Synthesis of 1-aryl(hetaryl)-1,2,3-triazoles with the use of ionic liquids

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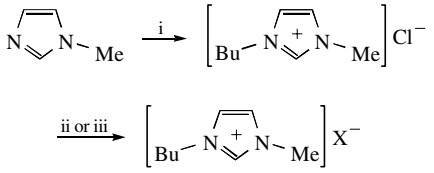
1-Phenyl(furazanyl)-1,2,3-triazoles can be synthesised by the 1,3-dipolar cycloaddition of phenylazide **1** or 4-amino-3-azidofurazan **2** to acetylenes (or to 1-morpholinyl-2-nitroethene for **2**) in ionic liquids {1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) for **1** or 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) for **2**}.

Ionic liquids are promising reaction media for organic synthesis, which can be repeatedly used for performing reactions in place of ordinary organic solvents.[1] Ionic liquids were used in the Friedel–Crafts reaction,[2] the dimerisation of alkenes,[3] the alkylation of carbonyl compounds,[4] the Heck reaction,[5,6] and the Diels–Alder reaction.[7] As a rule, these reactions were considerably accelerated in ionic liquids; therefore, the reactions can be carried out under milder conditions. The regioselectivity increases in the case of ambident substrates.[8] In this context, the synthesis of heterocyclic compounds in ionic liquids seems to be promising. Only several works concerning this problem were published, in particular, the synthesis of oxazoline or imidazoline derivatives by the 1,3-dipolar cycloaddition of imidates, which were prepared from diethylaminomalonate, to 2-ethoxybenzaldehyde or imines as dipolarophiles,[9(a),(b)] the preparation of indoles[9(c)] and the synthesis of 3,4-dihydropyrimidine-2(1*H*)-one.[9(d)]

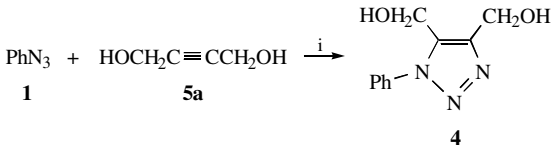
Recently, 3-(4-nitro-1,2,3-triazol-1-yl)-4-R-furazans and 3-[4(5)-alkyl- or 4,5-dialkyl-1,2,3-triazol-1-yl]-4-R-furazans **3** were synthesised in our laboratory by the 1,3-dipolar cycloaddition of azidofurazanes to 1-morpholinyl-2-nitroethylene[10] and substituted acetylenes,[11] respectively, in standard solvents. In a number of cases, the reaction with monosubstituted acetylenes occurred regioselectively. These bicyclic compounds potentiate the NO-dependent activation of soluble guanylate cyclase; that is, they are nitrogen oxide donors.[12] However, compounds **3** can be synthesised under severe conditions (120 h at 110 °C for 1-morpholinyl-2-nitroethylene and 20–120 h at 65–80 °C for acetylene derivatives). We performed the above reactions in ionic liquids in order to develop a more efficient synthetic procedure for triazolylfurazans **3**.

At the first stage, we synthesised 4,5-bis(hydroxymethyl)-1-phenyl-1,2,3-triazole **4** by the 1,3-dipolar cycloaddition of phenylazide **1** to butynediol **5a**. According to published data,[13] this reaction can be performed only at 120 °C for 12 h. The following ionic liquids based on 1-methylimidazole were chosen: butylmethylimidazolium hexafluorophosphate [bmim][PF_6][14] and butylmethylimidazolium tetrafluoroborate [bmim][BF_4][15] (Scheme 1). These ionic liquids are readily available and stable to air and moisture.



Scheme 1 *Reagents and conditions*: i, BuCl, toluene, reflux, 24 h; ii, (for X = PF_6), HPF_6, H_2O, 20 °C, 12 h; iii, (for X = BF_4), NH_4BF_4, acetone, 20 °C, 24 h.

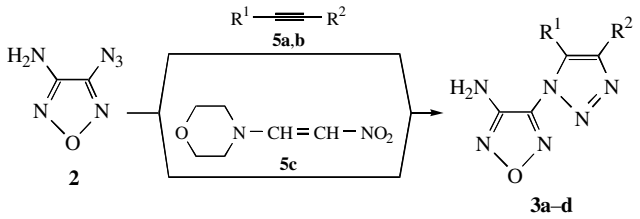
The interaction of phenylazide **1** with butynediol **5a** was studied in both of the ionic liquids at 80–120 °C. The use of [bmim][BF_4] at 120 °C for 3 h was found to be optimum; the yield of compound **4** was comparable to the yield obtained in accordance with the known procedure† (Scheme 2; Table 1, entry 1).[13] We found that the [bmim][PF_6] ionic liquid can be used in this reaction at temperatures no higher than 90 °C; however, the test reaction does almost not occur at this temperature. An increase in the temperature results in the partial decomposition of the ionic liquid.



Scheme 2 *Reagents and conditions*: i, [bmim][BF_4], 3 h, 120 °C.

Thus, using this model example, we found that ionic liquids that are stable in air at room temperature can serve as a reaction medium for the preparation of 1-substituted 1,2,3-triazoles by the 1,3-dipolar cycloaddition of azides to acetylene derivatives. This reaction occurred at a much higher rate than in standard organic solvents. Thus, we believed that the ionic liquids can also be successfully used for the synthesis of compounds **3**.

To evaluate the effect of ionic liquids, we examined the reaction between 3-azido-4-aminofurazan **2** and dipolarophiles (butynediol **5a**, propargyl alcohol **5b**, and 1-morpholinyl-2-nitroethylene **5c**), which were previously entered into the reaction with azide **2**, at 75–80 °C (Scheme 3). We found that under these conditions the reaction was considerably accelerated only in [bmim][PF_6]. Table 1 summarises the reaction conditions.



a $R^1 = R^2 = CH_2OH$ **c** $R^1 = H$, $R^2 = CH_2OH$
b $R^1 = CH_2OH$, $R^2 = H$ **d** $R^1 = H$, $R^2 = NO_2$

Scheme 3

Data given in Table 1 indicate that azide **2** more rapidly reacted with acetylene derivatives **5a**,**b** than in the case when published procedures were used. The yields of 4-amino-3-[4,5-bis(hydroxymethyl)-1,2,3-triazol-1-yl]furazan **3a** and a mixture of 4-amino-3-(5-hydroxymethyl-1,2,3-triazol-1-yl)furazan **3b**

† All compounds were previously described; thus, they were characterised by a comparison of their melting points and spectroscopic data with published data. ^{1}H NMR spectra were measured on Bruker WM-250 (250 MHz) and Bruker AM-300 (300 MHz) spectrometers. TLC monitoring was performed on Silufol UV 254 silica gel plates, the eluent was chloroform–acetone–methanol (10:2:1) or benzene–acetone (9:1). Melting points were determined on a Boetius PHMK 05 instrument.

4,5-Bis(hydroxymethyl)-1-phenyl-1,2,3-triazole **4**. A mixture of 0.85 mmol of phenylazide **1**, 0.80 mmol of a substituted acetylene and 1.5 mmol of [bmim]BF_4 was stirred at 120 °C for 3 h. The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3×10 ml). The solvent was evaporated, the residue was treated with a minimum volume of acetone, the precipitate was filtered off, washed with 10 ml of acetone and dried in air.

Table 1 Reagents, conditions and results of the synthesis of 1,2,3-triazoles in ionic liquids.

Entry	Azide	Dipolarophile	Ionic liquids and conditions	1,2,3-triazoles (yields)	Conditions and yields according to published data
1	**1**	**5a**	[bmim]BF_4, 120 °C, 3 h	**4** (65%)	Benzene, 120 °C, 12 h (73%)[13]
2	**2**	**5a**	[bmim]PF_6, 80 °C, 7.5 h	**3a** (75%)	EtOH, reflux, 30 h (57%)[11]
3	**2**	**5b**	[bmim]PF_6, 80 °C, 6.5 h	**3b**:**3c**, 4.5:1 (71%)	EtOH, reflux, 45 h, **3b**:**3c**, 2.5:1 (79%)[11]
4	**2**	**5c**	[bmim]PF_6, 70 °C, 12 h	**3d** (35%)	Toluene, reflux, 120 h (80%)[10]

and 4-amino-3-(4-hydroxymethyl-1,2,3-triazol-1-yl)furazan **3c** (entries 2,3)‡ were comparable or even higher. In the reaction with propargyl alcohol **5b**, the **3b**:**3c** ratio between isomers noticeably changed in favour of compound **3b**; that is the use of the [bmim][PF_6] ionic liquid as a reaction medium for the interaction of azidofurazan **2** with monosubstituted acetylene increased the regioselectivity of the reaction.

The reaction with compound **5c** was completed in 12 h at 70 rather than 110 °C.§ However, in this case, the yield of 4-amino-3-(4-nitro-1,2,3-triazol-1-yl)furazan **3d** was lower than the published value. Evidently, morpholine, which was released in the course of reaction, reacted with the final product to decrease its yield. It is likely that the rate of this reaction in the ionic liquid also increased. The accumulation of by-products in the course of reaction was detected by TLC monitoring.

The possibility of repeatedly using an ionic liquid was tested by the example of the synthesis of compound **3a**, which was performed three times in the same portion of an ionic liquid with almost no decrease in the yield.

Thus, we found that ionic liquids can be successfully used as reaction media for the synthesis of 1-aryl(hetaryl)-1,2,3-triazoles by the 1,3-dipolar cycloaddition of both aromatic and heterocyclic azides to substituted acetylenes and enamines. Both the rate and the regioselectivity of the reaction increased as compared to analogous reactions in standard organic solvents. These results form the basis for a promising new branch of the chemistry of heterocyclic compounds – the use of ionic liquids for performing heterocyclisation reactions.

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‡ *4-Amino-3-(4-R^2-5-R^1-1,2,3-triazol-1-yl)furazans* **3a**–**c** (general procedure). A mixture of 1 mmol of 4-amino-3-azidofurazan **2**, 1.25 mmol of a substituted acetylene and 2 mmol of [bmim]PF_6 was stirred at 75–80 °C for 3.5 to 7.5 h. The reaction mixture was cooled to room temperature and treated with a minimum volume of acetone, the precipitate was filtered off and washed with 10 ml of acetone. The solvent was evaporated and the residue was treated with 10 ml of acetone, the new precipitate was filtered off and washed with 5 ml of acetone. The last operation was repeated once more. Combined portions of the precipitate were dried in air. The ionic liquid can be easily recovered and reused after the evaporation of acetone. The ratio between compounds **3b** and **3c** in the mixture was calculated from ^{1}H NMR-spectroscopic data according to the integral intensities of corresponding proton signals in [$^2H_6$]DMSO: **3b**, 4.67 (d, 2H, 5′-CH_2), 5.44 (t, 1H, OH), 8.65 (s, 1H, 4′-CH); **3c**, 4.80 (d, 2H, 4′-CH_2), 5.69 (t, 1H, OH), 7.96 (s, 1H, 5′-CH).

§ *4-Amino-3-(4-nitro-1,2,3-triazol-1-yl)furazan* **3d**. A mixture of 8 mmol of 4-amino-3-azidofurazan **2** and 7 mmol of 1-morpholinyl-2-nitroethene was added to 8 mmol of [bmim]PF_6 and stirred at 70 °C for 12 h. The reaction mixture was cooled to room temperature and extracted with diethyl ether (3×20 ml). The solvent was evaporated under reduced pressure and the product was isolated by column liquid chromatography. The isolation of triazole **3d** was performed by column liquid chromatography using SiO_2 (40:100) as a stationary phase and a mixture of benzene and ethyl acetate (13:5) as an eluent.

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