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Quinoxalines. Part 12: Synthesis and structural study of 1-(thiazol-2-yl)-1*H*-pyrazolo[3,4-*b*]quinoxalines—the dehydrogenative cyclization with hydroxylamine hydrochloride☆

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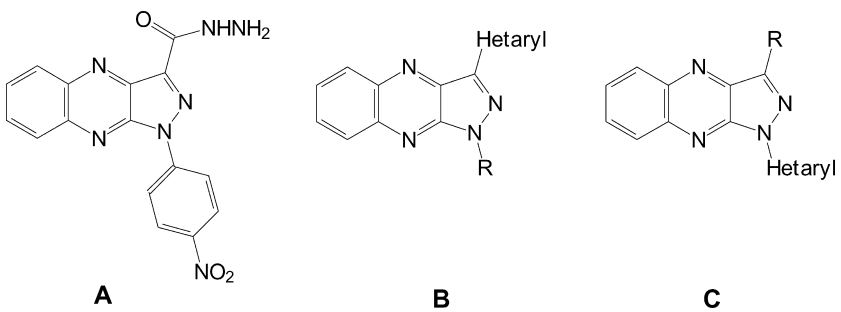
Abstract—Starting with 2-acetylquinoxaline a novel class of heterocyclic compounds, the 1-(thiazol-2-yl)-1*H*-pyrazolo[3,4-*b*]quinoxalines **4**, were prepared by following two different synthetic procedures: 2-acetylquinoxaline reacted with thiosemicarbazide to the thiosemicarbazones **1a** which was (i) cyclized with α-halogeno ketones to the thiazoles **3**. These compounds were dehydrogenated in acidic medium to the title compounds **4**. (ii) The thiosemicarbazone **1a** could be also dehydrogenated using $NH_2OH{\cdot}HCl$ to the thioamide **5a** and these, finally, were cyclized with α-halogeno ketones to the title compounds **4**. Only thiazole **3a** was isolated, the other thiazoles **3** were dehydrogenated in a one-pot procedure. From the thioamide **5a** also both the compounds **9**, by reacting with dibromodiacetyl, and **10**, by treatment with dimethyl acetylenedicarboxylate, were obtained. The analysis of both the ^1H and ^{13}C NMR spectra was not straightforward but could be attained finally by employing the whole arsenal of 1D and 2D NMR spectroscopy.

1. Introduction

In consequence of their interesting biologically active properties and synthetic utility, considerable interest has been demonstrated towards 1*H*-pyrazolo[3,4-*b*]quinoxalines; the parent compound was found in 1971 to be highly tuberkulostatic.[2] 1-(4-Nitrophenyl)-1*H*-pyrazolo[3,4-*b*]quinoxaline-3-carbohydrazide **A** (cf. Scheme 1) proved to be of highly anti-bacteriological activity vs. both gramopositive and gramonegative bacteria;[3] if the flavazole system in **A** is replaced by the pyridazino[3,4-*b*]quinoxaline moiety, the anti-bacteriological activity was lost.[4] On the other hand, if the pyrazolo[3,4-*b*]quinoxalines (**B**) are substituted in position 3 by another heteroaromatic moieties, they show fungicidal activity.[5]

Pyrazolo[3,4-*b*]quinoxalines with similar heteroaromatic substituents attached to position 1 (**C**) are still unknown but heavily expected to be of similar biological activity.

In the present study the syntheses of several 1-(thiazol-2-yl)-1*H*-pyrazolo[3,4-*b*]quinoxalines as representatives of the 1-hetaryl-1*H*-pyrazolo[3,4-*b*]quinoxalines **C** are reported.



Scheme 1.

☆ See Ref. 1.

Keywords: 1-(thiazol-2-yl)-1*H*-pyrazolo[3,4-*b*]quinoxalines; dehydrogenative cyclization; 2D NMR structure elucidation.
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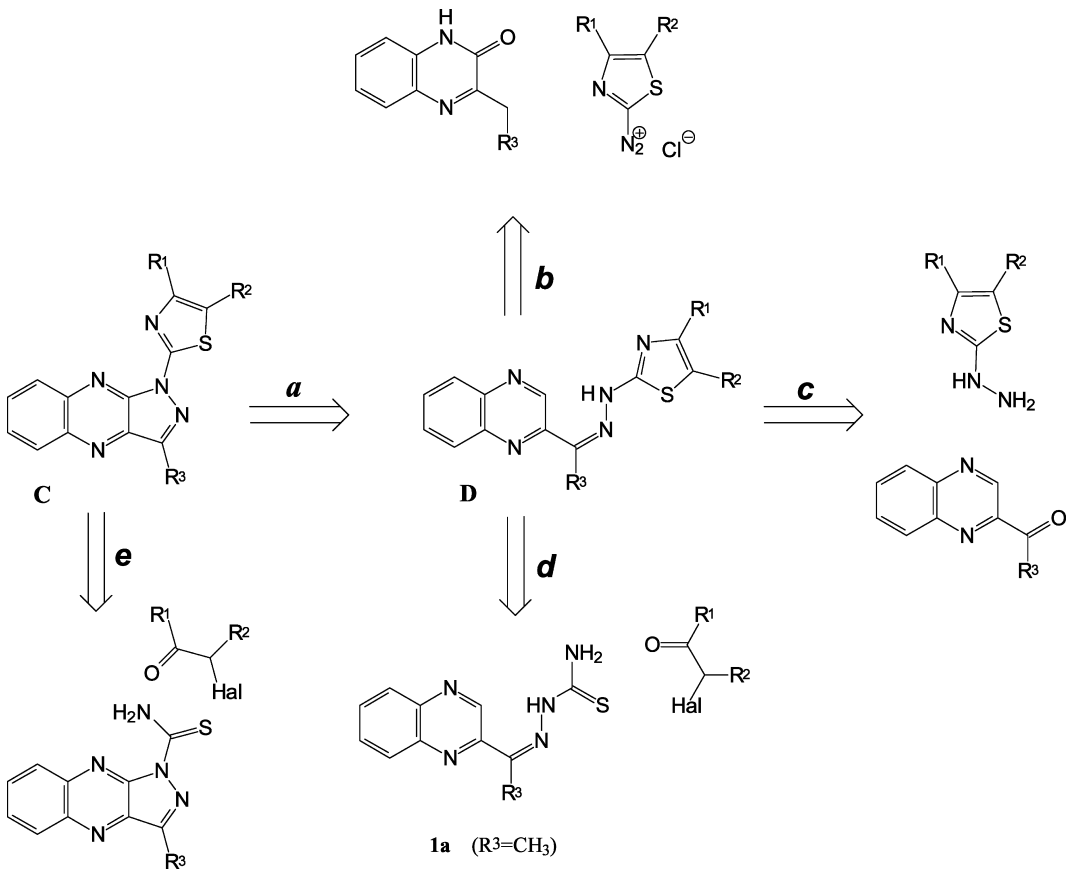


Scheme 2.

2. Results and discussion

2.1. Syntheses

The crucial last step of the synthesis of the aromatically substituted 1*H*-pyrazolo[3,4-*b*]quinoxalines of type **A** (cf. Scheme 1) is the closure of the pyrazolo ring by dehydrogenation,[6] dehydration[7] or dehydrohalogenation[8] employing a useful arylhydrazone. These arylhydrazones **D** (cf. Scheme 2) can be prepared from the corresponding quinoxaline derivatives by addition of aromatic hydrazines[6] or aromatic diazonium salts.[8c,d] So, we also expected to receive the corresponding hydrazones of 3-methyl-1,2-dihydroquinoxalin-2-one[5a,8a] and ethyl-2-oxo-1,2-dihydroquinoxalin-3-yl acetate,[5b,8d] respectively, by coupling with the diazonium salt of 2-aminothiazole; further, the arylhydrazones, thus obtained, should be chlorinated with $POCl_3$ and, finally, the heteroaromatic ring closed by dehydrochlorination in the presence of strong bases. However, we could not succeed in following this reaction path.

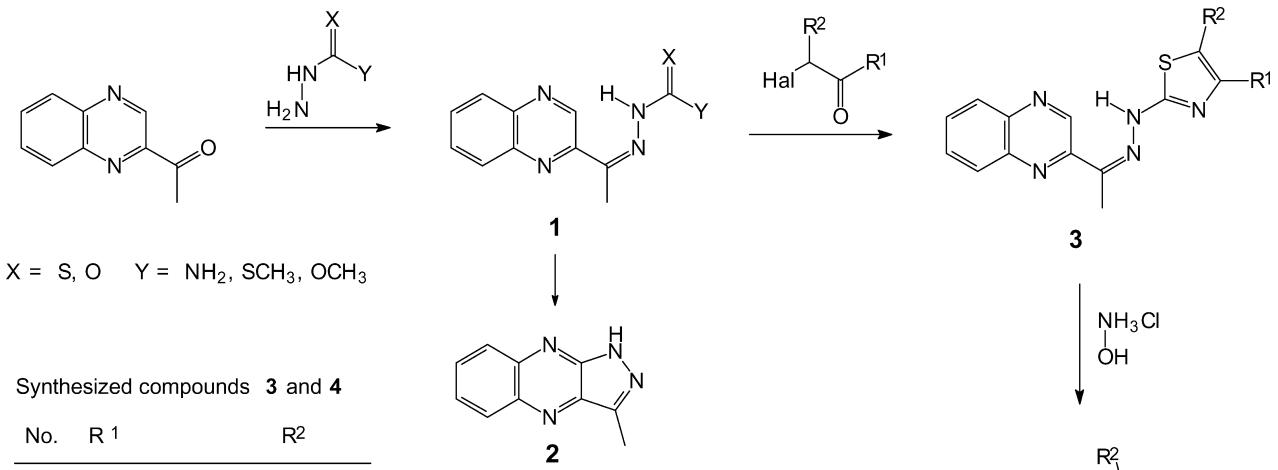
It is very well known that hydrazinothiazoles are very sensible to oxidation;[9] especially in acidic media, giving isomeric mixtures of the corresponding thiazoles, thiazolines and 2-amino-1,3,4-thiadiazines.[9] For these reasons and in order to synthesize the first representative of the 1-(thiazol-2-yl)-1*H*-pyrazolo[3,4-*b*]quinoxalines, unknown so far, two new and independent synthetic routes will be reported.

In the retrosynthesis, given in Scheme 2, the reaction paths ***b*** and ***c***, known so far, are depicted: The hydrazone **D** is obtained from the quinoxaline derivative and a thiazole carrying the N–N sequence; the formation of the C–N bond is crucial similarly to the N(2)–C(3) bond in the flavazole analogue.

In reaction path ***d*** (also given in Scheme 2), the much more stable thiosemicarbazides were employed for the construction of the N–N sequence; the syntheses of the less stable diazonium salts and the hydrazinothiazoles, respectively, are unnecessary. In addition, the use of a protective group (benzaldehyde, which has to be removed later),[9b] strongly recommended for the preparation of the hydrazinothiazoles, could be simplified and modified: the reaction partner itself adopts the function of the protecting group and its removal is not necessary.

As the first step of our synthetic path ***d*** (cf. Scheme 2) the thiosemicarbazone **1a** of 2-acetylquinoxaline was synthesized in nearly quantitative yield through reaction of 2-acetylquinoxaline with thiosemicarbazide; the product was clean enough to be further used without additional purification.

It should be mentioned that **1a** was not giving a consistent melting point due to its thermal decomposition near the melting point to the thermally more stable and higher melting 3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline **2**.[6d,10] The thermal decomposition could be followed readily



Synthesized compounds **3** and **4**

No.	R^1	R^2
3a	$COOC_2H_5$	H
4a	$COOC_2H_5$	H
4b	COOH	H
4c	CH_3	H
4d	$CH_2COOC_2H_5$	H
4e	CH_3	$COOC_2H_5$
4f	$COOC_2H_5$	$COOC_2H_5$
4g	C_6H_5	H
4h	4-Cl-C_6H_4	H
4i	4-Br-C_6H_4	H

Synthesized compounds **1** and **5**

No.	X	Y
1a	S	NH_2
1b	S	SCH_3
1c	O	NH_2
1d	O	OCH_3
5a	S	NH_2
5b	S	SCH_3

Scheme 3.

with the microscope: Beginning at 195°C the crystals of **1a** decompose mainly by sublimation (dependent on the purity of **1a** and the heating velocity also more or less liquid portions of **1a** occur) to **2** which finally melts sharply at 224–226°C (**2** can be also synthesized in a larger scale—cf. Section 3).

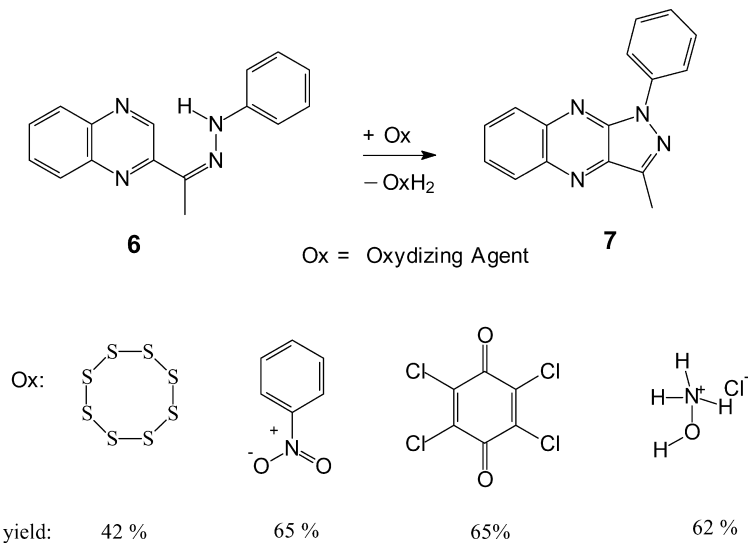
Then, treatment of the 2-acetylquinoxaline thiosemicarbazone **1a** with α-halogeno ketones gave the thiazoles **3** along the HANTZSCH thiazole synthesis. However, in the reaction mixture not only **3** was obtained, but along a redox process (caused by the formation of the corresponding hydrogen halogenides) from the hydrazones **3** also the 1*H*-pyrazolo[3,4-*b*]quinoxalines **4** could be obtained (cf. Scheme 3).

Ethyl 3-bromopyruvate, as expected, proved to be highly reactive to the nucleophilic thioamide **1a**; the reaction was strongly exothermic. Dependent on the solvent used, two different reaction products were obtained: In 2-methoxyethanol the final product was **4a**, but in ethanol only the hydrazone **3a** was isolated, since due to its low solubility it crystallized already from boiling ethanol. The solubility of **3a** in 2-methoxyethanol, however, at 100°C is still good enough to allow it to react further to **4a**. The isolation of **3a** along the course of the present reaction is of two-fold interest: First, it proves that this reaction proceeds via **3a**, and second, it offers the opportunity to study the synthesis of **4a** separately from **3a** and, hereby, to find out optimal reaction conditions.

The ring closure of the hydrazones **3** occurs in competition with the FISCHER indole synthesis.[11] The formation of the 1*H*-pyrazolo[3,4-*b*]quinoxalines **4** is preferred due to the presence of the quinoxaline moiety in the molecule which can be easily protonated; hereby, an electrophilic center in position 3 is generated reacting readily under ring closure with the spatially adjacent nucleophilic sp^3-hybridized nitrogen atom. In case of the phenyl hydrazone **6**, where the heterocyclic thiazole ring has been replaced by phenyl, no indole derivatives could be obtained in the present reaction. The pyrazole ring closure does not seem to be limited to quinoxalines; Rykowski et al.[12] published the synthesis of pyrazolo[4,3-*c*][1,2,4]-triazines via the acid promoted ring closure of the phenylhydrazones of 5-acyl-1,2,4-triazines.

The present dehydrogenative cyclization proceeds already under inert atmosphere when boiling the acidic solution; yields around 50% were obtained. If oxidizing agents (including air oxygen) are added, the yields improve essentially, corroborating that addition of oxidizing agents proves profitable and that both starting materials and reaction products could be self-oxidizing.

In part X of this series,[6d] we reported a convenient synthesis of 1*H*-pyrazolo[3,4-*b*]-quinoxalines and interpreted the formation of these compounds from the corresponding oximes as a redox process in which hydroxylamine, generated in situ, was reduced to water and ammonia by absorbing both two electrons and two protons. Now, we learned that hydroxylamine hydrochloride, as an oxidizing agent in acidic media, can be also employed to proceed with the ring closure of the corresponding hydrazones **3**



Scheme 4.

(cf. Scheme 3). This is extremely useful in cases where a necessary elongated boiling in acidic media decomposes the molecules aimed at; with this procedure, **4a** was formed easily from the corresponding hydrazone **3a** in 62% yield. Through the same pathway, the corresponding carboxylic acid **4b** can be synthesized from bromopyruvic acid; instead of the acid we used the ester **4a**, hydrolyzed it with KOH and, by acidifying the solution, prepared the free carboxylic acid **4b**.

As further oxidizing agents, to be employed in the dehydrogenative cyclization reaction, azobenzene, phenylhydrazine and hydrazine itself have been found useful.[6] Along our study, in addition, sulfur, nitrobenzene, *p*-chloroanil and hydroxylammoniumchloride, respectively, were tested as oxidizing agents for the cyclization of the phenylhydrazone of 2-acetylquinoxaline **6** to 3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoxaline **7** (cf. Scheme 4); the yields obtained—except for sulfur—were very close to each other.

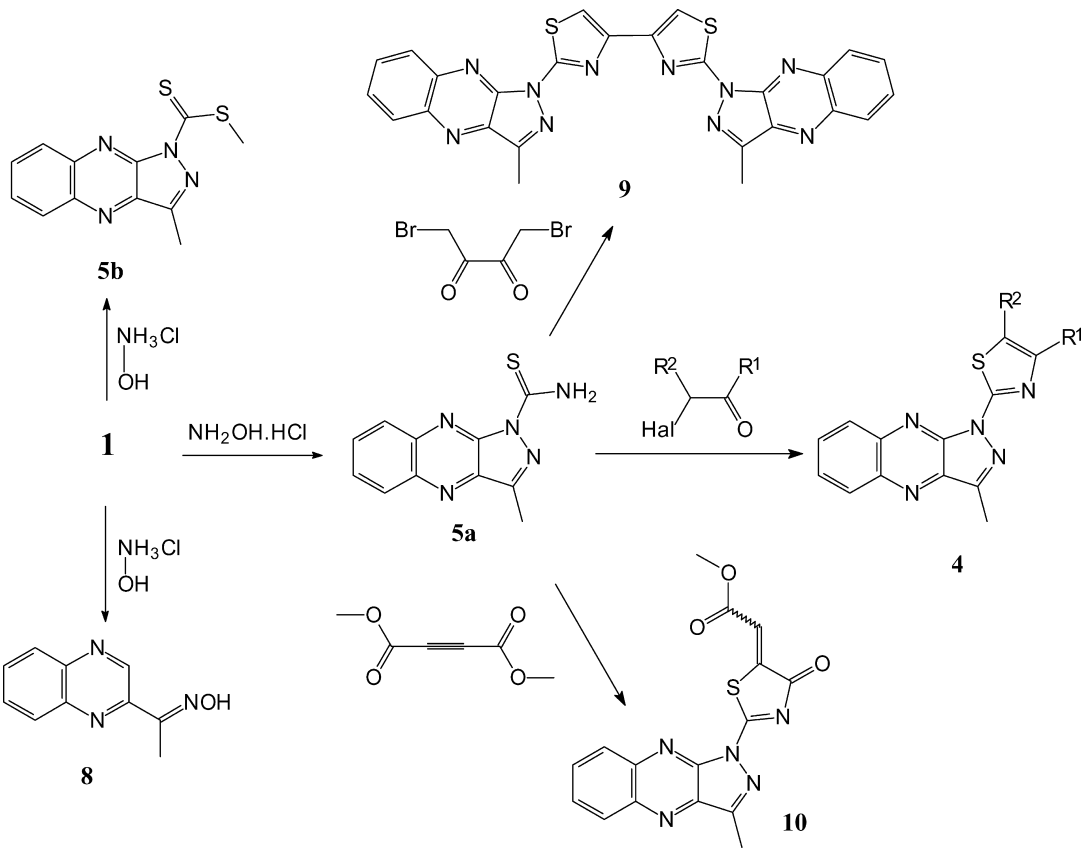
Hydroxylammoniumchloride, however, proved to be the most useful reaction agent: The structure is optimal (with the hydrogen atoms at periphery of the molecule and the electronegative atoms in the centre) in both electronic and steric respect, its solubility in water is unlimited, the reaction proceeds sufficiently fast in boiling ethanol and the products formed beside the product of ring closure, water and ammonia, can be separated easily.

Employing a concentrated aqueous solution of hydroxylammoniumchloride, the 1*H*-pyrazolo[3,4-*b*]quinoxalines **4a**–**i** were synthesized from the hydrazone **1a** with chloroacetone, ethyl-2-chloro-acetoacetate, ethyl-4-chloro-acetoacetate, chloro-oxaloacetate, phenacyl bromide, 4-chlorophenacyl bromide and 4-bromophenacyl bromide, respectively, in a one-pot reaction without isolating the intermediate products **3**.

Finally, along the dehydrogenative cyclization reaction with hydroxylamine hydrochloride as oxidizing agent, we found a second path to the 1-(thiazol-2-yl)-1*H*-pyrazolo[3,4-*b*]-quinoxalines **4**, e.g. 1*H*-pyrazolo[3,4-*b*]-quinoxaline-1-thiocarboxamide **5a** could be obtained from the thiosemicarbazone **1a**. In **5a**, a thioamide group is attached directly to a ring nitrogen atom (a substituted thiourea or thiosemicarbazide); thus, starting from **5a** the same compounds **4** (e.g. **4a** and **4g**) could be prepared by reaction with halogeno ketones and dimethyl acetylene-dicarboxylate (DMAD), respectively (cf. Schemes 2 and 5, path **e**).

Not unexpected, the reaction of **5a** with 1,4-dibromo-butan-2,3-dione, in a molar ratio of 2:1, yielded **9** as the reaction product because of the two halogeno ketone moieties in the reagent. This compound was obtained from the solution of the starting materials at 100°C as yellow crystals; it is thermally very stable (not yet melting at 360°C), insoluble in organic solvents, only a solid-state ^{13}C NMR spectrum could be obtained, however, both the IR and the mass spectrum together with the elemental analysis proved the structure unequivocally.

The reaction of **5a** with DMAD, in a molar ratio of 1:1, yielded a colourless product **10**, melting at 298–300°C; it could be concluded from the molecular ion in the mass spectrum that the molar mass of the product is m(DMAD)+m(**5a**)−m(CH_3OH). It should be mentioned that, principally a 5-membered 1,3-thiazolin-4-one ring and/or a six-membered 1,3-thiazin-4-one ring could be expected. It is generally accepted that, as the first step of the reaction, the tautomeric SH function of the thioamide group is added to the triple bond of DMAD (caused by bonding of sulfur to one of the former acetylenic carbon atoms of DMAD). As the second step, the thioamide nitrogen in a nucleophilic attack at one of the two ester carbonyl carbons forms the heterocyclic ring system; in analogous reactions only the formation of the 5-membered thiazolinone ring was observed.[13] For this reason, the 6-membered ring was excluded and the structure given in Scheme 5 assigned to product **10** (based on MS, IR and CP-MAS ^{13}C NMR data). The *E*/*Z* isomerism at the *exo*-cyclic C=C double bond could not be determined from the NMR due to insolubility in organic solvents.



Scheme 5.

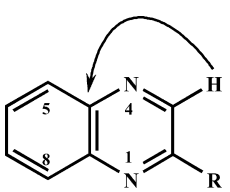
Finally (cf. Scheme 5) the reactivity of heteroanalogous compounds was studied: The reaction of 2-acetyl-quinoxaline with methyl dithiocarbazate yielded the dithiocarbazate **1b**, with semicarbazide the semicarbazone **1c**, with methyl carbazate the carbazate **1d**.

From the dithiocarbazate **1b**, the dithioester **5b** could be prepared by dehydrogenative cyclization employing hydroxylamine hydrochloride as the oxidizing agent (cf. Scheme 5); the yield of the crude product (mp 197–199°C) was 80%, and of the clean product (mp 199–200°C) 74%. Instead, the expected carboxylic acid derivatives were not obtained from the oxygen analogues **1c**,**d** but the oxime of 2-acetylquinoxaline **8** was isolated and the structure assigned unequivocally by mass spectrometry, IR and NMR spectroscopy.[6d] However, this result is completely in line with the behaviour of acylhydrazones, which, opposite to alkyl- and aryl-hydrazones, could not be cyclized in acidic media when employing the oximes as starting material.[6d]

2.2. Structure elucidation of the compounds

All synthesized compounds were investigated by 1D and 2D NMR spectroscopic methods to elucidate their structures unambiguously (**4b** and **10**, caused by their insolubility in common organic solvents, could be characterized solely by 1D solid state ^{13}C CP-MAS NMR spectra). Crucial for the assignment of both the ^{1}H and ^{13}C NMR spectra proves the benzylidene ring moiety: Within this ring the assignment of the chemical shifts is readily available employing H,H-COSY, HMQC and HMBC NMR experiments. The definition of the attachment with the heterocyclic quinoxaline ring system is the problem. In compounds **1**, **3**, and **6** a long-range C–H correlation ($^{3}J_{C,H}$) between the hydrogen nucleus at position 3 and the 4a-carbon atom was observed and can be used for an unambiguous assignment of the chemical shifts in the benzylidene ring moiety (cf. Scheme 6); the ^{13}C chemical shift of carbon 4a can be employed as starting point for the assignment of the other ^{1}H and ^{13}C chemical shifts using (i) the long-range C,H connectivities (HMBC) to find the ^{1}H chemical shifts of H-6 and H-8, (ii) the $^{3}J_{H,H}$ connectivities (H,H-COSY) to determine the ^{1}H chemical shifts of positions 5 and 7, (iii) the $^{1}J_{C,H}$ connectivities (HMQC) to determine the ^{13}C chemical shifts of the carbons attached directly to the protons, and (iv) the long-range connectivities (HMBC) of H-5 and 7-H to C-8a.

Unfortunately, in compounds **4** and **5** the corresponding position is no longer hydrogen substituted since it is involved in a further ring closure to yield the pyrazolo-[3,4-*b*]quinoxalines. An assignment of the chemical shifts of the benzylidene moiety in these compounds was therefore done only by analogy to the known behaviour of these substances, which is the topic of other investigations.[14]



Scheme 6.

2.3. Conclusions

The synthesis of a new and biologically very interesting class of compounds, the 1-(thiazol-2-yl)-1*H*-pyrazolo[3,4-*b*]-quinoxalines **4**, was reported. Starting from 2-acetyl-quinoxaline, in three steps, (i) formation of the hydrazone, (ii) closure of the thiazole ring, and (iii) final closure of the pyrazol ring [steps (ii) and (iii) could be exchanged] this new class of compounds could be readily obtained in good yields. For the ring closure of step (iii) the dehydrogenative cyclization with hydroxylamine hydrochloride proved very useful.

3. Experimental

All melting points were determined on a Boetius micro hotstage microscope (Fa. Analytik Dresden). The IR spectra (potassium bromide) were recorded with a Perkin Elmer FTIR 1600 spectrometer (cm^{-1}). The mass spectra were obtained on a Finnigan-MAT SSQ 710 (70 eV). Elemental analyses were performed on the autanalyser CHNS-932 (Fa. Leco Instruments GmbH); satisfactory microanalyses were obtained for all substances (C, H, N, S ±0,4%). For the NMR spectra the samples were dissolved in $CDCl_3$ or DMSO-d_6 and the spectra acquired with Bruker NMR spectrometers (ARX 300, Avance 300 and 500); the chemical shifts are given in the δ scale (ppm) downfield from tetramethylsilane (TMS) as internal standard. Solid state CP-MAS ^{13}C NMR spectra were recorded on a BRUKER DMX 400. All 1D and 2D NMR spectra were acquired using the standard BRUKER software.

3.1. General procedure for the synthesis of 1a–d

A solution of 2-acetylquinoxaline (3.44 g, 20 mmol) in ethanol (50–500 ml) and a solution of the hydrazino compound (22 mmol) in ethanol or water were mixed and heated under reflux for 5–60 min. When a solid product was not obtained after 10–15 min, the mixture was acidified weakly with acetic acid or hydrochloric acid and further heated under reflux. The reaction mixture was allowed to cool to room temperature and overnight in the refrigerator. The crystals were filtered under suction and washed with a small volume of ethanol. Normally, the products were sufficiently pure for the subsequent syntheses; if not, they were purified by recrystallisation from the given solvents.

3.1.1. 2-Acetylquinoxaline thiosemicarbazone (1a). The compound was prepared from thio-semicarbazide (2.00 g), dissolved in water (25 ml), at 75°C. The yield of **1a** was 4.71 g (96%). Recrystallized from 2-ethoxy-ethanol, dioxane or pyridine, pale yellow needles, which convert into prisms at ca. 196–199°C, were obtained; mp 224–226°C. MS: *m/z* (%) 246 (29) $(M+1)^+$, 245 (100) M^+, 244 (34) $(M-1)^+$, 232 (12), 203 (25), 200 (14), 185 (33) $(M-CSNH_2)^+$ 184 (16), 171 (15), 158 (14), 157 (94) $(185-N_2)^+$, 156 (29), 155 (20), 130 (26), 129 (86) (quinoxalin-2-yl)$^+$, 118 (19), 116 (72), 103 (21), 102 (63), 77 (18), 76 (26), 75 (23), 60 (28), 51 (18), 50 (15), 43 (14). IR: 3394, 3265, 3144, 3054, 1619, 1546, 1491, 1456, 1417, 1370, 1323, 1275, 1209, 1127, 1093, 1051, 977, 952, 907, 888, 835, 760, 711, 682, 634, 580, 483, 407. ^1H NMR (DMSO-d_6): δ 10.59 (s, 1H, NH), 9.95 (s, 1H, 3-H), 8.58 (s, 1H, NH_2), 8.46 (s, 1H, NH_2), 8.10–8.05 (m, 2H, H-5, H-8), 7.86–7.80 (m, 2H, H-6, H-7), 2.49 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 179.3 (C═S), 149.5 (C-2), 146.5 (*C*═N), 144.5 (C-3), 141.3 (C-4a), 140.5 (C-8a), 130.3, 130.1 (C-6, C-7), 129.1, 128.8 (C-5, C-8), 11.6 (CH_3). Analysis: calculated for $C_{11}H_{11}N_5S$: C, 53.36; H, 4.52; N, 28.55; S, 13.07; found: C, 53.74; H, 4.57; N, 28.37; S, 12.92.

3.1.2. Methyl 3-[1-(quinoxalin-2-yl)ethyliden]dithiocarbazate (1b). The compound was obtained from methyl dithiocarbazate[15] (2.70 g) as pale yellow, nearly colorless needles. The yield of **1b** was 4.31 g (78%); mp 206–208°C (recrystallised from 1,2-dichloroethane). MS: *m/z* (%) 228 (61) $(M(CH_3SH)^+$, 200 (26) $(M(CS_2)^+$, 199 (24), 167 (18), 156 (20), 149 (30), 130 (18), 129 (92), 102 (57), 97 (24), 85 (34), 83 (39), 71 (27), 69 (25). IR: 3203, 2916, 1598, 1547, 1486, 1463, 1419, 1368, 1335, 1269, 1232, 1146, 1111, 1064, 978, 958, 928, 882, 760, 744, 678, 635, 561, 541, 484, 463, 413. ^1H NMR ($CDCl_3$): δ 10.15 (s, 1H, NH), 9.71 (s, 1H, H-3), 8.14–8.08 (m, 2H, H-5, H-8), 7.81–7.76 (m, 2H, H-6, H-7), 2.71 (s, 3H, S–CH_3), 2.56 (s, 3H, C–*C*H_3). ^{13}C NMR (DMSO-d_6): δ 201.6 (C═S), 149.7, 149.1 (C-2, *C*═N), 143.2 (C-3), 141.4, 140.6 (C-4a, C-8a), 130.6 (2C, C-6, C-7), 129.2, 128.8 (C-5, C-8), 17.2 (S–CH_3), 12.3 (C–*C*H_3). Analysis: calculated for $C_{12}H_{12}N_4S_2$: C, 52.15; H, 4.38; N, 20.27; S, 23.20; found: C, 52.36; H, 4.45; N, 20.29; S, 22.90.

3.1.3. 2-Acetylquinoxaline semicarbazone (1c). The compound was prepared from semicarbazide hydrochloride (2.45 g, 22 mmol) and sodium acetate trihydrate (3.40 g, 25 mmol) both dissolved in water (20 ml). The crude yield was 4.00 g (87%), recrystallization from DMF/Pyridin (10:1) gave 3.30 g (72%) of **1c**; mp 278–282°C. MS: *m/z* (%) 229 (21) M^+, 186 (19), 185 (80) $(M-CONH_2)^+$, 171 (8) $(M-NHCONH_2)^+$, 158 (12), 157 (100) $(185(N_2)^+$, 156 (13), 155 (11), 130 (10), 129 (42) (quinoxalin-2-yl)$^+$, 118 (10), 102 (22) $(129-HCN)^+$, 76 (12), 75 (11). IR: 3478, 3196, 1707, 1585, 1550, 1484, 1431, 1405, 1375, 1346, 1320, 1239, 1207, 1144, 1097, 983, 958, 929, 887, 763, 731, 626, 472, 413: ^1H NMR (DMSO-d_6): δ 9.89 (s, 1H, H-3), 9.86 (s, 1H, NH), 8.11–8.06 (m, 2H, H-5, H-8), 7.88–7.80 (m, 2H, H-6, H-7), 6.88 (s, br, 2H, NH_2), 2.39 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 156.8 (C═O), 150.0 (*C*═N), 144.4 (C-3), 143.7 (C-2), 141.1 (C-4a), 140.7 (C-8a), 130.4 (C-7), 130.0 (C-6), 129.1, 128.9 (C-5 and C-8), 11.1 (CH_3). Analysis: calculated for $C_{11}H_{11}N_5O$: C, 57.64; H, 4.84; N, 30.55; found: C, 57.71; H, 5.08; N, 30.20.

3.1.4. Methyl 3-[1-(quinoxalin-2-yl)ethyliden]carbazate (1d). The compound was obtained from methyl carbazate (2.00 g) dissolved in EtOH (10 ml) as colorless needles; yield 3.76 g (77%); mp 244–246°C (from toluene). MS: *m/z* (%) 245 (16), 244 (36) M^+, 185 (40) $(M-COOCH_3)^+$, 158 (13), 157 (100) $(185(N_2)^+$, 156 (16), 155 (11), 130 (11), 129 (57) (quinoxalin-2-yl)$^+$, 102 (28), 77 (11), 76 (15). IR: 2959, 1703, 1610, 1553, 1493, 1450, 1378, 1350, 1313, 1277, 1239, 1190, 1151, 1130, 1092, 1062, 962, 937, 879, 764, 687, 611, 490, 415. ^1H NMR (DMSO-d_6): δ 10.73 (s, 1H, NH), 9.51 (s, 1H, H-3), 8.13–8.08 (m, 2H, H-5, H-8), 7.89–7.85 (m, 2H, H-6, H-7), 3.80 (s, 3H, OCH_3), 2.42 (s, 3H, C–CH_3). ^{13}C NMR (DMSO-d_6): δ 154.5 (C═O),

149.9, 148.0 (C-2, *C*═N), 143.4 (C-3), 141.2, 140.6 (C-4a and C-8a), 130.7, 130.4 (C-7 and C-6), 129.2, 128.9 (C-5 and C-8), 52.5 (O–CH_3), 11.6 (C–*C*H_3). Analysis: calculated for $C_{12}H_{12}N_4O_2$: C, 59.01; H, 4.95; N, 22.94; found: C, 59.31; H, 5.27; N, 22.73.

3.1.5. 3-Methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (2). A suspension of **1a** (2.45 g, 10 mmol) in light petroleum (12 ml) was stirred vigorously and gently heated to 220°C; at ca. 190°C the ring closure reaction started, indicated readily by foaming of the suspension. The suspension was cooled down to ca. 110°C and the crude product boiled two times with 80 ml of toluene. The extracts, still boiling, were filtered, the filtrates combined, cooled to room temperature and, overnight, in the refrigerator. Compound **2** crystallized from the solution as golden-bright plates; the crystals were separated, washed with hexane and dried. The yield of the pure **2**; mp 222–224°C (from dioxane), was 0.98 g (53%). MS: *m/z* (%) 185 (28) $(M+1)^+$, 184 (100) M^+, 183 (42) $(M-1)^+$, 144 (12), 143 (80) $(M-CH_3CN)^+$, 116 (41) $(143-HCN)^+$, 102 (12), 90 (13), 89 (10). IR: ^1H and ^{13}C NMR data, cf. Ref. 6d. Analysis: calculated for $C_{10}H_8N_4$: C, 65.21; H, 4.38; N, 30.42; found: C, 65.46; H, 4.68; N, 30.70.

3.1.6. Ethyl 2-[1-(quinoxalin-2-yl)ethylidenhydrazino]-thiazol-4-carboxylate (3a). The solution of thiosemicarbazide (4.55 g, 50 mmol) in water (50 ml) was added to the solution of 2-acetylquinoxaline (8.61 g, 50 mmol) in ethanol (600 ml) and the mixture stirred at 50°C. After addition of acetic acid (6 g, 100 mmol) the reaction mixture was heated under reflux for 30 min, then, ethyl 3-bromopyruvate (9.75 g, 50 mmol) was added into the hot reaction mixture with further stirring. After a few minutes yellow crystals precipitated from the dark solution. The reaction mixture was cooled in the refrigerator overnight; the precipitate was collected by suction filtration (10.0 g, 59%). Recrystallization from pyridine afforded **3a** as pale yellow needles; mp 267–268°C. MS: *m/z* (%) 341 (5) M^+, 238 (4), $(M-C_6H_4NCH)^+$, 212 (28) (M−quinoxalinyl)$^+$, 184 (10), 171 (7), 159 (11), 158 (100), 157 (44, 156 (27), 155 (10), 143 (8), 130 (14), 129 (24), 116 (11), 115, (39), 114 (18), 113 (15), 102 (43), 89 (19), 76 (17), 75 (10). IR: 3255, 3057, 2974, 1690, 1614, 1567, 1549, 1504, 1492, 1465, 1438, 1410, 1372, 1331, 1293, 1246, 1234, 1153, 1102, 1018, 957, 940, 930, 878, 855, 814, 770, 746, 624, 607, 569, 534, 481, 410. ^1H NMR (DMSO-d_6): δ 12.16 (s, 1H, NH), 9.52 (s, 1H, H-3), 8.10–7.80 (m, 4H, aromatic), 7.85 (s, 1H, H-5), 4.26 (q, J=7.1 Hz, 2H, CH_2), 2.48 (s, 3H, CH_3–C═), 1.30 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 168.9 (C-2′), 161.0 (C═O), 149.4, 146.0 (C-2, *C*═N), 143.1 (C-3), 143.0, (C-4′), 141.0 (C-8a), 140.7 (C-4a), 130.6 (C-7), 130.1 (C-6), 129.1 (C-5), 128.8 (C-8), 120.3 (C-5′), 60.5 (CH_2), 14.2 (CH_3), 11.7 (*C*H_3–C═). Analysis: calculated for $C_{16}H_{15}N_5O_2S$: C, 56.29; H, 4.43; N, 20.51; S, 9.39; found: C, 56.17; H, 4.42; N, 20.31; S, 9.19.

3.1.7. Ethyl 2-(3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-1-yl)thiazol-4-carboxylate (4a). (i) To the solution of **3a** (3.41 g, 10 mmol) in boiling 2-methoxy-ethanol (400 ml) at ca. 105°C the solution of hydroxylamine hydrochloride (1.39 g, 20 mmol) in 2N HCl (5 ml, 10 mmol) was poured under stirring. The reaction mixture was hold at this temperature for 30 min and then concentrated in vacuo. The solid residue was separated by suction, washed with water and recrystallized from toluene; yield 2.10 g (62%) yellow needles; mp 206–208°C. (ii) Ethyl 3-bromopyruvate (1.95 g, 10 mmol), under stirring, was poured into the solution of **1a** (2.45 g, 10 mmol) in 2-methoxy-ethanol (100 ml) at ca. 105°C. The mixture was hold at this temperature for 30 min, cooled to room temperature and kept overnight in the refrigerator. The crystals were separated by suction, washed with ethanol; 1.68 g (50%) yellow needles, after recrystallization from toluene 1.40 g (41%) of **4a** could be isolated. (iii) Compound **5a** (2.43 g, 10 mmol) was solved in boiling 2-methoxy-ethanol (150 ml), the solution filtered and ethyl 3-bromopyruvate (2.15 g, 11 mmol) added. The reaction mixture was heated for 30 min at 115°C; along this time the colour changes from black dark to light dark near the end of the reaction. After cooling to room temperature the reaction mixture was stored overnight in the refrigerator. The precipitate was separated by suction filtration, washed first with $NaHCO_3$ solution, later with water. After recrystallisation from toluene 1.56 g (46%) **4a** was obtained as yellow needles. MS: *m/z* (%) 340 (38) $(M+1)^+$, 339 (46) M^+, 294 (11) $(M-CH_3CH_2O)^+$, 267 (33) $(M^+-COOC_2H_3)^+$, 227 (33), 226 (12), 209 (11), 195 (10), 186 (66), 184 (12), 154 (17), 128 (10), 103 (17), 102 (100) $(C_6H_4CN)^+$, 101 (12), 90 (15), 76 (32), 75 (37), 71 (13), 67 (40), 58 (16), 57 (13), 51 (24), 50 (13), 45 (34). IR: 3112, 2980, 2930, 1711, 1539, 1474, 1440, 1379, 1331, 1237, 1204, 1129, 1095, 1027, 960, 872, 827, 768, 649, 603, 546, 457, 418. ^1H NMR ($CDCl_3$): δ 8.29–8.23 (m, 2H, H-5, H-8), 8.07 (s, 1H, thiazol), 7.91–7.79 (m, 2H, H-6, H-7), 4.48 (q, J=7.1 Hz, 2H, CH_2), 2.87 (s, 3H, 3-CH_3), 1.47 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 161.1 (C═O), 157.7 (C-2′), 148.2 (C-3), 144.3 (C-4), 141.5, 141.3, 141.2 (C-4a, C-8a, C-9a), 137.8 (C-3a), 131.7 (C-7), 130.1 (C-5), 129.1 (C-8), 128.9 (C-6), 122.9 (C-5′), 61.4 (CH_2), 14.2 (CH_3), 11.6 (3-CH_3). Analysis: calculated for $C_{16}H_{13}N_5O_2S$: C, 56.63; H, 3.86; N, 20.64; S, 9.45; found: C, 56.95; H, 3.90; N, 20.90; S, 9.29.

3.1.8. 2-(3-Methyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-1-yl)-thiazol-4-carboxylic acid (4b). The reaction mixture was prepared from the ester **4a** (1.70 g, 5 mmol) in boiling ethanol and ethanolic KOH (0.56 g, 10 mmol KOH in 30 ml EtOH). The potassium salt, thus obtained, was suction filtrated, washed with ethanol and solved in heated water. The hot solution was filtered and acidified with acetic acid. The carboxylic acid **4b** precipitated and was recrystallised from 2-methoxy-ethanol; 0.55 g (35%) of **4b** as a yellow powder; mp 256°C. Even if the compound was stored in the desiccator with calcium chloride for several days under vacuum, the carboxylic acid bound 2 mole water per mole acid. MS: *m/z* (%) 312 (16) $(M+1)^+$, 311 (100) M^+, 267 (24) $(M-CO_2)^+$, 227 (16), 226 (16) $(267-CH_3CN)^+$, 187 (10), 186 (80) $(227-CH_3CN)^+$, 170 (14), 142 (11), 102 (36). IR: 3439, 3075, 1705, 1597, 1582, 1539, 1500, 1477, 1446, 1383, 1352, 1314, 1282, 1241, 1200, 1118, 1069, 1003, 952, 910, 866, 828, 764, 729, 695, 647, 614, 602, 552, 458, 420. CP-MAS (solid state) ^{13}C NMR: δ 114, broad (aromatic carbons), 13.1 (CH_3). Analysis: calculated for $C_{14}H_9N_5O_2S.2H_2O$: C, 48.41; H, 3.77; N, 20.16; S, 10.30; found: C, 48.03; H, 3.26; N, 20.17.

3.2. General procedure for the synthesis of 4c–i

The solution of the α-halogeno ketone in a useful solvent (10–20 ml of 2-methoxyethanol, 2-ethoxyethanol or 1,4-dioxane, respectively) was poured into the solution of **1a** (10 mmol, 2.45 g) in 150 ml of hot 2-methoxyethanol. The reaction mixtures were stirred at 100–110°C, and, after 5 min, the solution of hydroxylammonium chloride (10 mmol, 0.70 g) in a few ml water slowly added dropwise. Then, the mixture was stirred for 2–4 h at 100–110°C, concentrated in vacuo, neutralized with $NaHCO_3$, and crystallised in the refrigerator. The precipitated yellow crystals were suction filtrated, washed first with water, later with ethanol and recrystallized from the given solvent.

3.2.1. 3-Methyl-1-(4-methyl-thiazol-2-yl)-1*H*-pyrazolo-[3,4-*b*]quinoxaline (4c). The compound was obtained from chloroacetone (12.5 mmol, 1 ml) and **1a** (10 mmol, 2.45 g) as yellow needles, 0.98 g (35%); mp 162–163°C (from EtOH). MS: *m/z* (%) 282 (17) $(M+1)^+$, 281 (100) M^+, 248 (8) $(M-HS)^+$, 240 (10) $(M-CH_3CN)^+$, 195 (15) $(M-CHS)^+$, 169 (8) $(195-HCN)^+$, 126 (12), 102 (8), 71 (10), 55 (7). IR: 3087, 2972, 2919, 1583, 1568, 1535, 1509, 1475, 1440, 1380, 1348, 1320, 1253, 1197, 1141, 1123, 1067, 1036, 1015, 970, 912, 871, 824, 760, 728, 655, 604, 556, 536, 464, 420. ^{1}H NMR ($CDCl_3$): δ 8.24–8.20 (m, 2H, H-5, H-8), 7.84–7.74 (m, 2H, H-6, H-7), 6.74 (s, 1H, H-5′), 2.87 (s, 3H, 3-CH_3), 2.54 (s, 3H, 4′-CH_3). ^{13}C NMR ($CDCl_3$): δ 156.8 (C-2′), 149.9 (C-4′), 147.4 (C-3), 141.3, 141.2, 141.1 (C-9a, C-8a, C-4a), 137.8 (C-3a), 131.4, 128.5 (C-6, C-7), 130.1, 129.0 (C-5, C-8), 109.0 (C-5′), 17.5 (4′-CH_3), 11.6 (3-CH_3). Analysis: calculated for $C_{14}H_{11}N_5S$: C, 59.75; H, 3.94; N, 24.89; S, 11.40; found: C, 59.90; H, 4.03; N, 25.07; S, 11.20.

3.2.2. Ethyl 2-(3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-1-yl)thiazol-4-ylacetate (4d). The compound was obtained from ethyl 4-chloroacetoacetate (10.5 mmol, 1.73 g) and **1a** (10 mmol, 2.45 g) as yellow needles, 1.34 g (38%) **4d**; mp 122°C (from cyclohexane). MS: *m/z* (%) 355 (20) $(M+2)^+$, 354 (95) $(M+1)^+$, 353 (100) M^+, 326 (6) $(M-HCN)^+$, 307 (7), 282 (16), 281 (70), 280 (94) $(M-COOEt)^+$, 279 (10), 248 (11), 239 (30) $(280-CH_3CN)^+$, 236 (13), 195 (12), 169 (32) $(95-HCN)^+$, 154 (10), 102 (24), 71 (28), 45 (44). IR: 3106, 2985, 1738, 1635, 1583, 1518, 1475, 1381, 1350, 1243, 1200, 1127, 1067, 1028, 980, 868, 824, 766, 729, 660, 604, 566, 536, 464, 420. ^{1}H NMR ($CDCl_3$): δ 8.15–8.10 (m, 2H, H-5, H-8), 7.79–7.65 (m, 2H, H-6, H-7), 7.07 (s, 1H, thiazol), 4.18 (q, *J*=7.1 Hz, 2H, CH_2), 3.91 (s, 2H, thiazol-4-CH_2), 2.80 (s, 3H, 3-CH_3), 1.26 (t, *J*=7.1 Hz, 3H, ester-CH_3): ^{13}C NMR ($CDCl_3$): δ 170.1 (C=O), 156.4 (C-2′), 147.4 (C-3), 145.6 (C-4′), 141.0, 140.9, 140.9 (C-4a, C-8a, C-9a), 137.4 (C-3a), 131.4 (C-7), 129.9 (C-5), 128.7 (C-8), 128.5 (C-6), 111.7 (C-5′), 60.8 (O–CH_2), 36.9 (4′-CH_2), 14.1 (CH_3), 11.5 (3-CH_3). Analysis: calculated for $C_{17}H_{15}N_5O_2S$: C, 57.78; H, 4.28; N, 19.82; S, 9.07; found: C, 57.72; H, 4.25; N, 20.10; S, 9.08.

3.2.3. Ethyl 2-(3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-1-yl)-4-methyl-thiazol-5-yl-carboxylate (4e). The compound was obtained from ethyl 2-chloroacetoacetate (10.5 mmol, 1.73 g) and **1a** (10 mmol, 2.45 g) as yellow needles, 1.47 g (42%); mp 236–238°C (from DMF). MS: *m/z* (%) 355 (20) $(M+2)^+$, 354 (73) $(M+1)^+$, 353 (100) M^+, 325 (11), 308 (42) $(M-C_2H_5O)^+$, 284 (11), 281 (40) $(308-HCN)^+/(M-CO_2C_2H_4)^+$, 280 (11), 240 (12), 239 (18), 236 (12), 195 (40), 186 (10), 169 (19), 154 (12), 102 (18), 71 (17), 70 (17). IR: 2976, 2929, 1700, 1583, 1564, 1534, 1502, 1475, 1444, 1368, 1348, 1321, 1271, 1204, 1173, 1134, 1114, 1092, 1024, 827, 777, 760, 728, 658, 601, 544, 462, 417. ^{1}H NMR ($CDCl_3$): δ 8.17–8.14 (m, 2H, H-5, H-8), 7.79–7.71 (m, 2H, H-6, H-7), 4.33 (q, *J*=7.0 Hz, 2H, CH_2), 2.80 (s, 3H, 3-CH_3), 2.75 (s, 3H, 4′-CH_3), 1.38 (t, *J*=7.0, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 162.2 (C=O), 158.2 (C-4′), 157.6 (C-2′), 148.8 (C-3), 141.4, 141.3, 141.0 (C-4a, C-8a, C-9a), 137.9 (C-3a), 131.7 (C-7), 130.2 (C-5), 129.0 (C-8), 128.9 (C-6), 117.5 (C-5′), 61.0 (CH_2), 17.6 (4′-CH_3), 14.3 (CH_3), 11.7 (3-CH_3). Analysis: calculated for $C_{17}H_{15}N_5O_2S$: C, 57.78; H, 4.28; N, 19.82 S, 9.27; found: C, 57.73; H, 4.20; N, 20.24; S, 8.84.

3.2.4. Diethyl 2-(3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-1-yl)thiazol-4,5-dicarboxylate (4f). The compound was obtained from diethyl 3-chlorooxaloacetate (10.5 mmol, 2.34 g) and **1a** (10 mmol, 2.45 g) as yellow needles, 1.16 g (29%); mp 181–183°C (from EtOH). MS: *m/z* (%) 412 (13) $(M+1)^+$, 411 (70) M^+, 366 (9) $(M-C_2H_5O)^+$, 338 (8) $(M-C_2H_5OCO)^+$, 294 (9), 268 (14), 267 (100) $(M-2C_2H_4-2CO_2)^+$, 227 (9), 186 (22), 170 (8), 110 (9), 102 (14). IR: 3370, 2983, 2938, 1744, 1719, 1588, 1567, 1506, 1474, 1446, 1390, 1370, 1348, 1329, 1285, 1209, 1140, 1131, 1112, 1094, 1020, 858, 827, 798, 770, 746, 728, 684, 668, 654, 602, 586, 554, 468, 418. ^{1}H NMR ($CDCl_3$): δ 8.28–8.25 (m, 2H, H-5, H-8), 7.92–7.82 (m, 2H, H-6, H-7), 4.43 and 4.50 (2q, *J*=7.2 Hz, 4H, $2CH_2$), 2.87 (s, 3H, 3′-CH_3), 1.44 and 1.47 (2t, *J*=7.1 Hz, 6H, $2CH_3$). ^{13}C NMR ($CDCl_3$): δ 162.8, 160.2 (C=O), 158.6 (C-4′), 149.6 (C-3), 148.0 (C-2′), 141.5, 141.5, 141.0 (C-9a, C-4a, C-8a), 138.1 (C-3a), 132.1, 128.9 (C-6, C-7), 130.3, 129.3 (C-5, C-8), 123.4 (C-5′), 62.3, 62.1, (2-CH_2), 14.1, 14.0 (CH_3), 11.7 (3-CH_3). Analysis: calculated for $C_{19}H_{17}N_5O_4S$: C, 55.47; H, 4.16; N, 17.02; S, 7.79; found: C, 55.54; H, 4.07; N, 17.32; S, 7.94.

3.2.5. 1-(4-Phenyl-thiazol-2-yl)-3-methyl-1*H*-pyrazolo-[3,4-*b*]quinoxaline (4g). (i) The compound was obtained from phenacyl bromide (10.5 mmol, 2.09 g) and **1a** (10 mmol, 2.45 g) as yellow needles, 2.03 g (59%); mp 183–185°C (from 2-methoxy-ethanol). MS: *m/z* (%) 344 (18) $(M+1)^+$, 343 (100) M^+, 301 (20) $(M-CH_2CN)^+$, 195 (9), 134 (15). IR: 3060, 2360, 2343, 1580, 1539, 1497, 1477, 1443, 1395, 1379, 1352, 1310, 1278, 1236, 1196, 1119, 1064, 1028, 1001, 964, 916, 868, 841, 819, 759, 711, 660, 616, 599, 560, 477, 457, 419. ^{1}H NMR ($CDCl_3$): δ 8.18–8.15 (m, 2H, H-5, H-8), 7.98 (d, *J*=7.2, 2H, *o*-Ph), 7.80–7.65 (m, 2H, H-6, H-7), 7.44–7.29 (m, 3H, *m*-Ph, *p*-Ph), 7.25 (s, 1H, H-5′), 2.84 (s, 3H, 3-CH_3). ^{13}C NMR ($CDCl_3$): δ 157.1 (C-2′), 152.2 (C-4′), 147.5 (C-3), 141.4, 141.3, 141.1 (C-4a, C-8a, C-9a), 137.6 (C-3a), 133.9 (*i*-Ph), 131.3 (C-7), 130.1 (C-5), 129.0 (C-8), 128.5 (C-6), 128.4 (*m*-Ph), 128.0 (*p*-Ph), 126.3 (*o*-Ph), 108.2 (C-5′), 11.7 (CH_3). Analysis: calculated for $C_{19}H_{13}N_5S$: C, 66.45; H, 3.81; N, 20.39; S, 9.33; found: C, 66.53; H, 3.81; N, 20.39; S, 9.06. (ii) The reaction mixture of 3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline-1-thiocarboxamide (**5a**) (10 mmol, 2.43 g), phenacylbromide (12.2 mmol, 2.43 g) and 2-methoxy-ethanol

(75 ml) was heated to 100°C for 2 h, concentrated in vacuo and neutralized with $NaHCO_3$. The precipitated product was suction filtered, recrystallized from butanol and dried in the air on filter paper; 1.89 g (55%) **4 g** as yellow needles were obtained; mp 183–185°C.

3.2.6. 1-[4-(4-Chlorophenyl)thiazol-2-yl]-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (4h). The compound was obtained from 4-chlorophenacyl bromide (10.5 mmol, 2.45 g) and **1a** (10 mmol, 2.45 g) as yellow needles, 2.36 g (63%); mp 212.5–213°C (from 2-methoxy-ethanol). MS: *m/z* (%) 380 (10) $(M+3)^+$, 379 (42) $(M+2)^+$, 378 (26) $(M+1)^+$, 377 (100) M^+, 335 (8), 195 (11), 168 (7). IR: 3033, 1638, 1586, 1570, 1530, 1501, 1474, 1443, 1402, 1377, 1355, 1320, 1290, 1258, 1198, 1142, 1132, 1121, 1100, 1090, 1056, 1014, 968, 928, 901, 870, 835, 820, 769, 737, 731, 702, 666, 612, 604, 566, 540, 488, 472, 441, 419. ^{1}H NMR ($CDCl_3$): δ 8.33–8.29 (m, 2H, H-5, H-8), 7.97 (d, 2H, J=8.7 Hz, H-2″), 7.96–7.82 (m, 2H, H-6, H-7), 7.41 (d, 2H, J=8.7 Hz, H-3″), 7.34 (s, 1H, H-5′), 2.92 (s, 3H, 3-CH_3). ^{13}C NMR ($CDCl_3$): δ 157.7 (C-2′), 151.4 (C-4′), 148.0 (C-3), 141.9, 141.7, 141.5 (C-4a, C-8a, C-9a), 138.0 (C-3a), 134.0 (C-4″), 132.6 (C-1″), 131.7 (C-7), 130.4 (C-5), 129.3 (C-8), 128.9 (C-6), 128.8 (C-3″), 127.7 (C-2″), 108.7 (C-5′), 11.8 (CH_3). Analysis: calculated for $C_{19}H_{12}ClN_5S$: C, 60.39; H, 3.20; N, 18.53; S, 8.48; found: C, 60.70; H, 3.18; N, 18.45; S, 8.36.

3.2.7. 1-[4-(4-Bromophenyl)thiazol-2-yl]-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (4i). The compound was obtained from 4-bromophenacyl bromide (10.5 mmol, 2.92 g) and **1a** (10 mmol, 2.45 g) as yellow needles, 2.41 g (57%); mp 232–233°C (from pyridine). MS: *m/z* (%) 424 (15), 423 (100) $(M+2)^+$, 421 (85) M^+, 381 (13), 379 (13), 214 (10), 212 (12), 195 (15), 151 (11), 133 (12), 102 (12), 89 (13). IR: 3098, 1734, 1586, 1570, 1530, 1501, 1472, 1443, 1397, 1376, 1356, 1320, 1290, 1260, 1198, 1142, 1132, 1122, 1070, 1056, 1010, 928, 901, 870, 832, 824, 771, 738, 730, 703, 668, 650, 614, 604, 566, 540, 502, 458, 441, 419. ^{1}H NMR ($CDCl_3$): δ 8.32–8.29 (m, 2H, H-5, H-8), 7.92 –7.79 (m, 4H, H-6, H-7, H-2″), 7.57 (d, J=8.7 Hz, 2H, H-3″), 7.35 (s, 1H, H-5′), 2.91 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 157.7 (C-2′), 151.4 (C-4′), 148.0 (C-3), 141.8, 141.7, 141.5 (C-4a, C-8a, C-9a), 138.0 (C-3a), 133.0 (C-1″), 131.7 (C-7 and C-3″), 130.4 (C-5), 129.3 (C-8), 128.9 (C-6), 128.0 (C-2″), 122.2 (C-4″), 108.8 (C-5′), 11.8 (CH_3). Analysis: calculated for $C_{19}H_{12}BrN_5S$: C, 54.04; H, 2.86; N, 16.58; S, 7.59; found: C, 54.43; H, 2.84; N, 16.88; S, 7.48.

3.2.8. 3-Methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline-1-thiocarboxamide (5a). Compound **1a** (6.13 g, 25 mmol) was dissolved in boiling 2-methoxy-ethanol (250 ml); at 100–110°C a solution of hydroxylamine hydrochloride (5.21 g, 75 mmol) in some water (10 ml) was added in portions within 10 min, with vigorous stirring of the reaction mixture. After further stirring for ca. 20 min at 110°C, **5a** precipitated as yellow needles from the dark solution. After cooling and storing in the refrigerator overnight, the crystals were suction filtrated and washed with ethanol. After further concentrating the reaction mixture, another fraction of **5a** could be isolated, washed with ethanol and water and recrystallized from 2-methoxyethanol or pyridine; the yield of **5a** is 3.98 g (66%); mp 222–223°C (from pyridine). MS: *m/z* (%) 243 (10) M^+, 185 (41), 184 (100) $(M-HNCS)^+$, 183 (52), 157 (13), 155 (15), 143 (83) $(184-CH_3CN)^+$, 130 (10), 116 (56) $(143-HCN)^+$, 102 (20), 90 (18), 89 (14), 76 (13). IR: 3357, 3221, 3168, 1598, 1526, 1500, 1477, 1444, 1347, 1307, 1239, 1162, 1103, 1010, 969, 903, 853, 820, 762, 734, 681, 628, 604, 548, 416. ^{1}H NMR ($CDCl_3$): δ 10.05, 9.88 (2 s, 2H, NH_2), 8.34– 8.25 (m, 2H, H-5, H-8), 8.04–7.94 (m, 2H, H-6, H-7), 2.73 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 177.5 (C=S), 147.7 (C-3), 142.5 (C-9a), 140.4, 139.6 (C-4a, C-8a), 139.1 (C-3a), 132.2 (C-7), 129.9 (C-5), 129.5 (C-6), 128.5 (C-8), 11.5 (CH_3). Analysis: calculated for $C_{11}H_9N_5S$: C, 54.31; H, 3.73; N, 28.79; S, 13.18; found: C, 54.10; H, 3.68; N, 29.11; S, 12.82.

3.2.9. Methyl 3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxaline-1-dithiocarboxylate (5b). Compound **1b** (2.74 g, 10 mmol) was dissolved in boiling 2-methoxy-ethanol (100 ml, 120°C); later, at 100–110°C, a solution of hydroxylamine hydrochloride (1.40 g, 20 mmol) in 2N hydrochloric acid (5 ml, 10 mmol) was added in portions within 10 min, with vigorous stirring of the reaction mixture. After further stirring for ca. 30 min at 95–100°C, **5b** precipitated as yellow needles. After cooling and storing in the refrigerator overnight, the crystals were suction filtrated and washed twice with ethanol. The raw material (yield 2.20 g, 80%) was recrystallized from 2-methoxyethanol; finally 2.04 g (74%) of **5b** was obtained; mp 199–200°C. MS: *m/z* (%) 275 (12) $(M+1)^+$, 274 (98) M^+, 228 (30), 227 (22) $(M-SCH_3)^+$, 198 (78) $(M-CS_2)^+$, 197 (23), 188 (16), 187 (39), 186 (100) $(M-SCH_3-CH_3CN)^+$, 102 (43), 91 (63). IR: 2988, 2913, 1578, 1570, 1546, 1497, 1443, 1417, 1356, 1344, 1317, 1286, 1250, 1239, 1228, 1196, 1156, 1133, 1120, 1026, 1010, 983, 902, 834, 775, 728, 665, 601, 446, 419. ^{1}H NMR ($CDCl_3$): δ 8.27–8.21 (m, 2H, H-5, H-8), 7.88–7.81 (m, 2H, H-6, H-7), 2.82 (s, 3H, S–CH_3), 2.74 (s, 3H, 3-CH_3). ^{13}C NMR ($CDCl_3$): δ 196.4 (C=S), 148.4 (C-3), 144.2 (C-9a), 141.8, 141.5 (C-4a, C-8a), 139.1 (C-3a), 131.7 (C-7), 130.1 (C-5), 129.8 (C-8), 129.6 (C-6), 18.9 (3-CH_3), 11.6 (S–CH_3). Analysis: calculated for $C_{12}H_{10}N_4S_2$: C, 52.54; H, 3.67; N, 20.42; S, 23.37; found: C, 52.44; H, 3.76; N, 20.66; S, 23.14.

3.2.10. 2-Acetylquinoxaline phenylhydrazone (6). Freshly distilled phenylhydrazine (27.5 mmol, 2.97 g) was added to the solution of 2-acetylquinoxaline (25 mmol, 4.30 g) in ethanol (250 ml). After 10 min the reaction mixture was heated and refluxed for 5 min only. After cooling down to room temperature and two days in the refrigerator, **6** was obtained as yellow needles (6.03 g) in 92% yield; mp 227–228°C (from ethanol)—222°C.[16] MS: *m/z* (%) 264 (20) $(M+2)^+$, 263 (95) $(M+1)^+$, 262 (100) M^+, 261 (44) $(M-1)^+$, 247 (15), 246 (16), 245 (20) $(M-NH_3)^+$, 220 (20), 157 (25) $(M-C_6H_5N_2)^+$, 156 (17), 155 (11), 133 (11), 130 (10), 129 (36) (quinoxalin-2-yl)$^+$, 102 (11) $(129-HCN)^+$, 77 (32), 76 (12), 65 (12). IR: 3260, 3057, 3026, 2936, 1700, 1647, 1600, 1564, 1545, 1494, 1405, 1365, 1304, 1256, 1236, 1167, 1128, 1084, 984, 952, 886, 760, 725, 690, 624, 599, 411. ^{1}H NMR ($CDCl_3$): δ 9.74 (s, 1H, H-3), 8.08–8.02 (m, 2H, H-6, H-7), 7.85 (s, 1H, NH), 7.73–7.67 (m, 2H, H-5, H-8), 7.35 (t, J=7.0 Hz, 2H, *m*-Ph), 7.27 (d, J=6.8 Hz, 2H, *o*-Ph), 6.98 (t, J=7.2 Hz, 1H, *p*-Ph), 2.49 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ 150.5 (*C*=N),

143.8, 143.7 (*i*-Ph and C-3), 141.6 (C-2), 140.9, 140.5 (C-4a, C-8a), 129.9 (C-6 or C-7), 129.5 (*m*-Ph), 129.1 (C-6 or C-7), 129.1, 128.9 (C-5, C-8), 121.5 (*p*-Ph), 113.6 (*o*-Ph), 9.0 (CH_3). Analysis: calculated for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36; found: C, 73.28; H, 5.49; N, 21.58.

3.2.11. 3-Methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (7). (i) The mixture of **6** (2.62 g, 10 mmol) and sulfur (0.40 g, 1.56 mmol S_8) was heated to 220–260°C for 20 min with stirring (CAUTION); along the reaction H_2S was prepared (fume hood!). The reaction mixture solidified upon cooling, had to be reduced to smaller parts and, finally, was stirred with 150 ml ethylacetate; insoluble residues were removed by filtration. The solvent was removed in vacuo and the residue recrystallized from ethanol. 1.10 g (42%) of **7** as yellow needles (mp 134–135°C) was obtained. (ii) The mixture of **6** (2.62 g, 10 mmol) and nitrobenzene (25 ml) was heated to 210°C for 5 h. Volatile components were removed by water steam distillation, the residue dissolved in chloroform, dried and purified by column chromatography. 2.26 g (87%) of raw product was obtained, after recrystallization from ethanol 1.70 g (65%) of **7**. (iii) The reaction mixture of **6** (2.62 g, 10 mmol), chloroanil (2.46 g, 10 mmol) and xylene (75 ml) was heated under reflux for 4 h. After cooling to room temperature, the reaction mixture was extracted with diluted KOH, the xylene was removed in vacuo and the residue, solved in CH_2Cl_2, purified by column chromatography. 1.70 g (65%) of **7** recrystallized from ethanol was obtained. (iv) To the golden yellow solution of **6** (2.62 g, 10 mmol) in boiling ethanol (300 ml) hydroxylamine hydrochloride (1.39 g, 20 mmol) in 2N HCl (10 ml) was added while stirring the reaction mixture. The dark mixture, obtained hereby, was heated under reflux for 30 min and concentrated in vacuo. After one night in the refrigerator, the yellow reaction product could be suction filtered, chromatographed in CH_2Cl_2 on silicagel and recrystallized from ethanol. 1.60 g (62%) of **7** was obtained.

3.2.12. 1,1′(4,4′-Bisthiazol-2,2′-diyl)bis(3-methyl-1H-pyrazolo[3,4-*b*]quinoxaline) (9). 10 mmol **5a** (2.34 g), dissolved in DMF (100 ml) at 100°C, was mixed with the solution of 1.4-dibromobutan-2,3-dione (5 mmol, 1.22 g) in DMF (30 ml, 30°C) with vigorous stirring of the reaction mixture. Afterwards, the stirring was continued for ca. 15 min at 100°C; during this time compound **9** readily crystallized from the hot solution as microcrystalline, intensively yellow substance. After washing with cool DMF or ethanol and drying, 1.92 g (72%) analytically pure **9** was obtained, although it was not melting up to 360°C. MS: *m/z* (%) 534 (12) $(M+2)^+$, 533 (30) $(M+1)^+$, 532 (100) M^+, 389 (6) $(M-143)^+$, 349 (5) $(M-183)^+$, 308 (14) $(349-CH_3CN)^+$, 294 (20), 184 (44) (1*H*-pyrazolo[3,4-*b*]-quinoxaline)$^+$, 143 (15) $(184-CH_3CN)^+$, 102 (12) $(C_6H_4CN)^+$. IR: 3120, 2924, 1655, 1583, 1568, 1529, 1476, 1455, 1380, 1352, 1317, 1254, 1200, 1128, 1063, 1008, 918, 867, 830, 770, 729, 673, 643, 602, 461, 420. CP-MAS (solid state) ^{13}C NMR: δ 114, broad (aromatic carbons), 13.6 (CH_3). Analysis: calculated for $C_{26}H_{16}N_{10}S_2$: C, 58.63; H, 3.03; N, 26.30; S, 12.04; found: C, 58.26; H, 3.22; N, 26.69; S, 11.73.

3.2.13. Methyl 2-(3-methyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-1-yl)-4-oxo-4*H*-thiazol-5-yliden-acetate (10). The solution of **5a** (10 mmol, 2.43 g) in 1,4-dioxane (75 ml, 100°C) was mixed with 1.56 g DMAD (11 mmol) and heated to 95–100°C for ca. 6 h. After cooling and storing the reaction mixture overnight in the refrigerator, the precipitate was suction filtered, washed with methanol and recrystallized from DMF; 1.41 g (40%) of compound **10** as pink coloured rods of mp 298–300°C were obtained. MS: *m/z* 354 (10) $(M+1)^+$, 353 (45) M^+, 312 (30) $(M-CH_3CN)^+$, 294 (30) $(M-COOCH_3)^+$, 237 (18) $(M(C_6H_4CN_2)^+$, 210 (14), 209 (22), 196 (14) $(237-CH_3CN)^+$, 185 (10), 184 (72), 183 (14), 169 (14) $(209-NCN)^+$, 168 (56), 144 (34) $(C_3HOS-COOCH_3)^+$, 143 (32) $(M-C_6H_4CN-CH_3CN)^+$, 128 (16) (quinoxalindiyl)$^+$, 116 (60), 102 (34), 85 (34). IR: 3036, 2956, 1725, 1700, 1588, 1548, 1527, 1501, 1476, 1432, 1381, 1361, 1328, 1192, 1128, 1099, 1055, 994, 896, 866, 819, 725, 704, 650, 626, 601, 513, 460, 417. CP-MAS (solid state) ^{13}C NMR: δ 162.5 (C═O), 112 (aromatic carbons), 12.8 (CH_3). Analysis: calculated for $C_{16}H_{11}N_5O_3S$: C, 54.39; H, 3.14; N, 19.82; S, 9.07; found: C, 54.80; H, 3.21; N, 20.28; S, 9.07.

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References

1. Part XI: Starke, I.; Sarodnick, G.; Ovcharenko, V. V.; Pihlaja, K.; Kleinpeter, E. *Rapid Commun. Mass Spectrom.* **2002**, *16*, 169.
2. Buu-Hoi, N. P.; Vallat, J.-N.; Saint-Ruf, G.; Lambelin, G. *Chim. Ther.* **1971**, 245.
3. (a) Kim, H. S.; Chung, J. Y.; Kim, E. K.; Park, Y. T.; Hong, Y. S.; Lee, M. K.; Kurasawa, Y.; Takada, A. *J. Heterocycl. Chem.* **1996**, *33*, 1855. (b) Makino, K.; Kim, H. S.; Kurasawa, Y. *J. Heterocycl. Chem.* **1999**, *36*, 321.
4. Kim, S. H.; Kim, E. K.; Kim, S. S.; Park, Y. T.; Hong, Y. S.; Kurasawa, Y. *J. Heterocycl. Chem.* **1997**, *34*, 39.
5. (a) Kurasawa, Y.; Muramatsu, M.; Yamazaki, K.; Tajima, S.; Okamoto, Y.; Takada, A. *J. Heterocycl. Chem.* **1986**, *23*, 1379. (b) Kurasawa, Y.; Muramatsu, M.; Yamazaki, K.; Tajima, S.; Okamoto, Y.; Takada, A. *J. Heterocycl. Chem.* **1986**, *23*, 1391.
6. (a) Ohle, H.; Melkonian, G. A. *Ber. Dtsch. Chem. Ges.* **1941**, *74*, 398. (b) Henseke, G.; Dose, W.; Dittrich, K. *Angew. Chem.* **1957**, *69*, 479. (c) Pillai, P. M.; Ramabhadran, P. *Indian J. Chem. Sect. B* **1986**, *215*, 901. (d) Sarodnick, G.; Linker, T. *J. Heterocycl. Chem.* **2001**, *38*, 829.
7. (a) Romanenko, V. D.; Burmistrov, S. I. *Khim. Geterotsikl. Soedin.* **1973**, 852. *Chem. Abstr.* **1973** *79*, 92158q. (b) El Ashry, E. S. H.; Kholy, E. S. H.; Kilany, Y. E. *Carbohydr. Res.* **1978**, *60*, 303. (c) Pillai, M. P. M.; Ramabhadran, P. *Indian J. Chem., Sect. B* **1986**, *25B*, 960. (d) Somogyi, L. *Carbohydr. Res.* **1992**, *329*, 89.
8. (a) Sauer, W.; Henseke, G. *Z. Chem.* **1970**, *10*, 381. (b) Yoshida, K.; Otomasu, H. *Chem. Pharm. Bull.* **1984**, *32*, 3361. (c) Kurasawa, Y.; Yamazaki, K.; Tajima, S.; Okamoto, Y.; Takada, A. *J. Heterocycl. Chem.* **1986**, *23*, 281. (d) Kurasawa, Y.; Muramatsu, M.; Yamazaki, K.; Tajima, S.; Okamoto, Y.; Takada, A. *J. Heterocycl. Chem.* **1986**, *633*,

959. (e) Monge, A.; Palop, J. A.; Pinol, A.; Martinez-Crespo, F. J.; Narro, S.; Gonzalez, M.; Sainz, Y.; Lopez de Cerain, A.; Hamilton, E.; Barker, A. J. *J. Heterocycl. Chem.* **1994**, *31*, 1135.
9. (a) Moiseev, I. K.; Zemtsova, M. N.; Makarova, N. V. *Chem. Heterocycl. Comp.* **1994**, *30*, 745. (b) Enders, E. *Methoden der organischen Chemie*; *Houben-Weyl*, Georg Thieme Verlag: Stuttgart, 1967; Vol. X/2. 321 pp.
10. Ohle, H.; Iltgen, A. *Ber. Dtsch. Chem. Ges.* **1943**, *76*, 1.
11. Sundberg, R. J. In *Best Synthetic Methods*; *Indoles*, Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic: San Diego, 1996.
12. Rykowski, A.; Mojzych, M.; Karczmarzyk, Z. *Heterocycles* **2000**, *53*, 2175.
13. Bereseneva, V. S.; Morzhin, Y.; Yu. Dehaen, W.; Luyten, I.; Bakulev, V. A. *Tetrahedron* **2001**, *57*, 2179.
14. Heydenreich, M.; Koch, A.; Sarodnick, G.; Kleinpeter, E, in preparation.
15. Körösi, J.; Berencsi, P. *Chem. Ber.* **1968**, *101*, 1979.
16. Henseke, G.; Bähner, K.-J. *Chem. Ber.* **1958**, *91*, 1605.