (entry 9). In all the cases, the ILs were regenerated and reused 3 times in the same reactions (*e.g.*, entry 16).

To prepare 1,5-disubstituted tetrazoles **2**, PhCN, 4-$O_2NC_6H_4CN$, 3-cyanopyridine and activated nitriles PhC(O)CN and EtO_2CCN were heated with BnN_3 or BuN_3 in different ILs at 100 °C. It was found that PhCN, 4-$O_2NC_6H_4CN$, 3-cyanopyridine did not react with BnN_3 or BuN_3 in any ILs ([emim][HSO_4], [bmim][BF_4] or [bmim][PF_6]). Instead of tetrazoles, the corresponding benzamides, hydrolysis products of the starting nitriles, were obtained in low yields (~20–25%). Only use of activated nitriles EtO_2CCN and PhC(O)CN in reaction with aliphatic azides in ILs [bmim][PF_6] and [bmim][BF_4] comprised anions derived from corresponding strong Lewis acid resulted in 1,5-disubstituted tetrazoles **2a–c** (Scheme 2, Table 1, entries 10–13).‡ The acidic IL [emim][HSO_4] also appeared efficient for preparing 1,5-disubstituted tetrazoles **2a**,**b** from nitriles and aliphatic azides, however, for this purpose rather longtime heating was necessary and small amounts of phenylglyoxylic acid amide and polymeric compounds were identified in the reaction products (entries 14, 15). The conditions found were significantly milder than previously reported (heating at 110–145 °C in a sealed tube without solvent[18,19]).

The structures of the synthesized compounds were established by elemental analysis and physicochemical methods. For the known compounds, characteristics were close to the reported data.

To conclude, we have developed a general and simple procedure for the synthesis of both 5-mono- and 1,5-disubstituted tetrazoles based on heating of aromatic, heteroaromatic or aliphatic nitriles with NaN_3 or activated nitriles with aliphatic azides in ILs proved to be appropriate reaction medium and catalysts in these reactions.

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1d: R_f 0.35 (eluent, $CHCl_3$–acetone, 10:1), yield 0.63 g (79%), mp 125–126 °C (lit.,[23] 121–123 °C).

1e: R_f 0.17 (eluent, $CHCl_3$), yield 0.44 g (80%), mp 63–64 °C (lit.,[24] 56–58 °C).

1f: R_f 0.50 (eluent, $CHCl_3$–acetone, 5:1), yield 0.52 g (78%), mp 230–231 °C (lit.,[8] 231–232 °C).

‡ *General procedure for the synthesis of 1,5-disubstituted tetrazoles* **2a–c** *in 1-butyl-3-methylimidazolium tetrafluoroborate (hexafluorophosphate) [bmim][BF_4]([PF_6]).* The synthesis of **2a–c** from nitrile (5 mmol) and corresponding organic azide (6.6 mmol) in 2 ml of [bmim][BF_4] or [bmim][PF_6] was carried out analogously to the synthesis of compounds **1a–f**. Spectral characteristics of compounds **2a** and **2c** were identical to those described in literature.

2a: R_f 0.45 (eluent, $CHCl_3$), yield 0.65 g (50%), nondistilled oil (*cf.* ref. 25).

5-Benzoyl-1-butyltetrazole **2b**: R_f 0.35 (eluent, $CHCl_3$–CCl_4, 2:1), yield 0.82 g (72%), nondistillable oil. ^{1}H NMR (DMSO-d_6) δ: 0.9 (t, 3H, Me), 1.35 (m, 2H, CH_2), 1.95 (m, 2H, CH_2), 4.75 (t, 2H, N–CH_2), 7.65 (dd, 2H, Ph), 7.75 (dd, 1H, Ph), 8.40 (d, 2H, Ph). ^{13}C NMR (DMSO-d_6) δ: 13.65 (Me), 19.52 (MeCH_2), 28.85 ($CH_2CH_2CH_2$), 48.15 (NCH_2), 128.55, 130.67, 134.65, 135.82 (Ph), 142.45 ($C_{tetrazole}$), 181.36 (C=O). MS, *m*/*z* (%): 230 (M^+, 65). IR (ν/cm^{-1}): 3316, 3072, 2964, 2936, 2876, 1668, 1600, 1452, 1416, 1336, 1272, 1176, 1104, 1000, 920, 744, 716, 688.

2c: R_f 0.16 (eluent, $CHCl_3$), yield 0.85 g (74%), mp 56–58 °C (lit.[26] 58–60 °C).

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