Reactions of σ^H-adducts of 1-ethyl-1,4-diazinium salts with arylalkynes as a one-step approach to pyrrolo[1,2-*a*]pyrazine derivatives*

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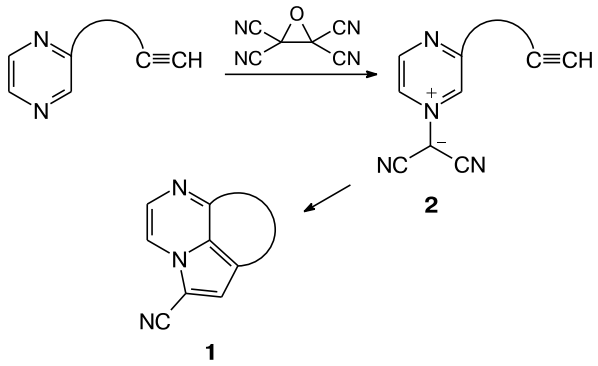
The O- and C-adducts of 5-aryl and 5-hetaryl-2,3-dicyano-1-ethylpyrazinium salts are hidden sources of ylides, which can be used for the cyclization with arylacetylenes giving rise to pyrrolo[1,2-*a*]pyrazines.

Key words: *N*-alkylpyrazinium ylides, 1,2-dihydropyrazines, σ^H-adducts, hidden 1,3-dipoles, phenylacetylene, 4-bromophenylacetylene, pyrrolo[1,2-*a*]pyrazines.

Azoloazines containing a bridging nitrogen atom are uncommon in nature; however, the synthesis of these compounds has attracted great attention with the main aim to design biologically active compounds.[1] Thus, pyrrolo[1,2-*a*]pyrazine derivatives, *viz.*, azaindolizines, have a wide spectrum of physiological activities, such as antihypoxic,[2] psychotropic,[3] antimalarial,[2,4] antidiabetic,[5,6] *etc*.

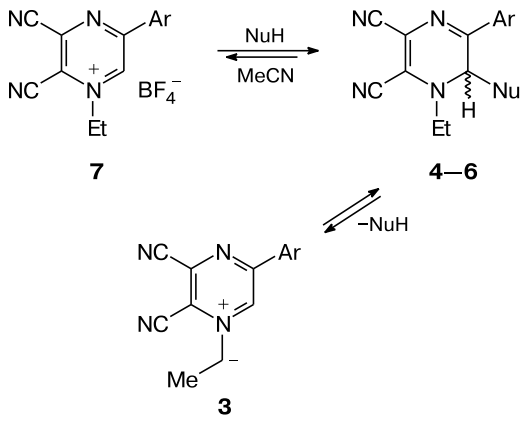
Azaindolizines **1** can be synthesized from ylides of pyrazinium salts **2** through the 1,3-dipolar [3+2]-cycloaddition[7] (Scheme 1).

Scheme 1



In the present study, we showed that ylides **3** can be synthesized starting from σ^H-adducts **4—6** of 1,4-diazines of different nature. These adducts are formed by the reactions of 5-aryl- and 5-hetaryl-2,3-dicyano-1-ethylpyrazinium salts **7** with O- (water and alcohols) and C-nucleophiles (enolates of dicarbonyl compounds, indoles, *etc*.)[8] (Scheme 2).

Scheme 2



NuH = C- and O-nucleophiles

A convincing evidence for the generation of ylides **3** as a result of dissociation of σ^H-adducts **4—6** was obtained by studying the reactions of the latter compounds with phenyl- (**8a**) or 4-bromophenylacetylenes (**8b**) in boiling *ortho*-xylene. These reactions afforded 8-phenyl-, 8-(4-bromophenyl)-3-aryl-, and 8-(4-bromophenyl)-3-hetaryl-6-methylpyrrolo[1,2-*a*]pyrazine-1-carbonitriles **9a—d** (Scheme 3). The structures of compounds **9a—d** were established by ^1H and ^{13}C NMR spectroscopy and by the X-ray diffraction study of 6-methyl-3,8-diphenylpyrrolo[1,2-*a*]pyrazine-1-carbonitrile **9a** (Fig. 1).

It should be noted that the reaction of hydroxy adduct **6** with phenylacetylene affords cyclization product **9a** in a substantially lower yield (15%) and is accompanied by strong resinification, which is apparently attributed to lower stability of hydroxy compound **6** compared to C-adducts **4** and **5**. This fact can be a consequence of

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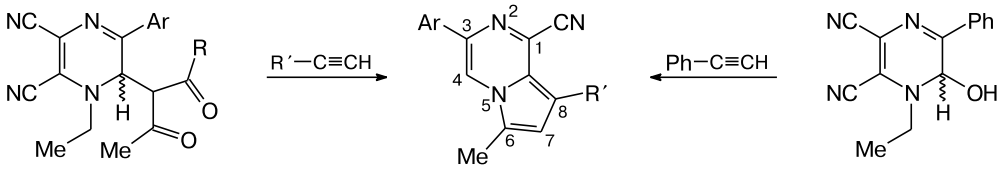
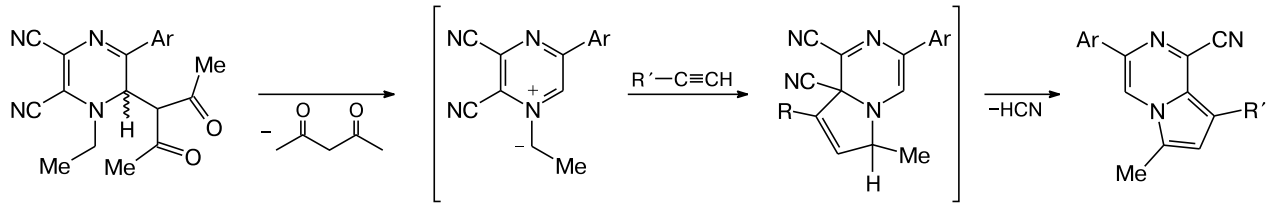
Scheme 3



4a,b, 5 **9a—d** **6**

Starting compound	Substituents			Product	Yield (%)
	R	Ar	R′		
4a, **8a**	Me	Ph	Ph	**9a**	46
4b, **8a**	Me	3-thienyl	Ph	**9b**	54
4a, **8b**	Me	Ph	4-BrC_6H_4	**9c**	44
4b, **8b**	Me	3-thienyl	4-BrC_6H_4	**9d**	40
5, **8a**	OEt	Ph	Ph	**9a** + **5**	14 + 44
6, **8a**	—	Ph	Ph	**9a**	15

Scheme 4



4a,b **3** **10** **9a—d**

the lower strength of the C—O bond compared to the C—C bond.[9]

A decrease in the yield of product **9a** in the reaction of adduct **5** with phenylacetylene can be associated with the lower reactivity of **5** than that of adducts **4a,b** and, as a consequence, with a lower degree of completion of the reaction under analogous conditions. Nevertheless, this question is still debated.

Attempts to generate ylides directly from *N*-ethylpyrazinium salts **7** in the presence of bases and the involvement of the latter in the reaction with arylacetylenes failed because of the formation of complex multicomponent mixtures (TLC data).

The reaction under consideration proceeds apparently as the 1,3-dipolar cycloaddition of the generated ylides **3** with arylacetylenes followed by the aromatization of cycloadducts **10** through the elimination of hydrocyanic acid (Scheme 4).

To sum up, we showed that the σ^H-adducts that are formed as a result of the addition of nucleophiles to 1-ethyl-5-aryl- and 1-ethyl-5-hetaryl-2,3-dicyanopyrazinium salts can be used as hidden 1,3-dipoles for the synthesis of pyrrolo[1,2-*a*]pyrazine derivatives.

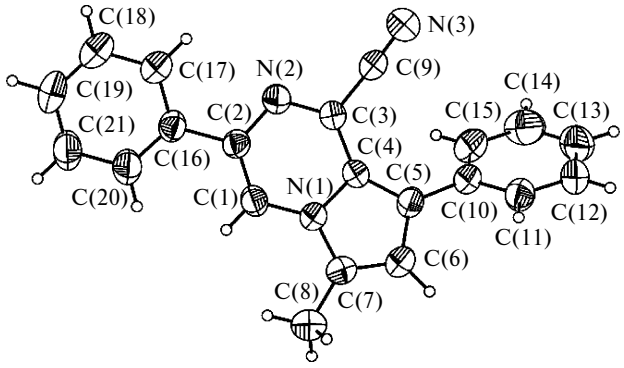


Fig. 1. Molecular structure of **9a** in the crystals.

Experimental

The solvents and reagents were dried and purified according to known procedures.[10] The starting compounds **4—6** were synthesized according to a procedure described previously.[8]

The ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 instrument (400 and 100 MHz, respectively) with Me_4Si as the internal standard. The APCI (atmospheric pressure chemical ionization) and ESI (electrospray ionization) mass spectra were obtained on a Shimadzu LCMS-2010 quadrupole LC-mass spectrometer in CH_3CN at a scanning rate of 0.25 mL min^{-1} with the use of a Supelco LC-18 column (4.6×250 mm) operating in the positive or negative ion mode;

the working voltage was 4.5 kV; nitrogen was used as the carrier gas; the flow rate was 2.5 L min^{-1}. The elemental analysis was carried out on an automated Perkin—Elmer PE-2400 analyzer. The melting points were determined on combined Boetius hot stages and are uncorrected. The flash chromatography was performed with the use of silica gel Lancaster 0.040—0.063 mm (230—400 mesh).

The course of the reactions was monitored and the purity of the products was checked by TLC on Sorbfil plates; spots were visualized under UV light or by spraying with I_2 vapor.

The X-ray diffraction study of compound **9a** was carried out on a Xcalibur 3 diffractometer equipped with a CCD detector at 295(2) K (λMo-Kα, graphite monochromator, φ- and ω-scanning technique). All structures were solved by direct methods with the use of the SHELXS-97 program package and refined using the SHELXL-97 program package with anisotropic displacement parameters (isotropic displacement parameters for H atoms). The results of the X-ray diffraction study were deposited with the Cambridge Crystallographic Data Centre* (CCDC 730052).

Synthesis of 3-aryl- and 3-hetaryl-6-methyl-8-phenyl-pyrrolo[1,2-*a*]pyrazine-1-carbonitriles 9a,b (general procedure). A solution of compound **4a (4b**, **5**, or **6)** (1 mmol) and phenylacetylene (1 mmol) in *ortho*-xylene (7 mL) was refluxed for 1 h, the solvent was distilled off *in vacuo*, and the residue was chromatographed on a column using elution with a 1 : 1 $CHCl_3$—hexane mixture. The reaction product was recrystallized from a 2 : 1 MeCN—MeOH mixture.

6-Methyl-3,8-diphenylpyrrolo[1,2-*a*]pyrazine-1-carbonitrile (9a). Red-orange crystalline powder, m.p. 158—159 °C. ^{1}H NMR ($CDCl_3$), δ: 2.63 (s, 3 H, C<u>H</u>$_3$); 6.91 (s, 1 H, C(7)<u>H</u>); 7.42—7.56 (m, 8 H, Ph); 7.94—7.97 (m, 2 H, Ph); 8.11 (s, 1 H, C(4)<u>H</u>). Found (%): C, 81.25; H, 4.74; N, 13.39. $C_{21}H_{15}N_3$. Calculated (%): C, 81.53; H, 4.89; N, 13.58. LC/MS, *m/z* (*I* (%)): 310 $[M + H]^+$ (70), 352 $[M + 2 H + CH_3CN]^+$ (100).

6-Methyl-8-phenyl-3-(3-thienyl)pyrrolo[1,2-*a*]pyrazine-1-carbonitrile (9b). Red crystalline powder, m.p. 193—195 °C. ^{1}H NMR ($CDCl_3$), δ: 2.61 (s, 3 H, C<u>H</u>$_3$); 6.88 (s, 1 H, C(7)<u>H</u>); 7.41—7.55 (m, 7 H, Ph and 3-thienyl); 7.89 (dd, 1 H, H(2″)-3-thienyl, *J* = 3.0 Hz, *J* = 1.3 Hz); 8.11 (s, 1 H, C(4)<u>H</u>). Found (%): C, 71.97; H, 4.37; N, 13.21. $C_{19}H_{13}N_3S \cdot 0.1H_2O$. Calculated (%): C, 71.94; H, 4.19; N, 13.25. LC/MS, *m/z* (*I* (%)): 316 $[M + H]^+$ (100), 358 $[M + 2 H + CH_3CN]^+$ (85).

8-(4-Bromophenyl)-3-aryl- and 8-(4-bromophenyl)-3-hetaryl-6-methylpyrrolo[1,2-*a*]pyrazine-1-carbonitriles 9c,d were synthesized from compounds **4a** or **4b** (1 mmol) and 4-bromophenylacetylene (1 mmol) in *ortho*-xylene (7 mL) by analogy with compounds **9a,b**.

8-(4-Bromophenyl)-6-methyl-3-phenylpyrrolo[1,2-*a*]pyrazine-1-carbonitrile (9c). Red crystalline powder, m.p. 207—208 °C. ^{1}H NMR ($CDCl_3$), δ: 2.62 (s, 3 H, C<u>H</u>$_3$); 6.88 (s, 1 H, C(7)<u>H</u>); 7.36—7.61 (m, 7 H, Ph); 7.93—7.96 (m, 2 H, Ph); 8.10 (s, 1 H, C(4)<u>H</u>). Found (%): C, 64.96; H, 3.49; N, 10.93. $C_{21}H_{14}N_3Br$. Calculated (%): C, 64.96; H, 3.63; N, 10.82. LC/MS, *m/z* (*I* (%)): 388 $[M]^+$ (70), 389 $[M + H]^+$ (20), 390 $[M + 2H]^+$ (74), 429 $[M + CH_3CN]^+$ (94), 431 $[M + 2 H + CH_3CN]^+$ (100).

8-(4-Bromophenyl)-6-methyl-3-(3-thienyl)pyrrolo[1,2-*a*]pyrazine-1-carbonitrile (9d). Orange crystalline powder, m.p. 246—247 °C (decomp.). ^{1}H NMR ($CDCl_3$), δ: 2.61 (s, 3 H, C<u>H</u>$_3$); 6.86 (s, 1 H, C(7)<u>H</u>); 7.40 (d, 2 H, Ph, *J* = 8.5 Hz); 7.44 (dd, 1 H, H(5″) 3-thienyl, *J* = 5.0 Hz, *J* = 3.0 Hz); 7.54 (dd, 1 H, H(4″) 3-thienyl, *J* = 5.0 Hz, *J* = 1.3 Hz); 7.59 (d, 2 H, Ph, *J* = 8.5 Hz); 7.90 (dd, 1 H, H(2*I*) 3-thienyl, *J* = 3.0 Hz, *J* = 1.3 Hz); 8.01 (s, 1 H, C(4)<u>H</u>). Found (%): C, 57.62; H, 3.01; N, 10.69. $C_{19}H_{12}N_3SBr$. Calculated (%): C, 57.88; H, 3.07; N, 10.66. LC/MS, *m/z* (*I* (%)): 394 $[M]^+$ (56), 395 $[M + H]^+$ (15), 396 $[M + 2 H]^+$ (55), 435 $[M + CH_3CN]^+$ (98), 436 $[M + H + CH_3CN]^+$ (27), 437 $[M + 2 H + CH_3CN]^+$ (100).

Crystallographic data for compound 9a. Crystals of compound **9a**, $C_{21}H_{15}N_3$, monoclinic, space group $P2_1/C$, were obtained by recrystallization from a 1 : 3 MeCN—MeOH mixture. The unit cell parameters at 295 K are a = 8.6274(13) Å, b = 16.470(5) Å, C = 11.6320(9) Å, α = 90.00°, β = 97.721(10)°, γ = 90.00°, V = 1637.8(5) Å^3, Z = 4. 26.36 ≥ θ ≥ 3.03. The intensities of 3341 reflections were measured, of which 1279 reflections were with $I > 2\sigma$. The final R factors are R = 0.0421, R_w = 0.0742.

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* These data can be obtained, free of charge, on application to www.ccdc.cam.ac.uk/data_request/cif.