Unexpected Approach to the Synthesis of 2-Phenylquinoxalines and Pyrido[2,3-*b*]pyrazines *via* a Regioselective Reaction

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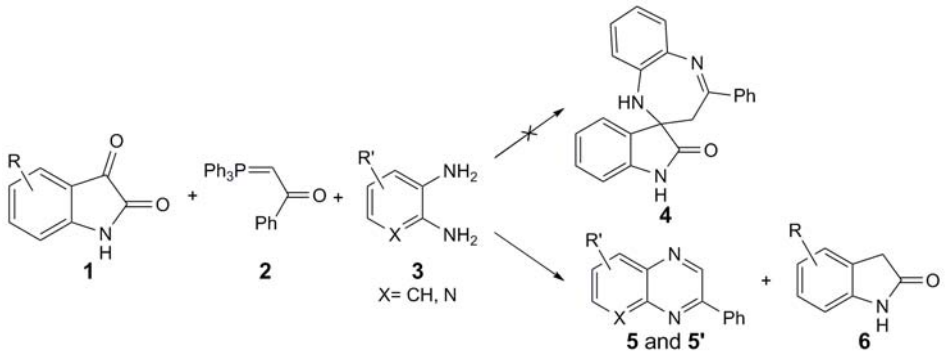
An unexpected approach to the preparation of quinoxaline and pyrido[2,3-*b*]pyrazine derivatives **5** is described. The reaction between 1*H*-indole-2,3-diones **1**, 1-phenyl-2-(triphenylphosphoranylidene)-ethanone (**2**), and benzene-1,2- or pyridine-2,3-diamines **3** proceeds in MeOH under reflux in good to excellent yields (*Scheme 1* and *Table*). No co-catalyst or activator is required for this multi-component reaction (MCR), and the reaction is, from an experimental point of view, simple to perform. The structures of **5**, **5′**, and **6** were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS) and were confirmed by comparison with reference compounds. A plausible mechanism for this type of reaction is proposed (*Scheme 2*).

Introduction. – Quinoxaline derivatives are the subject of considerable interest from both an academic and an industrial perspective. Among the various classes of N-containing heterocyclic compounds, quinoxalines are important components of several pharmacologically active compounds [1–3].

Although rarely observed in nature, the quinoxaline ring is a part of a number of synthetic antibiotics which are known to inhibit the growth of *gram*-positive bacteria and are also active against various transplantable tumors [4]. The most common method for the synthesis of quinoxaline relies on the condensation of an arene-1,2-diamine with a 1,2-dicarbonyl compound in refluxing EtOH or AcOH for 2–12 h. The modification of this reaction has been focused on the use of 1,2-diketone alternatives and related catalysts [5]. Thus, reactions of phenyl epoxides, phenacyl bromides, α-hydroxy ketones, and benzene-1,2-diamines with catalysts such as manganese octahedral molecular sieves [6], $HClO_4/SiO_2$ [7], β-cyclodextrin (β-CD) [8], Me_3SiCl [9], 1,4-diazabicyclo[2.2.2]octane (DABCO) [10], transition metals (Mn, Ru, Pd, and Cu) [11], $Ga(ClO_4)_3$ [12], ion-exchanged molybdophosphoric acid [13], KF–alumina surface in solid phase [14], and also under microwave irradiation [15] have been reported. In a particular case, the I_2-catalyzed reaction gives high yields of the products at room temperature, while the method suffers from environmental problems due to iodine and solvents toxicity [16][17].

In the context of our continuing efforts in syntheses of spiro-heterocyclic compounds [18e][18f], we envisaged that it could be promising to develop a simple and novel method to construct spiro[1*H*-1,5-benzodiazepine-2,3′-[3*H*]indol]-2′(1′*H*)-one derivatives **4** *via* the reaction of isatines (=1*H*-indole-2,3-diones) **1**, 1-phenyl-2-(triphenylphosphoranylidene)ethanone (**2**), and benzene-1,2-diamines **3**, but we observed a different pathway of the reaction (*Scheme 1*).

Scheme 1. *Unexpected Synthesis of Quinoxaline and Pyrido[2,3-*b*]pyrazines*



Results and Discussion. – In previous studies on the use of 1,3-dihydro-3-(2-oxo-2-phenylethylidene)-2*H*-indol-2-one (**7**) for the synthesis of spiro-heterocyclic compounds, we observed that the nucleophilic attack occurred at positions a and c (*Fig.*) [18e][18f]. But, in the reaction of **1**, **2**, and **3**, the nucleophilic attack took place at positions b and c, leading to the undesirable products **5** and **6** (*Scheme 1*).

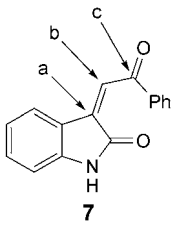
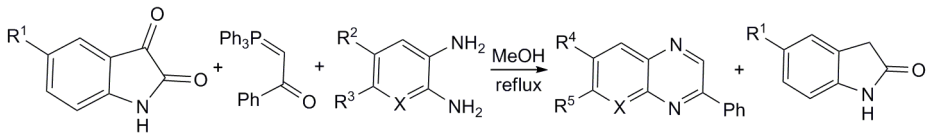


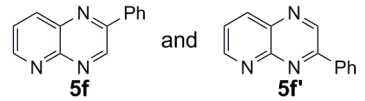
Figure. *Electrophilic Sites of 1,3-Dihydro-3-(2-oxo-2-phenylethylidene)-2*H*-indol-2-one* (**7**)

To explore the scope of this novel transformation, the reaction of various benzene-1,2-diamines and pyridine-2,3-diamines **3** with various isatins **1** was evaluated (*Table*). Benzene-1,2-diamines bearing electron-donating or electron-withdrawing groups gave the products **5** and **6** in good yields within 6 h. The results showed that the substituents of **3** played a significant role in the regioselectivity of the product formation. As shown in the *Table*, when 4-methylbenzene-1,2-diamine (**3b**) was used, we observed two products **5b** and **5b′** in a ratio of 63 : 37. This phenomenon can be explained as follows: Both NH_2 groups in *para* and *meta* position to the Me group of **3b** have suitable electron density for the nucleophilic attack, but the electron density of the NH_2 group in *para* position is higher. Also when pyridine-2,3-diamine (**3f**) was used as diamine, two products **5f** and **5f′** were obtained in a ratio of 50 : 50 because the two NH_2 groups of **3f** have similar electron density. Interestingly, reactions of benzene-1,2-diamines **3c** and **3d** yielded the corresponding quinoxalines **5c** and **5d** as single isomers, respectively (*Table*). This phenomenon can be explained as follows: The NH_2 group in *para* position to the NO_2 group of **3d** has low electron density and is not suitable for the nucleophilic attack. But the electron density of the NH_2 group in *meta* position to the NO_2 group of

Table. *Synthesis of Different Quinoxaline and Pyrido[2,3-*b*]pyrazines*



1 **2** **3** **5 and 5'** **6**

Isatine **1**	Diamine **3**	Product **5**/**5a**[a])	Ratio **5**/**5′**	Product **6**	Yield of **5** [%]
$R^1 = H$	**3a** ($R^2 = R^3 = H$, X = CH)	**5a** ($R^4 = R^5 = H$, X = CH)	–	**6a** ($R^1 = H$)	76
$R^1 = H$	**3b** ($R^2 = H$, $R^3 = Me$, X = CH)	**5b** ($R^4 = Me$, $R^5 = H$, X = CH)/**5b′** ($R^4 = H$, $R^5 = Me$, X = CH)	63 : 37	**6a** ($R^1 = H$)	78
$R^1 = H$	**3c** ($R^2 = H$, $R^3 = Cl$, X = CH)	**5c** ($R^4 = Cl$, $R^5 = H$, X = CH)	–	**6a** ($R^1 = H$)	82
$R^1 = H$	**3d** ($R^2 = H$, $R^3 = NO_2$, X = CH)	**5d** ($R^4 = H$, $R^5 = NO_2$, X = CH)	–	**6a** ($R^1 = H$)	84
$R^1 = H$	**3e** ($R^2 = R^3 = Me$, X = CH)	**5e** ($R^4 = R^5 = Me$, X = CH)	–	**6a** ($R^1 = H$)	79
$R^1 = H$	**3f** ($R^2 = R^3 = H$, X = N)	 **5f** and **5f'**	50 : 50	**6a** ($R^1 = H$)	87
$R^1 = Br$	**3g** ($R^2 = R^3 = H$, X = CH)	**5b** ($R^4 = R^5 = H$, X = CH)	–	**6b** ($R^1 = Br$)	75

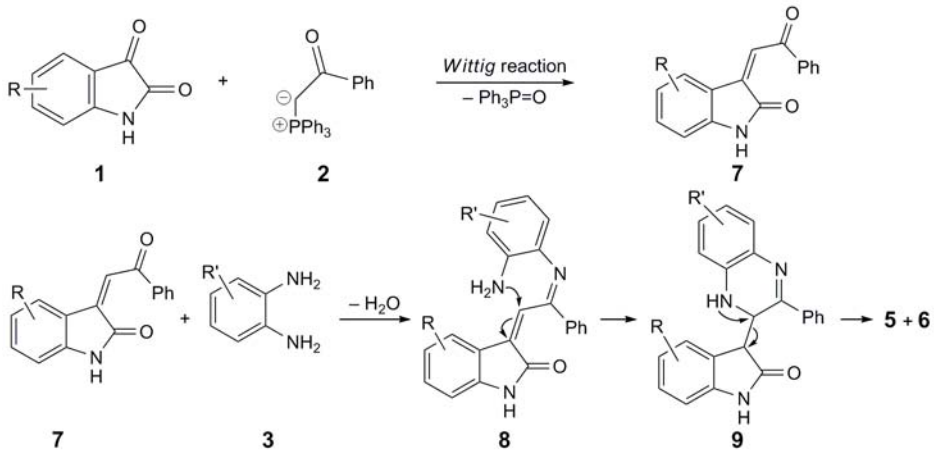
[a]) Compounds **5a**, **5b**, **5b′**, **5c**, **5d**, **5e**, and **5f**, have been described in [12].

3d and *para* position to the Cl-atom of **3c** is suitable for the nucleophilic attack, and thus these reactions lead to only one product.

The molecular structure of compounds **5**, **5′**, and **6** were deduced from their IR, high-field ^{1}H- and ^{13}C-NMR, and mass spectra as described for **5a**. The MS of **5a** displayed the molecular-ion peak at *m*/*z* 206, which is in agreement with the proposed structure. The IR spectrum showed absorption bands due to the CH and C=N moieties at 2927 and 1624 cm^{-1}, respectively. The ^{1}H-NMR spectrum of **5a** showed one sharp *s* for CH (δ(H) 9.29) and *m*s for the aromatic moieties (δ(H) 7.49 – 8.15) and the ^{1}H-decoupled ^{13}C-NMR spectrum exhibited 12 distinct resonances in agreement with the suggested structure [12].

Although we have not established the mechanism of the reaction experimentally, a possible explanation is proposed in *Scheme 2*. Compound **5** could result from the initial addition of the benzene-1,2-diamine to 1,3-dihydro-3-(2-oxo-2-phenylethylidene)-2*H*-indol-2-one (**7**) to yield intermediate **8**. Cyclization of **8** and subsequent loss of 1,3-dihydro-2*H*-indol-2-one **6** lead to compound **5**. To ascertain the proposed mechanism, the reaction between the proposed intermediate **7** and **3** were performed separately, and we observed similar products **5** and **6**.

Scheme 2. *Plausible Mechanism for the Formation of Compound* **5**



In summary, we developed an unexpected regioselective reaction for the synthesis of quinoxaline and pyrido[2,3-*b*]pyrazine derivatives, which are of potential synthetic interest. High yields of the products, relatively short reaction times, and starting from simple and available materials are the main advantages of this method. Also, the products were highly diverse since electron-donating and electron-withdrawing groups in the starting diamines **3** gave the desired products in good yields.

Experimental Part

General. The reagents and solvents used in this work were obtained from *Fluka* (Buchs, Switzerland) and used without further purification. M.p.: *Electrothermal-9100* apparatus. IR Spectra: *Shimadzu-IR-*

460 spectrometer; in KBr; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker-DRX-500-Avance* FT-NMR instrument at 500.1 and 125.7 MHz, resp., in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. EI-MS: *Finnigan-MAT 8430* mass spectrometer; ionization potential 70 eV; in *m*/*z*.

General Procedure (exemplified for **5a** and **6a**). A soln. of 1-phenyl-2-(triphenylphosphoranylidene)ethanone (**2**; 0.38 g, 1 mmol), 1*H*-indole-2,3-dione (**1a**; 0.15 g, 1 mmol) in MeOH (3 ml) was magnetically stirred for 20 min. Then, benzene-1,2-diamine (**3a**; 0.11 g, 1 mmol) was added. The mixture was stirred for 5 h while heating under reflux (TLC monitoring). After completion, the solvent was evaporated and the residue separated by CC (hexane/AcOEt 6:1) [12].

General Procedure for Control Experiment (exemplified for **5a** and **6a**). A soln. of **2** (0.38 g, 1 mmol) and **1a** (0.15 g, 1 mmol) in MeOH (3 ml) was magnetically stirred for 20 min. After completion, the solvent was evaporated and the residue separated by CC (hexane/AcOEt 8:1) to yield **7** (95%). Then, **3a** (0.11 g, 1 mmol) was added to the soln. of compound **7** in MeOH (5 ml), and the mixture was stirred for 5 h while heating under reflux (TLC monitoring). After completion, the solvent was evaporated, and the residue was separated by CC (hexane/AcOEt 6:1): **5a** (75%) and **6a** (71%).

*2-Phenylpyrido[2,3-*b*]pyrazine* (**5f**).Yield 0.09 g (43%). White crystals. M.p. 88–100°. IR: 2927 (CH), 1711 (C=N), 1465 (Ar). ^1H-NMR: 7.56–7.61 (*m*, 3 H); 7.74 (*dd*, *J* = 8.3, 4.2, 1 H); 8.22 (*dd*, *J* = 7.7, 1.1, 2 H); 8.48 (*dd*, *J* = 8.2, 1.8, 1 H); 9.15 (*dd*, *J* = 4.1, 1.8, 1 H); 9.55 (*s*, 1 H). ^{13}C-NMR: 125.62; 128.04; 129.18; 130.72; 135.72; 136.79; 138.16; 146.25; 150.85; 152.91; 153.47. EI-MS: 207 (M^+, 34), 179 (42), 103 (88), 76 (100).

*3-Phenylpyrido[2,3-*b*]pyrazine* (**5f′**): Yield 0.09 g (43%). White crystals. M.p. 88–100°. IR: 2927 (CH), 1711 (C=N), 1465 (Ar). ^1H-NMR: 7.56–7.61 (*m*, 3 H); 7.71 (*dd*, *J* = 12.5, 4.2, 1 H); 8.34 (*dd*, *J* = 7.7, 1.1, 2 H); 8.51 (*dd*, *J* = 8.2, 1.8, 1 H); 9.19 (*dd*, *J* = 4.1, 1.8, 1 H); 9.46 (*s*, 1 H). ^{13}C-NMR: 124.75; 127.83; 129.27; 131.02; 135.90; 137.54; 138.54; 144.32; 150.46; 154.48; 154.65. EI-MS: 207 (M^+, 34), 179 (42), 103 (88), 76 (100).

*1,3-Dihydro-2*H*-indol-2-one* (**6a**): Yield 0.1 g (70–75%). White crystals. M.p. 122–124°. IR: 3150 (NH), 1717 (C=O), 1465 (Ar). ^1H-NMR: 3.55 (*s*, 2 H); 6.90 (*d*, *J* = 7.6, 1 H); 7.02 (*t*, *J* = 7.5, 1 H); 7.22 (*t*, *J* = 7.6, 1 H); 7.23 (*t*, *J* = 7.6, 1 H); 9.03 (*s*, 1 H). ^{13}C-NMR: 36.24; 109.75; 122.31; 124.59; 125.28; 127.91; 142.56; 177.86. EI-MS: 133 (M^+, 54), 104 (94), 78 (48), 57 (100).

*5-Bromo-1,3-dihydro-2*H*-indol-2-one* (**6b**): Yield 0.15 g (70%). White crystals. M.p. 224–226°. IR: 3160 (NH), 1697 (C=O), 1458 (Ar). ^1H-NMR: 3.55 (*s*, 2 H); 6.77 (*d*, *J* = 8.3, 1 H); 7.35 (*d*, *J* = 7.8, 2 H); 7.36 (*s*, 1 H); 8.48 (*s*, 1 H). ^{13}C-NMR: 35.43; 110.39; 114.43; 126.75; 127.35; 130.31; 141.53; 176.56. EI-MS: 213 ($[M+1]^+$, 77), 184 (42), 104 (92), 77 (100).

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