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Unexpected regioselectivities of [3+2] cycloaddition of azomethine imines to acrylonitrile and 4-nitrophenyl vinyl sulfone

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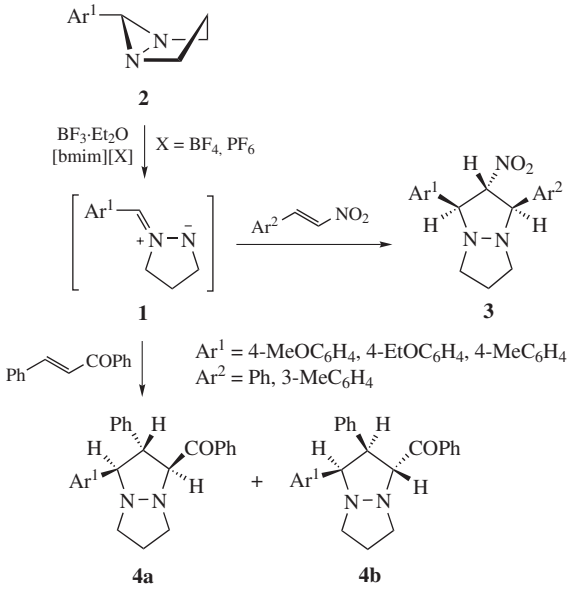
The [3+2] cycloaddition of azomethine imines derived from 6-aryl-1,5-diazabicyclo[3.1.0]hexanes to acrylonitrile and 4-nitrophenyl vinyl sulfone proceeds with high diastereoselectivity, but with opposite regioselectivity, which has been clarified by quantum chemical calculations.

The cycloaddition of 1,3-dipolar species to different dipolarophiles is a classic reaction of organic chemistry for the synthesis of five-membered rings.[1–5] Over the past years we have developed new efficient methods for synthesizing various nitrogen-containing heterocycles[6–14] involving azomethine imines **1** as 1,3-dipoles generated *in situ* by the catalytic diaziridine ring opening (catalyst, $BF_3 \cdot Et_2O$) of available 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **2**. Such reactions proceeded best in ionic liquids (ILs) with both high regio- and stereoselectivity resulting in bicyclic compounds in which tetrahydropyrazole rings were fused with pyrazolidine, pyrazolium, 1,3,4-thiazolidine-2-thione or 1,2,4-triazolium moieties.[15–20] To extend this synthetic approach to the preparation of other fused pyrazolidine derivatives, this research was focused on the interaction of azomethine imines **1** with electrophilic terminal alkenes such as acrylonitrile and 4-nitrophenyl vinyl sulfone.

Earlier we performed the [3+2] cycloaddition of azomethine imines **1** to other activated olefins – β-nitrostyrenes and 1,3-diphenylprop-2-enone.[12,13] Both reactions proceeded only in ILs. β-Nitrostyrenes were added to 1,3-dipoles of azomethine imines **1** completely regioselectively [with the exception of reaction with 1-nitro-2-(3-nitrophenyl)ethylene] according to the classical Michael addition mechanism and stereoselectively with the formation of only one stereoisomer **3** with the *trans-trans*-position of substituents in the newly formed pyrazolidine ring. 1,3-Diphenylpropen-2-one entered a reaction with azomethine imines **1** also completely regioselectively (though, contrary to the Michael addition mechanism) and diastereoselectively with the formation of a mixture of diastereomers **4a**,**b** with predominance (1.6–6.4 : 1) of diastereomer **4a** also with *trans-trans*-position of substituents (Scheme 1). Since in both reactions the most hindered substituents proved to be attached to remote carbon atoms of the pyrazolidine ring and in the *cis*-position to each other, it was assumed that the reactions were subject to steric control.

The [3+2] cycloaddition of azomethine imines **1** to terminal alkenes has not been investigated so far. Taking into account the above results and different size of CN and SO_2Ar groups, it is likely to expect that the interaction between azomethine imines **1** and acrylonitrile should occur by the classical Michael addition pathway and with 4-nitrophenyl vinyl sulfone – with the opposite regiochemistry.

The diaziridine ring expansion of 6-aryl-1,5-diazabicyclo-[3.1.0]hexanes **2a**–**g** with acrylonitrile† was performed in ILs ([bmim][BF_4] and [bmpyrr][NTf_2]), in MeCN and in acrylonitrile



Scheme 1

excess under the $BF_3 \cdot Et_2O$ catalysis (20 mol%). Optimization of the conditions was made for bicyclic diaziridine **2a** chosen as a

† *Compounds* **6** *and* **6′**. To a magnetically stirred solution of compound **2** (0.5 mmol) in 1.5 ml of [bmpyrr][NTf_2], acrylonitrile (1.5 mmol, 3 equiv.) and $BF_3 \cdot OEt_2$ (20 mol%) were added and the mixture was stirred at 50 °C for 3–18 h until the initially formed azomethine imine dimer was consumed (TLC). The products were separated from IL by extraction (CH_2Cl_2 – Et_2O, 1:5, 4×3 ml). Both *endo*- and *exo*-adducts were isolated by column chromatography using ethyl acetate–light petroleum mixtures as an eluent.

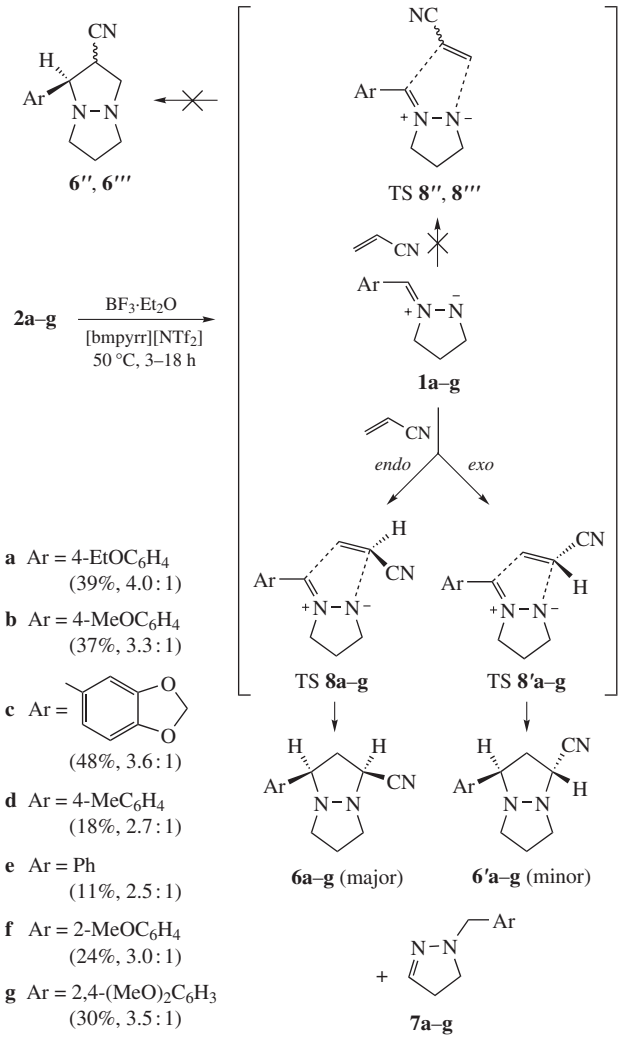
3-(4-Ethoxyphenyl)hexahydropyrazolo[1,2-a]pyrazole-1-carbonitrile **6a** (*cis*-adduct). ^{1}H NMR (600 MHz, $CDCl_3$, 30 °C) δ: 7.26, 6.80 (2d, 2H, Ar, *J* 8.6 Hz), 3.97 (q, 2H, OCH_2, *J* 7.0 Hz), 3.93 (m, 1H, H-1), 3.67 (dd, 1H, H-3, *J* 8.0 Hz, 8.8 Hz), 3.08, 2.80 (2m, 2H, H-7), 2.98, 2.64 (2m, 2H, H-5), 2.95, 2.34 (2m, 2H, H-2), 2.18, 2.07 (2m, 2H, H-6), 1.32 (t, 3H, Me, *J* 7.0 Hz). ^{13}C NMR (150 MHz, $CDCl_3$, 30 °C) δ: 158.64, 132.14, 128.69, 114.65 (Ar), 119.66 (CN), 65.32 (C-3), 63.45 (OCH_2), 51.44 (C-1), 49.93 (C-7), 49.28 (C-5), 42.47 (C-2), 25.61 (C-6), 14.77 (Me). ^{15}N NMR (60 MHz) δ: –119.50 (CN), –234.40 (N-4), –245.50 (N-8). HRMS (ESI), *m/z*: 258.1595 (calc. for $C_{15}H_{19}N_3O$ [M + H]$^+$: 258.1601).

For characteristics of compounds *trans*-**6a**, **6b**,**c** and **6′b**,**c**, synthesis and characteristics of compounds **9a**,**b** and **9′a**,**b**, see Online Supplementary Materials.

model. The reaction began only at slight heating (40–50 °C) and proceeded completely regioselectively under all the studied conditions and with high diastereoselectivity, but yet unexpectedly according to the Michael addition mechanism resulting in a mixture of diastereomers 3-aryltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazoles **6a** and **6′a** with the *cis*- and *trans*-arrangement of Ar and CN groups with a moderate total yield and preferable formation of diastereomer **6a** (**6a**:**6′a** = 2.5–4:1). The best yield (39%) was achieved in [bmpyrr][NTf_2] with the acrylonitrile excess (3 equiv.) at 40 °C within 15 h. Under all the studied conditions a small amount of pyrazoline **7a** (2–10%) was obtained as a result of a 1,4-H shift in initial azomethine imine **1a**.

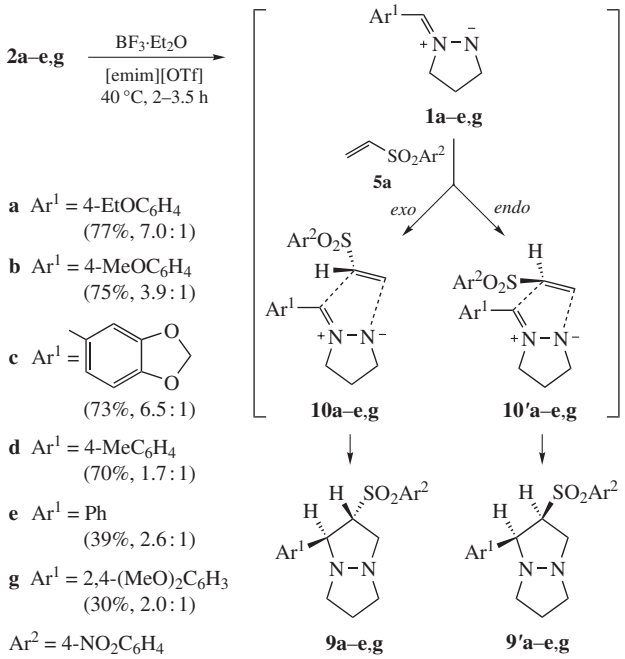
The found optimal conditions were applied to the reaction of acrylonitrile with other 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **2b–g**, which occured with the same regio- and diastereosectivity and resulted in a mixture of diastereomers **6b–g** and **6′b–g** with the predominance of *cis*-diastereomers **6a–g** and a small amount of pyrazolines **7b–g**. Products **6**, **6′** and **7** were separated by column chromatography on SiO_2. The formation of two diastereomers is associated with the concerted *endo*- or *exo*-approach of acrylonitrile to the 1,3-dipole plane of azomethine imines **1** (transition states **8a–g** and **8′a–g**) (Scheme 2).

The cycloaddition of 4-nitrophenyl vinyl sulfone **5a** to azomethine imines **1a–g**[†] was also studied both in ILs ([bmpyrr][NTf_2], [bmim][BF_4], [emim][OTf]) and in MeCN. The optimization of the conditions was performed for azomethine imine **1b** as a model. The best results were attained in [emim][OTf], although the reaction occurred in MeCN as well. The cycloaddition proceeded regiospecifically and with high diastereoselectively in all cases



Scheme 2

with the formation of two diastereomers **9b** and **9′b** with a considerable predominance of *trans*-diastereomer **9b**. However, again unexpectedly, the cycloaddition proceeded according to the Michael addition mechanism, with both hindered 4-$MeOC_6H_4$ and 4-$NO_2C_6H_4SO_2$ substituents located at the neighbouring carbon atoms of the newly formed pyrazolidine ring. The diastereomeric ratio was higher (**9b**:**9′b** = 20:1) in MeCN. The total yield was as low as 50%, whereas in [emim][OTf] **9b**:**9′b** = 3–5:1 and the yield of **9b** was 75%. *trans*-Diastereomer **9b** was formed upon concerted *exo*-approach of dipolarophile **5a** to azomethine imine **1b** (TS **10b**), while *cis*-diastereomer **9′b** – at the *endo*-approach of **5a** to **1b** through TS **10′b** (Scheme 3).



Scheme 3

Other bicyclic diaziridines **2a**,**c–g** on reacting with 4-nitrophenyl vinyl sulfone **5a** under the found conditions gave mixtures of diastereomers **9a**,**c–g** and **9′a**,**c–g** with predominance of diastereomers **9** to be then separated by column chromatography on SiO_2. Therefore, both reactions were not subject to steric control.

To explain the unexpected regioselectivity the frontier molecular orbital energies (FMO) of azomethine imine **1b**, acrylonitrile and a model compound – phenyl vinyl sulfone **5b**, and atomic Fukui indexes of the interacting atoms were calculated in the framework of the density functional theory [DFT B3LYP 6-31G(d)]. The calculations showed that $HOMO_{dipole}$–$LUMO_{alkene}$

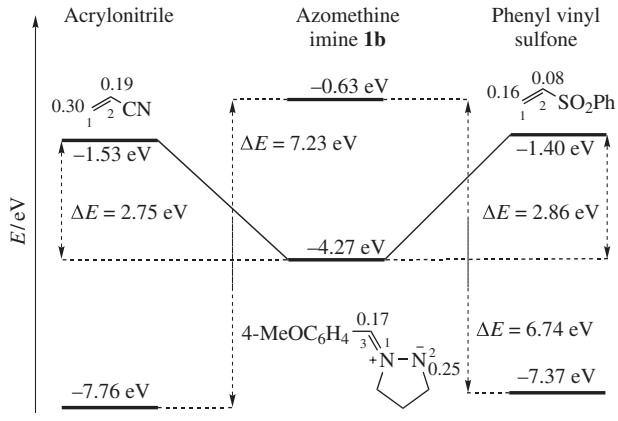


Figure 1 FMO energies (eV) and atomic Fukui indexes for azomethine imine **1b**, acrylonitrile and phenyl vinyl sulfone **5b**.

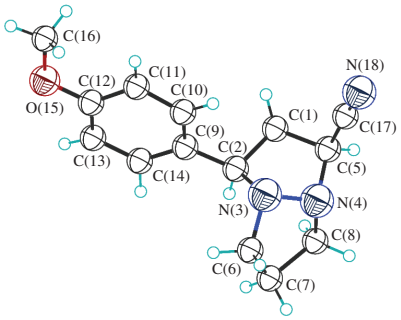


Figure 2 General view of molecule **6b**. Atoms are represented by spheres indicating their isotropic thermal displacements (p = 50%).

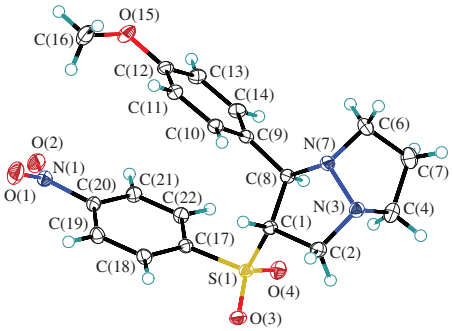


Figure 3 General view of molecule **9b** in crystal. Atoms are represented by thermal displacement ellipsoids (p = 50%).

interactions (ΔE = 2.75 and 2.85 eV, respectively) were the determinant factor for both reactions (Figure 1). The calculated atomic Fukui indexes here predict a nucleophilic attack of the N(2) atom of azomethine imine **1b** at C(1) atoms of both alkenes, which correlates with regiochemistry found for the reaction of compounds **1b** and **5b**; however, does not correlate with the *anti*-Michael cycloaddition of azomethine imine **1b** to acrylonitrile. A charge transfer (CT) in the transition state is often used to describe cycloaddition processes.[21] Its maximal value shows the dipole and dipolarophile optimal orientation. It was elucidated from the CT calculations of four possible transition states **8**, **8′**, **8″** and **8‴** of the cycloaddition of azomethine imine **1b** to acrylonitrile that the CT maximal value (0.4 a.u.) had transition state **8** corresponding to the acrylonitrile *endo*-approach to 1,3-dipole **1b** (Scheme 2). The other CTs had close values (~0.37 a.u.) and the Michael addition probably was not realized due to low thermodynamic stability of respective adducts **6″** and **6‴**.

Structures of the synthesized compounds were established by combination of elemental and spectral analysis data, 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 ^{1}H NMR spectra of diastereomers **9b** and **9′b** consists in different character of proton chemical shifts of unsubstituted pyrazolidine ring. In major isomers, all protons appear individually, whereas in minor isomers heminal protons of C(7)H$_2$ group appear as one multiplet. However, distinctions in spectral data of diastereomers **6b** and **6′b** did not allow one to assign them to particular isomers. The structures of compounds **6b**, **6′b** and **9b** were ultimately proven by X-ray diffraction study. In this paper crystallographic data only for compounds **6b** and **9b** are presented (Figures 2 and 3),‡ those for compound **6′b** will be published elsewhere.

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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.2013.09.011.

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‡ *Crystal data for compound* **6b**. The powder pattern of **6b** was measured on a Bruker D8 Advance Vario diffractometer with LynxEye detector and Ge (111) monochromator, λ(CuKα_1) = 1.54060 Å, $\theta/2\theta$ scan from 3° to 90°, stepsize 0.0104788°. The measurement was performed in transmission mode, with **6b** deposited between two kapton films.

The penalty function P in the 'Morse' restrained refinement is defined as follows: $P = K_1 \sum_i \kappa_i \{1 - \exp[-a_i(D_i - d_i)]\}^2$, where K_1 is a global penalty function weighting, κ_i is the weighting of the individual bond penalty, a_i is a coefficient corresponding to the bond force constant, D_i is the defined length of a given bond and d_i is its refined length at current minimization step. For details, see Online Supplementary Materials.

Crystal data for compound **9b**. Single crystals of **9b** were grown from ethanol. A suitable crystal was selected and studied on a Bruker APEX-II CCD diffractometer at 100 K. Using Olex2,[21] the structure was solved with the XS[22] structure solution program using Direct Methods and refined with the XL[22] refinement package using least-squares minimisation.

Crystal of **9b** ($C_{19}H_{21}N_3O_5S$, M = 403.45) is monoclinic, a = 9.3530(3), b = 21.9827(7) and c = 18.6010(6) Å, β = 103.7550(10)°, V = 3714.8(2) Å^3, T = 100 K, space group $P2_1/c$ (no. 14), Z = 8, μ(MoKα) = 0.212. 59060 reflections measured, 14197 unique (R_{int} = 0.0454) which were used in all calculations. The final wR_2 = 0.1164 (all data) and R_1 = 0.0412 [$\sigma > 2\sigma(I)$].

CCDC 928480 and 928481 contain 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. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2013.