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Quinoxalines XV. Convenient Synthesis and Structural Study of Pyrazolo[1,5-*a*]quinoxalines

Gerhard Sarodnick,[†] Torsten Linker,*[,†] Matthias Heydenreich,[‡] Andreas Koch,[‡] Ines Starke,[‡] Sylvia Fürstenberg,[‡] and Erich Kleinpeter*[,‡]

Department of Chemistry, University of Potsdam, Karl-Liebknecht-Str. 24-25, D-14476 Potsdam, Germany

linker@chem.uni-potsdam.de; kp@chem.uni-potsdam.de

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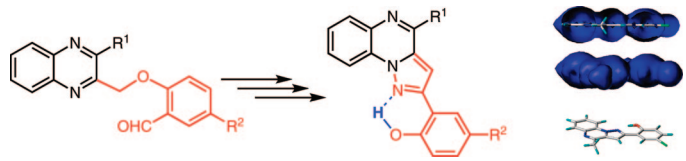
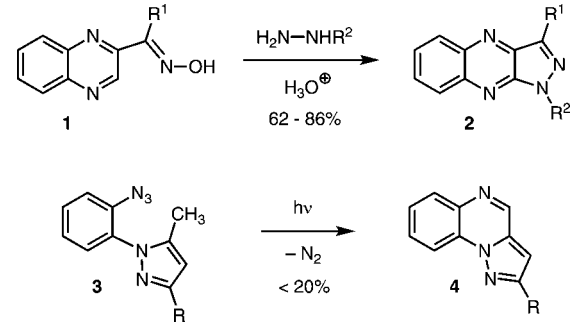


A series of aryloxymethylquinoxaline oximes, hitherto unknown and synthesized from the corresponding aldehydes, afforded in only one step pyrazolo[1,5-*a*]quinoxalines in the presence of acetic anhydride at high temperatures. A formal [3,5]-sigmatropic rearrangement was proposed as the mechanistic rationale for this unprecedented transformation. Saponification with potassium hydroxide furnished the free phenol derivatives which were studied by NMR spectroscopy and accompanying theoretical DFT calculations, establishing intramolecular hydrogen bonding and the spatial magnetic properties. Additionally, mass spectrometric fragmentation was investigated by B/E-linked scans and collision-induced dissociation experiments. The fragmentation pattern devoted a new gas phase rearrangement process, which proved to be unique and characteristic for pyrazolo[1,5-*a*]quinoxalines.

Introduction

Heterocycles are of current interest for biological and medical studies, and new synthetic strategies are a challenging task for organic chemists.[1] For instance, nitrogen-containing tricyclic compounds were obtained from quinolines by a radical methodology very recently.[2] In general, tricyclic heteroaromatic compounds have found various applications as fungicides or herbicides and are potential enzyme inhibitors. Common structures are 1*H*-pyrazolo[3,4-*b*]quinoxalines (flavazoles) **2**, which can be easily synthesized by oxidative cyclization of the corresponding quinoxaline hydrazones **1** and are nowadays well-established.[3] Interestingly, the structurally related pyrazolo[1,5-*a*]quinoxalines **4** were studied less intensively and were obtained

SCHEME 1. Synthetic Strategies to Heterocycles 2 and 4[3,4]



in only low yields as byproduct from the photodecomposition of azides **3** (Scheme 1).[4] This is surprising since such heterocycles **4** exhibit important properties as HIV integrase inhibitors and in vivo antitumor activities, which were discovered only very recently.[5] Herein we present a new and convenient synthetic strategy to pyrazolo[1,5-*a*]quinoxalines **4**, which proceeds presumably by an interesting [3,5]-sigmatropic rear-

[†] Organische Chemie.
[‡] Analytische Chemie.

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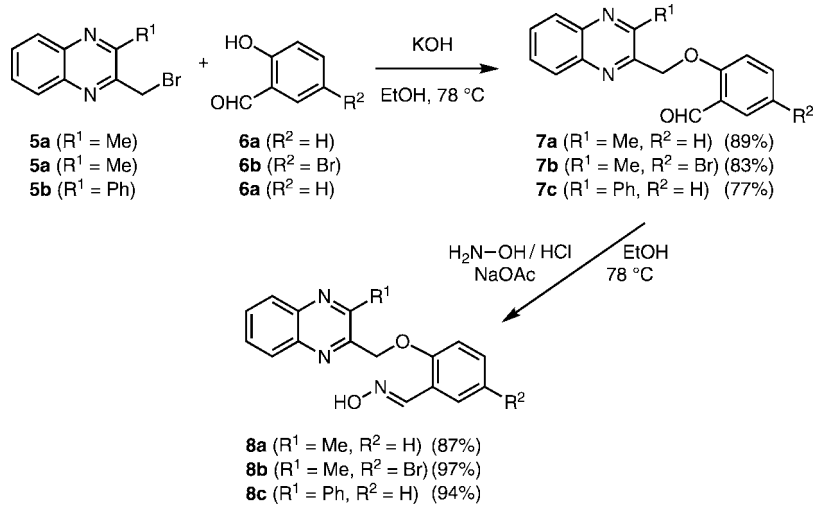
SCHEME 2. Synthesis of Oximes 8



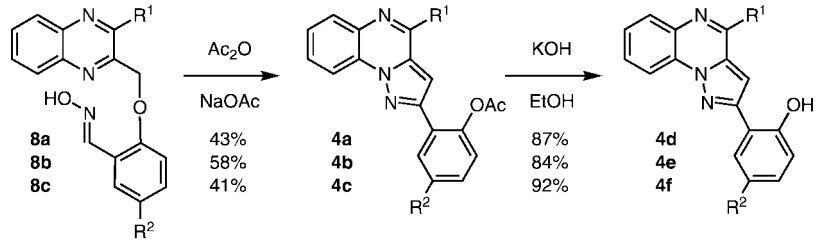
5a (R^1 = Me)
5a (R^1 = Me)
5b (R^1 = Ph)

6a (R^2 = H)
6b (R^2 = Br)
6a (R^2 = H)

7a (R^1 = Me, R^2 = H) (89%)
7b (R^1 = Me, R^2 = Br) (83%)
7c (R^1 = Ph, R^2 = H) (77%)

8a (R^1 = Me, R^2 = H) (87%)
8b (R^1 = Me, R^2 = Br) (97%)
8c (R^1 = Ph, R^2 = H) (94%)

SCHEME 3. Synthesis of the Pyrazolo[1,5-*a*]quinoxalines 4a−f



8a 43% **4a** 87% **4d**
8b 58% **4b** 84% **4e**
8c 41% **4c** 92% **4f**

a,d: R^1 = Me, R^2 = H; **b,e**: R^1 = Me, R^2 = Br; **c,f**: R^1 = Ph, R^2 = H

rangement. Additionally, we focus on the physical organic properties of these rarely available pyrazolo[1,5-*a*]quinoxalines and studied this heterocyclic ring system in detail by an experimental and theoretical study. In particular, the aromaticity of the various ring units subject to spatial magnetic properties, intramolecular hydrogen bonding, steric hindrance within the molecules, and the unique and characteristic mass spectrometric fragmentation of the pyrazolo[1,5-*a*]quinoxalines will be reported.

Results and Discussion

Synthesis of Pyrazolo[1,5-*a*]quinoxalines 4. During the course of our investigations on synthetic transformations of quinoxalines,[3c−e] we developed an easy entry to the benzyl ethers **7** from the corresponding benzyl bromides **5** and commercially available salicylaldehydes **6**.[6] The reaction of the aldehydes **7** with hydroxylamine hydrochloride proceeded smoothly, and the hitherto unknown oximes **8a−c** were isolated in analytically pure form and excellent yields by simple crystallization (Scheme 2).

Treatment of the oximes **8** with an excess of acetic anhydride in the presence of sodium acetate at high temperatures afforded directly the pyrazolo[1,5-*a*]quinoxalines **4a−c** in moderate yields. Finally, the free phenols **4d−f**, which were of interest from the possibility of intramolecular hydrogen bonding, were obtained by saponification of the acetates with potassium hydroxide (Scheme 3).

The formation of the pyrazolo[1,5-*a*]quinoxalines **4** is unprecedented and significant from the mechanistic point of view. Obviously, a C−O bond is broken in favor of a newly formed N−N bond, with the driving force being aromatization to the pyrazole ring. In the first step, the acetylation to the *O*-acetyloximes **9** in the presence of acetic anhydride is likely. Such compounds are very reactive in Beckmann rearrangements,[7] and even adjacent amines can form a N−N bond with the oxime.[8] Therefore, we propose a nucleophilic attack of the quinoxaline nitrogen under cleavage of the C−O bond (Scheme 4). Formally, this transformation is a [3,5]-sigmatropic rearrangement, which is rarely described in literature, but was observed during the reaction of arylhydrazones.[9] The resulting enamines **10** undergo intramolecular vinylogous Michael additions to the activated enone, regenerating the aromatic phenolate **11**. Finally, tautomerization and elimination of acetic acid affords the phenols **4d−f**, which react with acetic anhydride to the acetates **4a−c**. This trapping step is in accordance to the reaction of similar zwitterionic intermediates with trimethylsilylcyanide, observed during the photodegradation of merocyanines.[10] Overall, the formation of a conjugated aromatic system and the entropically favorable elimination in the last step should provide enough energy for this unusual [3,5]-sigmatropic rearrangement.

Structural Study of the Pyrazolo[1,5-*a*]quinoxalines 4. Most interesting in the ^{1}H NMR spectra of the free phenol

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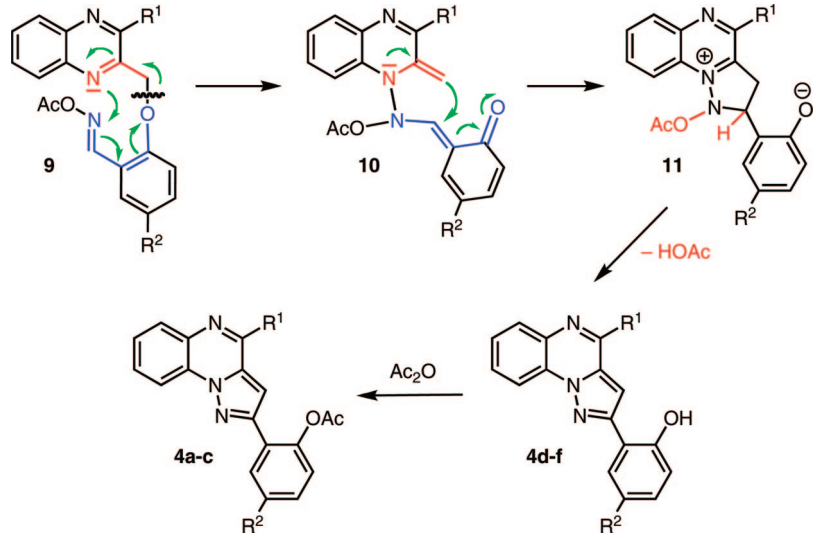
SCHEME 4. Proposed Mechanism for the Formation of Pyrazolo[1,5-*a*]quinoxalines 4a−f



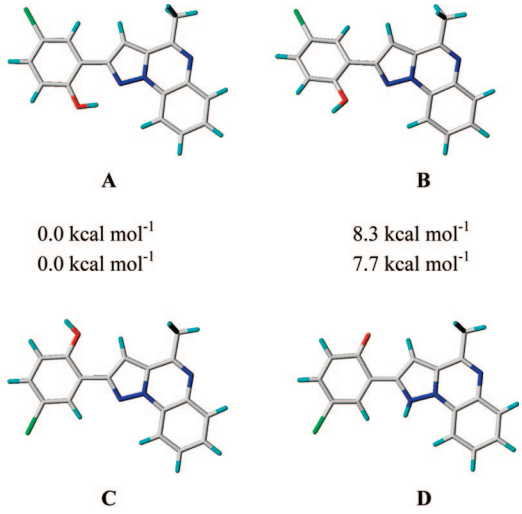


FIGURE 1. Structures of the pyrazolo[1,5-*a*]quinoxaline derivative **4e** [global minimum (**A**), without H-bonding (**B**), 180° rotamer (**C**), and NH tautomer (**D**)].

derivatives **4d−f** is the low field position of the OH protons (δ 10.25−10.70) pointing to the existence of an intramolecular hydrogen bond to the nitrogen atom of the pyrazol ring moiety; variation in both solution concentration and temperature are supportive of this assumption. Thus, initially this structure **A**, the one without hydrogen bond **B**, and also the 180° phenyl rotamer **C** were theoretically calculated employing the DFT theory at the B3LYP/6-311G** level. Both water and chloroform were considered as NMR solvents applying the self-consistent reaction field (SCRF) method and the self-consistent isodensity polarized continuum model (SCIPCM).[11] Structures, thus obtained, and their relative energies are given for compound **4e** in Figure 1.

The structure of the pyrazolo[1,5-*a*]quinoxaline **4e** with the intramolecular H-bond **A** as suggested proves to be the most stable conformer which is completely planar. Planarity was obtained also for the structure of the 180° phenyl rotamer **C**. This conformer **C**, however, was found to be 4.3 kcal mol^{-1} (in water) and 4.9 kcal mol^{-1} (in chloroform) less stable than conformer **A**; the same energy amount as molecular stabilization energy of the pyrazolo[1,5-*a*]quinoxalines **4d−f** due to the intramolecular hydrogen bond can be suggested. The structure of the pyrazolo[1,5-*a*]quinoxaline conformer without H-bond **B** proves to be even less stable (7.7 kcal mol^{-1} in water and 8.3 kcal mol^{-1} in chloroform) than the 180° rotamer **C**. In addition, the phenyl moiety is twisted from the plane of the pyrazolo[1,5-*a*]quinoxaline moiety by ca. 40°. The additional potential energy of **B** with respect to **C** (3.4 kcal mol^{-1} in water and 3.3 kcal mol^{-1} in chloroform) can be assigned to steric destabilization subject to H···H contacts of pyrazolo[1,5-*a*]quinoxaline and phenyl moieties.

The NH tautomers of pyrazolo[1,5-*a*]quinoxalines **4e** were also calculated; only the 180° rotamer **D** was found as a local minimum on the potential energy surface (PES) but was 27.6 kcal mol^{-1} less stable than **A**. The corresponding NH tautomer similar to **A**, but NH at the pyrazol and C=O at the phenyl moiety, could not be identified as a minimum on the PES (the calculation starting with the corresponding initial structure delivered **A** as the energy minimum). Therefore, potential tautomers of **A** in the pyrazolo[1,5-*a*]quinoxalines **4d−f** can be disregarded.

Along the DFT calculations, the spatial magnetic properties of the pyrazolo[1,5-*a*]quinoxalines **4d−f** were calculated as through-space NMR shieldings (TSNMRS)[12] which had been successfully applied to visualize and qualitatively inform about the aromaticity of potential aryl compounds.[13] The TSNMRS of the pyrazolo[1,5-*a*]quinoxalines **4e**, thus obtained, are visualized as iso-chemical-shielding surfaces (ICSS) of different size and direction and are given for the preferred conformer **A** in Figure 2.

As expected, a thorough conjugated aromatic π-system is existent: the spatial magnetic properties of pyrazolo[1,5-*a*]quinoxalines **4e** as TSNMRS, visualized as common deshield-

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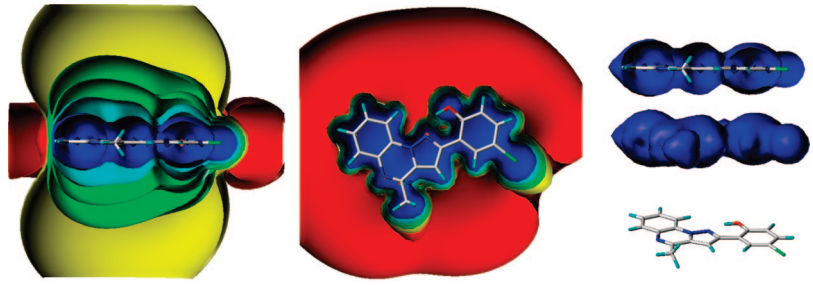

FIGURE 2. TSNMRS of pyrazolo[1,5-*a*]quinoxaline derivative **4a** visualized (a,b) as ICSS −0.1 ppm (deshielding, red), +0.1 ppm (shielding, yellow), +0.5 ppm (green), +1 ppm (green-blue-cyan), +2 ppm (cyan), and +5 ppm (blue) and (c) as visualized as ICSS of 5 ppm (blue) only.

ing [−0.1 ppm (red)] and shielding ICSS [+0.1 ppm (yellow) and +0.5 ppm (green)], spectacularly confirm the implication. Incipient with the shielding ICSS of +1 ppm (green-blue) and increasingly at the shielding ICSS of +2 ppm (cyan) and + 5 ppm (blue), respectively, the TSNMRS, however, inform qualitatively about the different aromaticity of the four aromatic moieties of the pyrazolo[1,5-*a*]quinoxaline ring system (cf. Figure 2c): while the aromaticity of the two benzene rings together with the five-membered pyrazole unit proves obviously to be similar, the corresponding value of the pyrazine ring moiety is declining. This result can be construed only by a preferred π-electron conjugation between the two terminal benzene rings via the N−N=C connection and much less via the wider N=CH−C=C−C link changing the local aromaticity hereby.

The application of the same theoretical method for the corresponding acetates **4a**−**c** added up to four local minima on the PES, which are near in relative energy and similar in structure; these structures, relative energies, and, in order to show also the similarity in the twist dihedral angles between pyrazolo[1,5-*a*]quinoxaline and phenyl moieties and between the phenyl ring plane and the O-OC(O)Me group, respectively, the corresponding dihedral angles are given for **4b** in Figure 3. The theoretical study reveals the global minimum structure **E** to have a dihedral angle of 21.4° only and the ester group in *ring-out* conformation; this group in *ring-in* conformation (structure **H**) destabilizes the molecule by 2.9 kcal mol^{-1} but reduces the twist between the two aromatic moieties to 17.1° only.

Beyond the OH protons in the ^{1}H NMR spectra, both proton and ^{13}C chemical shifts are not further informative with respect to the structural assignment of the pyrazolo[1,5-*a*]quinoxaline derivatives **4**. ^{1}H and ^{13}C chemical shifts of the aromatic protons/carbon atoms are so similar that a detailed assignment proves useless; in addition, simultaneous theoretical calculation of the δ values employing the GIAO perturbation method[14] did not bring the assignment procedure really forward.

The final structural proof of the pyrazolo[1,5-*a*]quinoxaline derivatives **4** rendered the mass spectra, most important peaks in the EI mass spectra of the pyrazolo[1,5-*a*]quinoxalines **4** and of the oximes **8** hitherto unknown; the elemental composition of the ions was determined by accurate mass measurements, and the fragmentation pathways were clarified by B/E-linked scans and collision-induced dissociation. The corresponding data are given in Table S1 in the Supporting Information and Table 1.

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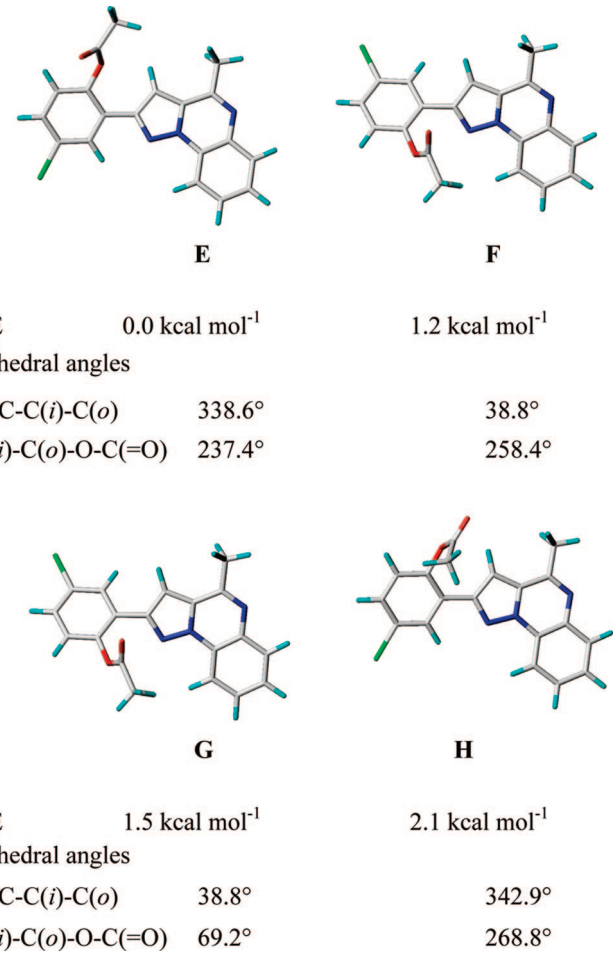


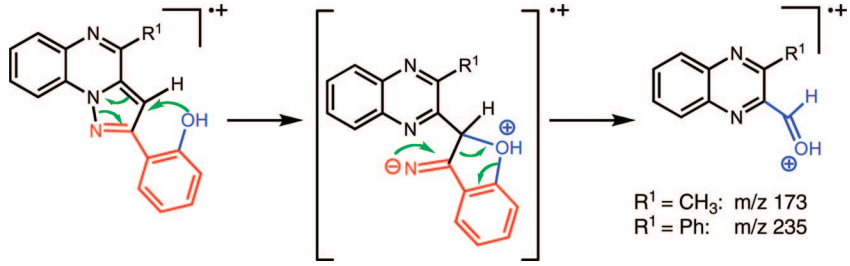
FIGURE 3. Structures of the pyrazolo[1,5-*a*]quinoxaline derivative **4b** [global minimum (**E**) and local minima structures (**F**−**H**); dihedral angles for the twist of the phenyl substituent (N−C−C(*i*)−C(*o*)) and of the $OCOCH_3$ moiety (C(*i*)−C(*o*)−O−C(=O)) are given (*i* ipso; *o* ortho).

Common fragment ions for the free phenol derivatives **4d**−**f** are compatible with losses of $CH_3^{\bullet}$, $OH^{\bullet}$, and CHO, respectively, in the corresponding acetates **4a**−**c**, the characteristic $[M - CH_3CO]^+$ ion could be detected. The EI mass spectra of the studied compounds **4** are characterized further by the presence of the ions $C_{15}H_{11}N_2$ and $C_{15}H_{10}N_2$ at *m*/*z* 219 and 218, respectively; in case of the pyrazolo[1,5-*a*]quinoxalines with R_1 = Ph (**4c** and **4f**), the ion $C_{15}H_{10}N_2$ at *m*/*z* 218 proves to be even the base peak in the mass spectrum. The latter ions together with $C_{14}H_9N_2$ at *m*/*z* 205, $C_{10}H_7N_2$ at *m*/*z* 155, and $C_9H_7N_2$ at

TABLE 1. Characteristic Fragment Ions of Compounds 4d−f as Proved by Linked Scan Measurements

compound no	result of the linked scans *m/z*
4d B/E *m/z* 275	260 $[M - CH_3]^+$, 258 $[M - OH]^+$, 246 $[M - CHO]^+$, 173 $[M - Ph - CN]^+$
4e B/E *m/z* 353	336 $[M - OH]^+$, 324 $[M - CHO]^+$, 173 $[M - Ph - CN - Br]^+$
4f B/E *m/z* 337	244 $[M - Ph - OH]^+$, 235 $[Ph - CN]^+$

SCHEME 5. Fragmentation of the Pyrazolo[1,5-*a*]quinoxaline Derivatives 4d−f



m/z 143 are well-known from the fragmentation patterns of simple quinoxalines and their alkyl and aryl derivatives, published already previously.[15]

Additionally, in the EI mass spectra of the pyrazolo[1,5-*a*]quinoxalines with $R_1 = CH_3$ (**4a**,**b**,**d**,**e**), the ion $C_{10}H_9N_2O$ at *m/z* 173 with RA (30−70%) was observed. On the basis of the linked scan B/E experiments, this fragment ion had to be attributed to the loss of Ph−CN and Ph−CN−Br, respectively, directly from the molecular ion (cf. Table 1). Also in the mass spectra of the analogues with R_1 = Ph (**4c**,**f**), a similar ion $C_{15}H_{11}N_2O$ at *m/z* 235 was detected. In the latter two compounds, the loss of Ph−CN can in principle originate from the phenyl substituent R_1 or from the one located on the pyrazolo ring moiety, due to similar rearrangement processes in the gas phase. In order to prove, for comparison purposes also the two chloro-labeled compounds ($R_1 = p$-C_6H_4Cl instead of C_6H_5 in **4c**,**f**) have been synthesized and EI-MS studied: in the corresponding mass spectra, the ion $[M - Ph - CN]^+$ was found, indicating that the fragment Ph−CN indeed is not originating from the quinoxaline unit of **4c**,**f** but rather from the pyrazolo unit.

The ions $[C_{10}H_9N_2O]$ at *m/z* 173, $[C_{15}H_{11}N_2O]$ at *m/z* 235, and of the complementary Ph−CN species in the mass spectra of the free phenol pyrazolo[1,5-*a*]quinoxaline derivatives **4d**−**f** originate from a fragmentation mechanism proximal to a back-reaction, which is given in Scheme 5. The splitting of Ph−CN directly from the molecular ion can only be explained by this gas phase rearrangement process, which proves similar to the Claisen rearrangement or to a [3,5]-sigmatropic rearrangement reaction. In any case, this fragmentation mechanism of elimination of Ph−CN from the molecular ion is unique and very characteristic for the pyrazolo[1,5-*a*]quinoxalines **4d**−**f** studied. Similar rearrangement reactions in the gas phase, for example, the Claisen rearrangement and the sigmatropic rearrangement, have been observed and well-documented.[16−18]

The ions $[C_{10}H_9N_2O]$ at *m/z* 173 and $[C_{15}H_{11}N_2O]$ at *m/z* 235 have been observed in the mass spectra of the acetyl-substituted pyrazolo[1,5-*a*]quinoxaline derivatives **4a**−**c**, as well.

Conclusions

We developed a new, short and convenient synthesis of pyrazolo[1,5-*a*]quinoxalines from simple quinoxalines. The key step was the reaction of an oxime with acetic anhydride, which proceeded under formation of a N−N bond and cleavage of a C−O bond. A mechanistic rationale was provided by an unusual [3,5]-sigmatropic rearrangement with the driving force of aromatization. Both the acetates **4a**−**c** and the free phenols **4d**−**f** of the pyrazolo[1,5-*a*]quinoxalines were theoretically calculated employing the DFT theory at the B3LYP/6-311G** level.[19−22] The free phenols form intramolecular hydrogen bonds to the pyrazol nitrogen atom (both the stabilizing molecular energy of this H-bond and the steric hindrance between pyrazol and *ortho*-phenyl protons could be determined quantitatively). The corresponding acetates form a number of preferred conformers with the planes of pyrazolo[1,5-*a*]quinoxaline and phenyl moieties slightly twisted and the ester group either in *ring-in* or *ring-out* conformation.

Furthermore, the aromaticity of the four different ring moieties of the pyrazolo[1,5-*a*]quinoxalines **4** were estimated qualitatively by calculating TSNMRS and visualizing[23] the latter as ICSS of different size and direction. The aromaticity of the two benzene rings together with the five-membered pyrazole unit of the molecules proves to be similar, and the corresponding value of the pyrazine ring moiety is declining as a consequence of the preferred π-conjugation between the two terminal benzene rings via the N−N=C link and much less via the wider N=C−C=C−C connection changing the local aromaticity hereby. Finally, the

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structure of the pyrazolo[1,5-*a*]quinoxalines **4** was proved by EI mass spectrometry via a unique and characteristic fragmentation pattern.

Experimental Section

General Procedure for the Synthesis of Oximes 8a−c: The aldehyde **7** (20 mmol) was dissolved in ethanol (100 mL) at 60 °C, and a solution of hydroxylamine hydrochloride (1.74 g, 25 mmol) and sodium acetate trihydrate (4.08 g, 30 mmol) in water (50 mL) was added at this temperature. After heating under reflux for 1 h, the mixture was cooled to rt, and the oximes **8** were precipitated at 4 °C for 12 h.

2-(3-Methylquinoxalin-2-ylmethoxy)benzoxime (8a): The compound was obtained from the aldehyde **7a** in 87% yield, mp 185 °C; IR 3240 (O−H), 3008 (C−H), 1626, 1602 (C═O); ^{1}H NMR ($CDCl_3$) δ 8.49 (1H, s), 8.08 (2H, m), 7.76 (3H, m), 7.35 (1H, dt, J = 8.3, 1.6 Hz), 7.16 (1H, d, J = 8.2 Hz), 6.99 (1H, t, J = 7.5 Hz), 5.45 (2H, s), 2.87 (3H, s); ^{13}C NMR ($CDCl_3$) δ 56.3, 153.8, 150.0, 146.1, 142.0, 140.5, 131.2, 130.4, 129.3, 129.1, 128.4, 126.8, 121.6, 121.2, 112.6, 71.1, 22.3; MS *m*/*z* (%) 276 (27), 174 (10), 157 (100). Anal. Calcd for $C_{17}H_{15}N_3O_2$ (293.12 g/mol): C, 69.61; H, 5.15; N, 14.33. Found: C, 69.44; H, 5.25; N, 14.31. HRMS: *m*/*z* calcd for $C_{17}H_{15}N_3O_2$* 293.1164, found 293.1170.

For **8b** and **8c**, see the Supporting Information.

General Procedure for the Synthesis of the Pyrazolo[1,5-*a*]quinoxalines 4a−c: A mixture of the oxime **8** (10 mmol), anhydrous sodium acetate (1.64 g, 20 mmol), and acetic anhydride (15.3 g, 150 mmol) was heated at 100 °C for 0.5−3 h until TLC showed complete conversion. If starting material remained, the mixture was heated at 130 °C for an additional 10 min. After cooling to rt, the crude product was precipitated at 4 °C for 12 h, and the pyrazolo[1,5-*a*]quinoxaline **4** was purified by recrystallization from 2-propanol.

2-(4-Methylpyrazolo[1,5-*a*]quinoxalin-2-yl)phenyl acetate (4a): The compound was obtained from the oxime **8a** in 43% yield, mp 169−170 °C; IR 3050 (C−H); ^{1}H NMR ($CDCl_3$) δ 8.39 (1H, dd, J = 8.0, 1.0 Hz), 7.97 (1H, dd, J = 8.0, 1.6 Hz), 7.94 (1H, dd, J = 9.0, 0.9 Hz), 7.53 (1H, t, J = 7.1 Hz), 7.48 (1H, t, J = 8.1 z), 7.39 (1H, dt, J = 7.5, 1.6 Hz), 7.32 (1H, dt, J = 7.4, 1.2 Hz), 7.17 (1H, dd, J = 7.8,1.0 Hz), 6.99 (1H, s), 2.73 (3H, s), 2.35 (3H, s); ^{13}C NMR ($CDCl_3$) δ 169.2, 152.2, 149.4, 147.9, 135.8, 133.8, 129.8, 129.5, 128.9, 128.3, 128.0, 126.2, 126.1, 125.4, 123.3, 114.4, 100.4, 22.2, 21.2; MS *m*/*z* (%) 275 (100), 260 (7), 258 (8), 246 (13), 219 (8), 205 (10), 173 (30). Anal. Calcd for $C_{19}H_{15}N_3O_2$ (317.12 g/mol): C, 71.91; H, 4.76; N, 13.24. Found: C, 71.84; H, 4.96; N, 13.17. HRMS: *m*/*z* calcd for $C_{19}H_{15}N_3O_2$* 317.1164, found 317.1154.

For **4b** to **4f**, see the Supporting Information.

Supporting Information Available: Experimental section, copies of the ^{1}H and ^{13}C NMR spectra of the studied compounds (**4** and **8**), and the coordinates and absolute energies at the B3LYP/6-311G** level of theory for compounds **4e(A−H)**. This material is available free of charge via the Internet at http://pubs.acs.org.

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