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Ionic liquid-promoted stereoselective [3+2] cycloaddition of 1-hetaryl-2-nitroethenes to azomethine imines generated *in situ*

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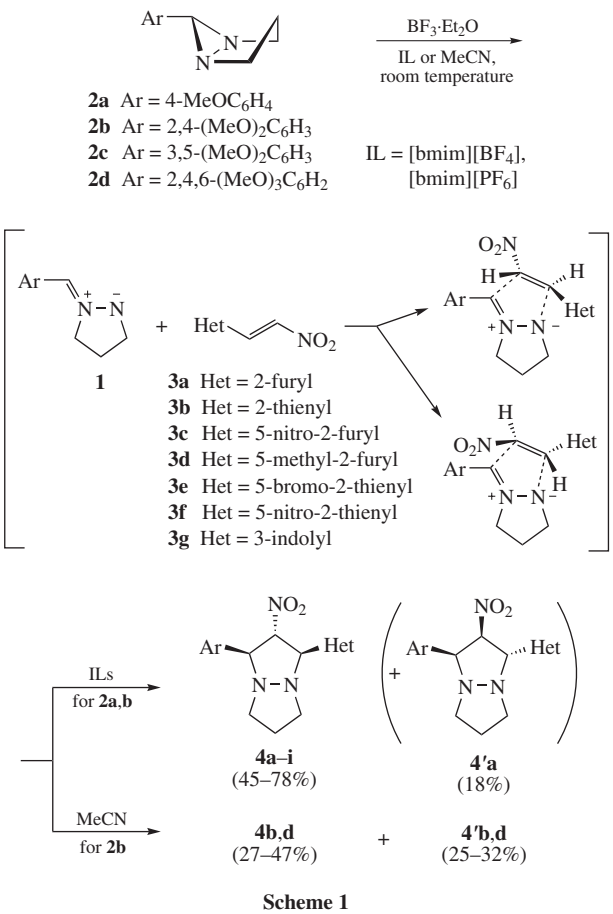
Ionic liquids facilitate regio- and stereoselective [3+2] cycloaddition of 1-hetaryl-2-nitroethenes to azomethine imines generated catalytically from 6-Ar-1,5-diazabicyclo[3.1.0]hexanes in the presence of $BF_3{\cdot}Et_2O$. The similar reaction is possible in MeCN only for azomethine imine with Ar = 2,4-$(MeO)_2C_6H_3$ to give a mixture of two diastereomers.

A search of optimal conditions for the *in situ* generation of azomethine imines **1** by the diaziridine ring opening in available[1] 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **2** has been a key area of our research over the past years. Azomethine imines **1** can be generated both thermally (by refluxing in toluene or xylene) and catalytically by the addition of 20 mol% Lewis acid ($BF_3{\cdot}Et_2O$) at room temperature or at slight heating. The reactions are usually performed in the presence of corresponding dipolarophiles, which undergo the [3+2] cycloaddition with azomethine imines **1** resulting in 1,5-diazabicyclo[3.3.0]octane derivatives.[2(a)–(g)] From the preparative standpoint, the catalytic generation of azomethine imines **1** has considerable benefits since not all dipolarophiles are thermally stable. However, most of investigated dipolarophiles remain inert under these conditions. Therefore, replacement of organic solvents by ionic liquids (ILs) becomes a good challenge to broaden a scope of dipolarophiles (CS_2, activated nitriles, chalcone, β-nitrostyrenes) for this purpose.[3(a)–(c)] In some cases [*e.g.*, addition to isatins or (het)arylmethylidenemalononitriles], the reactions succeeded both in organic solvents and in ILs though product yields and purity were always higher in ILs.[4(a)–(c)]

In this work we studied the [3+2] cycloaddition of azomethine imines **1** (generated from the corresponding **2**) to 1-hetaryl-2-nitroethenes **3a–g** (Scheme 1) † with a view to synthesize 1,5-diazabicyclo[3.3.0]octanes **4** containing pharmacophoric heterocyclic substituents (furan, thiophene, indole and their functional derivatives). Earlier[2(d),(e)] we managed to involve β-nitrostyrenes in a similar reaction, however, only in ILs at low heating (50 °C). So, at first, the reaction of 1-(2-furyl)-2-nitroethylene **3a** with azomethine imine **1a** generated catalytically from 6-(4-methoxyphenyl)-1,5-diazabicyclo[3.1.0]hexane **2a** was performed in IL [bmim][BF_4] (1-butyl-3-methylimidazolium tetrafluoroborate). In contrast to the analogous reaction with β-nitrostyrenes, compounds **1a** and **3a** reacted already at 20 °C with the same regioselectivity (according to the classical Michael addition mechanism) and diastereoselectivity to give a mixture of diastereomers **4a** and **4′a** with the *trans-trans* and *cis-trans* orientation of substituents in the formed pyrazolidine ring with a marked predominance (3.3 : 1) of diastereomer **4a** in total yield 78% (see Scheme 1, Table 1, entry 1).



Scheme 1

Evidently, 1-furyl-2-nitroethylene **3a** is more electrophilic than β-nitrostyrenes. However, the attempted carrying out this reaction in MeCN was unsuccessful (Table 1, entry 2). Previously we used azomethine imines **1**, including **1a**, prepared from bicyclic diaziridines **2** bearing only one electron-donating substituent (OAlk, Alk) in 4-position of the aromatic ring. The

† Heterocyclic nitroethenes **3a**,**b**,**d**,**e** were prepared *via* condensation of corresponding aldehydes with nitromethane.[5] Nitration of **3a** and **3b** gave compounds **3c** and **3f**, respectively.[6] Nitroalkene **3g** was prepared according to the published method.[7] New compounds were purified by column chromatography on silica gel, 0.060–0.200 mm, 60 A (ACROS) with AcOEt – light petroleum as eluent. For the successful isolation of some products, silica gel was deactivated with triethylamine.[8] Compounds **2b–d** were synthesized according to described procedure.[9] For characteristics of compounds **2b–d**, see Online Supplementary Materials.

role of this substituent is to stabilize the positive charge in the 1,3-dipole of azomethine imines **1**. We assumed that this reaction can be performed in MeCN on using reactants having more electron-donating substituents in the aromatic ring. For this, bicyclic diaziridines **2b–d** containing 2,4-$(MeO)_2C_6H_3$ (**2b**), 3,5-$(MeO)_2C_6H_3$ (**2c**) or 2,4,6-$(MeO)_3C_6H_2$ (**2d**) moieties in 6-position were synthesized. Desired cycloaddition products **4b** and **4′b** were obtained in MeCN only in a reaction of dipolarophile **3a** with azomethine imine **1b** generated from bicycle **2b** in the presence of $BF_3{\cdot}Et_2O$. This reaction also proceeded regio- and diastereoselectively with a predominance of diastereomer **4b** (**4b**:**4′b** ~ 2:1) in total yield 72% (Table 1, entry 3).‡ The similar reaction in IL was also successful though completely stereoselective with the formation of only one stereoisomer **4b** (entry 4). Both compounds **2c**,**d** and dipolarophile **3a** failed to interact in ILs and MeCN (entries 5, 6). Probably, the 3,5-$(MeO)_2C_6H_3$ fragment did not stabilize sufficiently the positive charge of azomethine imine **1c** due to an absence of conjugation with the aromatic ring, whereas the presence of three MeO groups in the 2,4,6-$(MeO)_3C_6H_2$ fragment (azomethine imine **1d**) sterically hindered the cycloaddition.

Table 1 Reactions of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **2** with 1-hetaryl-2-nitroethenes **3** in the presence of $BF_3{\cdot}Et_2O$ (20 mol%).

Entry	Diaziridine	Ethene	Solvent	Yield (%)	
1	**2a**	**3a**	[bmim][BF_4]	60 (**4a**)	18 (**4′a**)
2	**2a**	**3a**	MeCN	—	—
3	**2b**	**3a**	MeCN	47 (**4b**)	25 (**4′b**)
4	**2b**	**3a**	[bmim][BF_4]	56 (**4b**)	—
5	**2c**	**3a**	MeCN, [bmim][PF_6]	—	—
6	**2d**	**3a**	MeCN, [bmim][PF_6]	—	—
7	**2a**	**3b**	[bmim][BF_4]	64 (**4c**)	—
8	**2a**	**3b**	MeCN	—	—
9	**2b**	**3b**	[bmim][PF_6]	58 (**4d**)	—
10	**2b**	**3b**	MeCN	27 (**4d**)	32 (**4′d**)
11[a]	**2a**	**3c**	[bmim][PF_6]	52 (**4e**)	—
12	**2a**	**3d**	[bmim][PF_6]	46 (**4f**)	—
13	**2a**	**3e**	[bmim][BF_4]	78 (**4g**)	—
14[a]	**2a**	**3f**	[bmim][PF_6]	53 (**4h**)	—
15	**2a**	**3g**	[bmim][PF_6][b]	39 (**4i**)	—

[a] No catalyst added. [b] 40 °C.

Similarly, 1-nitro-2-thienylethene **3b** added azomethine imines **1a**,**b** in ILs regio- and stereoselectively to yield single stereoisomers **4c**,**d** having *trans-trans* orientation of substituents in a new pyrazolidine ring (see Table 1, entries 7, 9). In MeCN, the cycloaddition between **1b** and **3b** afforded a mixture of diastereomers **4d** and **4′d** (~1:1) only (entry 10). The attempted similar reaction of compounds **2a** and **3b** in MeCN was unsuccessful (Table 1, entry 8). Therefore, further reactions between 1-hetaryl-2-nitroethenes **3c–g** and bicyclic diaziridine **2a** (azomethine imine **1a**) were performed only in ILs. Along with non-substituted furan and thiophene groupings, nitro and methyl-substituted furans, bromo- and nitrothiophenes as well as indole were the substituents in 1,5-diazabicyclo[3.3.0]octanes **4e–i** thus obtained, with only one stereoisomer being formed in all cases (Scheme 1, Table 1, entries 11–15).

Structures of the synthesized compounds were established by elemental and spectral analyses (primarily 2D NMR spectra, using correlations such as {^{1}H–^{13}C}HMBC, {^{1}H–^{13}C}HSQC), and mass spectrometry. The main distinction in the ^{1}H NMR spectra of diastereomers **4** and **4′** pertains to $^3J_{H–H}$ of Ar*CH*–*CH*NO_2 and *CH*NO_2–*CH*Het fragments – in diastereomers **4**, $^3J_{H–H}$ were ~5 and 7 Hz, respectively, and in diastereomers **4′** ~7 and 8.5 Hz. In addition, all protons (with the exception of the 6-CH_2 group) in the non-substituted pyrazolidine ring of major isomers manifest themselves individually but in minor isomers geminal protons of

‡ *General procedure for the synthesis of compounds* **4a–i**. A mixture of 6-aryl-1,5-diazabicyclo[3.1.0]hexane **2a**,**b** (0.5 mmol), 1-hetaryl-2-nitroethene **3a–g** (0.5 mmol) and $BF_3{\cdot}Et_2O$ (20 mol%) was stirred at room temperature overnight in [bmim][BF_4] or [bmim][PF_6] (1.5 ml) (for **3c** and **3f** without $BF_3{\cdot}Et_2O$ and for **3g** at 40 °C). The reaction mixture was then quenched with saturated $NaHCO_3$ (aq.), extracted with CH_2Cl_2 [compounds **4c** and **4f** were extracted from IL with CH_2Cl_2–Et_2O (1:5), 4×3 ml] and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on SiO_2 using AcOEt–light petroleum as an eluent.

Synthesis of **4b**,**d** *and* **4′b**,**d** *in organic solvent*. A mixture of reactants **2b** (0.5 mmol) and **3a**,**b** (0.5 mmol) and $BF_3{\cdot}Et_2O$ (20 mol%) was stirred in dry MeCN (2 ml) at room temperature overnight. The mixture was quenched with saturated $NaHCO_3$ (aq.), extracted with CH_2Cl_2 and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography on SiO_2 using AcOEt–light petroleum as an eluent.

4-(2-Furyl)-2-(4-methoxyphenyl)-3-nitro-1,5-diazabicyclo[3.3.0]octane **4a** (*trans-trans*-adduct). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ: 7.42 (m, 3H, 5-H_{furan}, 2,6-H_{Ar}), 6.91 (d, 2H, 3.5-H_{Ar}, *J* 8.5 Hz), 6.44–6.31 (m, 2H, 3,4-H_{furan}), 5.33 (dd, 1H, 3-H, *J* 12.8 and 6.7 Hz), 4.85 (d, 1H, 2-H, *J* 5.8 Hz), 4.58 (d, 1H, H-4, *J* 6.2 Hz), 3.81 (s, 3H, OMe), 3.41–3.19 (m, 3H, 8,6a-H), 3.16–3.02 (m, 1H, 6b-H), 2.46–2.28 (m, 1H, 7a-H), 2.21–2.03 (m, 1H, 7b-H). ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C) δ: 159.70 (4-C_{Ar}), 151.18 (2-C_{furan}), 143.20 (5-C_{furan}), 130.71 (1-C_{Ar}), 128.62 (2,6-C_{Ar}), 114.31 (3,5-C_{Ar}), 110.51 (4-C_{furan}), 108.35 (3-C_{furan}), 99.58 (3-C), 71.64 (4-C), 65.43 (2-C), 55.30 (OMe), 50.97 (8-C), 50.42 (6-C), 23.95 (7-C). MS, *m*/*z* (%): 329 (19) $[M]^+$, 281 (10), 213 (100), 121 (42). Found (%): C, 62.14; H, 5.73; N, 12.90. Calc. for $C_{17}H_{19}N_3O_4$ (%): C, 62.00; H, 5.81; N, 12.76.

For **4′a** (*cis-trans*-adduct). ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ: 7.45 (s, 1H, 5-H_{furan}), 7.37 (d, 2H, 2,6-H_{Ar}, *J* 8.7 Hz), 6.87 (d, 2H, 3,5-H_{Ar}, *J* 8.7 Hz), 6.45–6.35 (m, 2H, 3,4-H_{furan}), 5.73 (dd, 1H, 3-H, *J* 9.1 and 6.9 Hz), 5.17 (d, 1H, 2-H, *J* 6.9 Hz), 4.31 (d, 1H, 4-H, *J* 9.1 Hz), 3.80 (s, 3H, OMe), 3.21–3.08 (m, 1H, 8a-H), 3.02–2.86 (m, 1H, 6a-H), 2.76–2.53 (m, 2H, 6b,8b-H), 2.37–2.19 (m, 2H, 7-H). ^{13}C NMR (75 MHz, $CDCl_3$, 30 °C) δ: 159.72 (4-C_{Ar}), 151.23 (2-C_{furan}), 138.22 (5-C_{furan}), 132.15 (1-C_{Ar}), 128.26 (2,6-C_{Ar}), 112.92 (3,5-C_{Ar}), 111.55 (4-C_{furan}), 109.23 (3-C_{furan}), 98.32 (3-C), 70.38 (4-C), 54.19 (2-C), 54.03 (OMe), 49.71 (8-C), 49.18 (6-C), 22.71 (7-C). Found (%): C, 61.93; H, 5.89; N, 12.69. Calc. for $C_{17}H_{19}N_3O_4$ (%): C, 62.00; H, 5.81; N, 12.76.

4-(5-Bromothiophen-2-yl)-2-(4-methoxyphenyl)-3-nitro-1,5-diazabicyclo[3.3.0]octane **4g**. ^{1}H NMR (300 MHz, $CDCl_3$, 30 °C) δ: 7.39 (d, 2H, 2,6-H_{Ar}, *J* 8.6 Hz), 6.98–6.86 (m, 3H, 3,5-H_{Ar}, 3-$H_{thienyl}$), 6.78 (d, 1H, 4-$H_{thienyl}$, *J* 3.7 Hz), 5.06 (t, 1H, 3-H, *J* 5.7 Hz), 4.96 (d, 1H, 2-H, *J* 5.4 Hz), 4.62 (d, 1H, 4-H, *J* 6.0 Hz), 3.81 (s, 3H, OMe), 3.43–3.17 (m, 3H, 8,6a-H), 3.15–3.01 (m, 1H, 6b-H), 2.45–2.26 (m, 1H, 7a-H), 2.23–2.07 (m, 1H, 7b-H). ^{13}C NMR (50 MHz, $CDCl_3$, 30 °C) δ: 159.78 (4-C_{Ar}), 145.26 (2-$C_{thienyl}$), 130.82 (1-C_{Ar}), 129.79 (4-$C_{thienyl}$), 128.56 (2,6-C_{Ar}), 125.53 (3-$C_{thienyl}$), 114.45 (3,5-C_{Ar}), 113.99 (5-$C_{thienyl}$), 102.72 (3-C), 71.66 (4-C), 67.99 (2-C), 55.39 (OMe), 50.77 (8-C), 50.71 (6-C), 24.14 (7-C). Found (%): C, 48.09; H, 4.35; Br, 18.87; N, 9.86; S, 7.57. Calc. for $C_{17}H_{18}BrN_3O_3S$ (%): C, 48.12; H, 4.28; Br, 18.83; N, 9.90; S, 7.56.

For characteristics of compounds **4b–f**,**h**,**i**, **4′b** and **4′d**, see Online Supplementary Materials.

§ *Crystal data for* **4b**. Crystals of $C_{18}H_{21}N_3O_5$ (from ethanol, M = 359.38) are monoclinic, space group $P2_1/n$ (no. 14), at 100 K: a = 7.7577(4), b = 22.8087(11) and c = 10.3037(5) Å, β = 105.5050(10)°, V = 1756.82(15) Å^3, Z = 4, μ(MoKα) = 0.101 mm^{-1}, d_{calc} = 1.359 g mm^{-3}, 23639 reflections (4.48 ⩽ 2θ ⩽ 61.02), 5359 unique reflections (R_{int} = 0.0396) were measured on a Bruker APEX-II CCD diffractometer and used in calculations. The structure was solved by SHELXS[10] structure solution program with the aid of Olex2[11] code using direct methods and refined with the SHELXL[10] refinement package using least-squares minimisation. The final R indexes are R_1 = 0.0503 [$I > 2\sigma(I)$] and wR_2 = = 0.1327 (all data).

CCDC 932603 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2013.

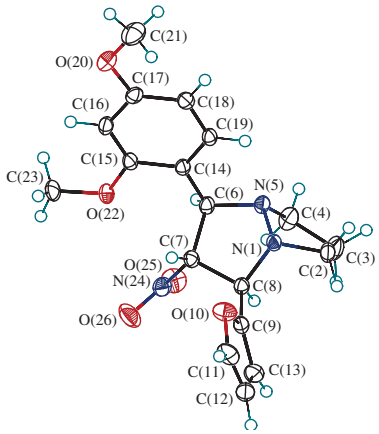


Figure 1 The general view of **4b** in crystal. Atoms are represented by thermal displacement ellipsoids (ρ = 50%).

the 7-CH_2 group appear as one broad multiplet. The structure of **4b** was additionally proven by an X-ray diffraction study (Figure 1).§

To conclude, IL-promoted [3+2] cycloaddition of azomethine imines to 1-hetaryl-2-nitroethenes proceeds regio- and stereoselectively according to the classical Michael addition mechanism resulting in 1,5-diazabicyclo[3.3.0]octanes with *trans-trans*-orientation of aromatic and heteroaromatic substituents in formed pyrazolidine ring. The sufficient structural prerequisite for the similar processing in MeCN is the presence of 2,4-$(MeO)_2C_6H_3$ substituent in the starting azomethine imine, however, in this case the mixture of diastereomers is formed.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.07.009.

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