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Pyrrolo[1,2-*a*]quinoxalines: Novel Synthesis via Annulation of 2-Alkylquinoxalines

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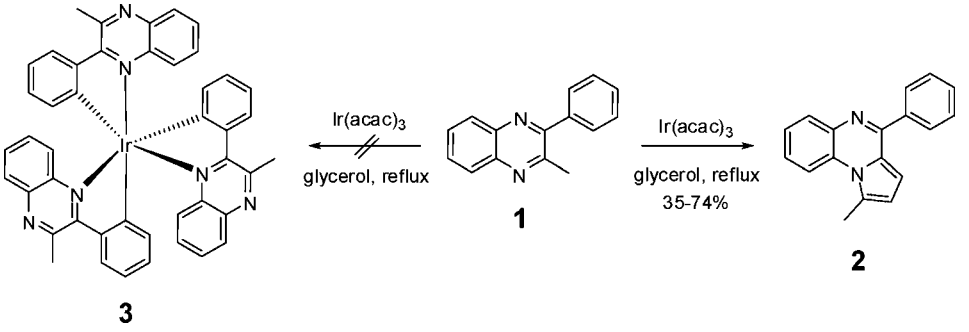
ABSTRACT



In an attempt to synthesize a novel homoleptic complex 3 from 2-methyl-3-phenylquinoxaline 1 and Ir(acac)$_3$ for application as a triplet emitter in OLEDs (organic light-emitting diodes) no cyclometalation was observed. Instead, an annulation to 1-methyl-4-phenylpyrrolo[1,2-*a*]quinoxaline 2 was observed. Since pyrroloquinoxalines are potentially bioactive and few paths for their synthesis are known, selected reactions and conditions were investigated, suggesting Ir(acac)$_3$ as catalyst and proving glycerol to be a reactant.

The motif of pyrrolo[1,2-*a*]quinoxaline has attracted attention because of its potential bioactivity. Derivatives of this motif have been investigated with respect to their use to inhibit microbial resistance to antibiotics,[1] their potential antitumor activity,[2] as specific high-affinity receptor ligands,[3,4] and as antileishmanial agents.[5] To date, reviews point out that only a few methods for synthesis of the pyrrolo[1,2-*a*]quinoxaline motif are described in the literature.[6−8] Many of the known methods proceed either via a cyclization starting from 1-arylpyrroles[7,9−11] or reaction paths involving 1,3-dipolar cycloaddition with propiolates or *N*-ylides.[12−15] Kaminskii et al.[16] describe a

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synthesis via reaction of 1,2-diaminobenzene with various 2-hydroxy-1,5-diketones in ethanol and acetic acid, and Blache et al.[17] demonstrate the synthesis via condensation of 2-methylquinoxalines with alkyl bromopyruvates. To the best of our knowledge, except for the 1,3-dipolar cycloaddition and the condensation reaction with alkyl bromopyruvates, the five-membered pyrrole ring is always present in the starting material and the six-membered pyrazine ring is assembled. The reaction type described herein has not been published elsewhere and demonstrates a unique path to alkyl-substituted pyrrolo[1,2-*a*]quinoxalines.

The current literature contains few publications on the application of quinoxalines for use as transport materials[18] or as light-emitting compounds[19,20] in OLEDs. Following the widely used procedure for synthesis of homoleptic facial metal complexes first described by Dedeian et al.,[21] we wished to synthesize a new emitting material **3**. The reaction repeatedly led to a yellow solid with unusually strong fluorescence when excited at 366 nm. Analysis of the spectroscopic data provided no evidence for the successful synthesis of **3**, and we concluded that the product was a purely organic compound arising via minor changes in the structure of **1**.

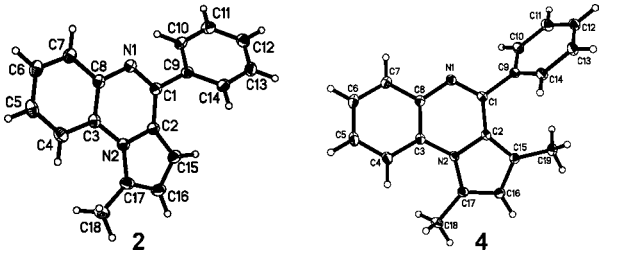
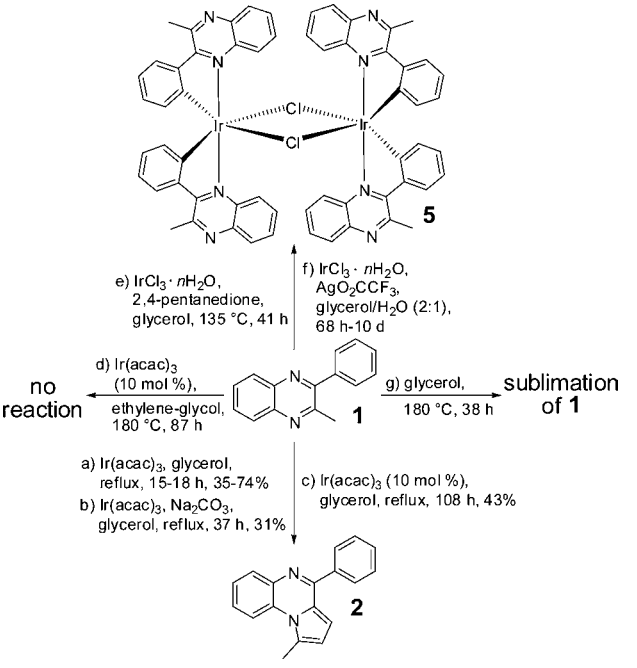


Figure 1. ORTEP representations of novel pyrrolo[1,2-*a*]-quinoxalines **2** and **4** with thermal ellipsoids drawn at the 50% probability level. Crystallized water is omitted in **2**.

This was verified by X-ray analysis. The crystal structure of **2** (obtained as a hemihydrate) is shown in Figure 1 and reveals the unexpected and novel structure of a methyl-substituted phenylpyrrolo[1,2-*a*]quinoxaline. This surprising structure prompted several questions: why does the annulation of a five-membered pyrrole ring occur, what is the source of the incorporated C_3 fragment, and does the iridium play a role as catalyst.

In the course of a few simple reactions, which are depicted in Scheme 1, we narrowed down the possibilities. First, we added the base Na_2CO_3 as a possible promoter of the cyclometalation, which formally depends on a deprotonation of the ligand **1**. Then we reduced the amount of $Ir(acac)_3$ to test the catalytic activity and at the same time lowered the reaction temperature, allowing a better comparison with some of the following experiments. In all cases we obtained roughly the same yield of **2**. In the absence of $Ir(acac)_3$, or after replacing glycerol by ethylene glycol, no reaction took place. The use of $IrCl_3 \cdot nH_2O$, another typical starting material for cyclometalation, with or without addition of 2,4-pentanedione or silver trifluoroacetate, led to the formation of a di-μ-chloro-bridged metal complex **5**. These metal complexes can be used to form suitable products for application in OLEDs and are described elsewhere.[22] All in all, these reactions showed the necessity for both $Ir(acac)_3$ and glycerol, and we tentatively assumed $Ir(acac)_3$ to be the catalyst and glycerol to be the source of the C_3 fragment.

Scheme 1. First Simple Experiments



To test our preliminary conclusions, we conducted a new series of reactions. A summary of the employed compounds is given in Figure 2. First, we substituted $Ir(acac)_3$ by the derivative $Ir(acac\text{-}Me)_3$ **6**. As verified by NMR and MS, we observed the synthesis of the already known 1-methyl-4-phenylpyrrolo[1,2-*a*]quinoxaline **2** in approximately the same yield of 38% without any evidence for the

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incorporation of an additional methyl group. Then we prepared 2,3,4-pentanetriol **7** and substituted it for glycerol. To our surprise, the main product isolated from flash chromatography was the already known quinoxaline **2**, but GC/MS analysis of other fractions clearly showed M + 14 and M + 28 compounds that still support the idea of the triol as the source of the C_3 fragment for annulation. A detailed GC/MS analysis can be found in the Supporting Information.

Encouraged by these results, we performed a reaction with glycerol-$^{13}C_3$ **8** under the initial conditions to prove the solvent to be the carbon source. After purification via flash chromatography and recrystallization, we obtained a yellowish solid in 16% yield with minor impurities which were not removable, even by reversed-phase HPLC. Because of the low yield, which possibly is a consequence of a kinetic isotope effect and the small scale of the reaction, we could not perform a complete analysis, but ^{13}C NMR and the mass spectrum proved the incorporation of glycerol.

In analogy to the Skraup[23,24] synthesis, we also performed a reaction after replacing glycerol by acrolein **9** dissolved in ethylene glycol, which already proved to be inert. Acrolein is a potential secondary product formed by dehydration of glycerol and is believed to be the active species in the Skraup synthesis. We initiated our reaction with equimolar amounts and increased these gradually, but found only very weak luminescence on the TLC, suggesting acrolein is not the active species.

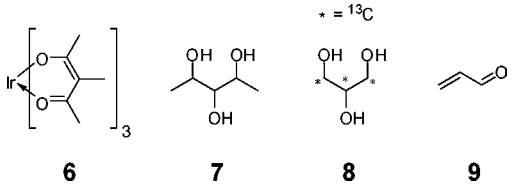

Figure 2. Other compounds used to substitute either Ir(acac)$_3$ (**6**) or glycerol (**7**–**9**).

In order to evaluate the scope of the reaction and for a better understanding of the possible mechanism, we specifically altered the quinoxaline body of **1** and performed analogous reactions. A summary of the reactants is given in Figure 3. We began with 2-ethyl-3-phenylquinoxaline **10** and found a compound **4** with a second methyl group. Since it was not possible to determine the exact position of the additional methyl group by NMR analysis, we verified the structure of **4** by X-ray analysis. The structure is depicted in Figure 1 and shows that the alkyl group of our starting material is preserved in the product. Starting from 2-phenylquinoxaline **11**, a compound without a methyl group, we expected and indeed found that almost no reaction occurred. According to TLC only traces of a fluorescent compound were formed but could not be isolated. Using reactant **12** we were confronted by a large number of products, probably associated with the lack of the phenyl group. Despite using HPLC a complete separation of all products was not successful, but the most promising fraction could be isolated and then further separated and analyzed via GC/MS. The mixture consisted of two compounds, with little difference in retention time, in the ratio of 1:4. Both compounds showed a similar mass spectrum with the expected formula indicating isomers of pyrrolo[1,2-*a*]quinoxaline.

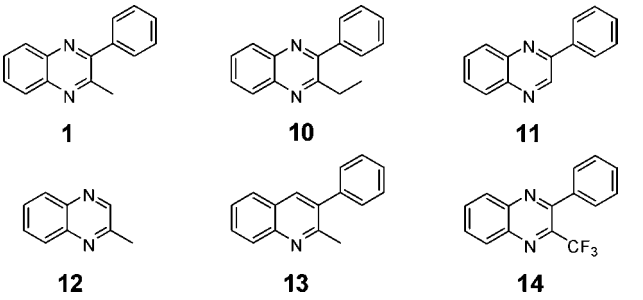

Figure 3. Employed reactants.

According to the above experiments, an alkyl group in the α-position to an imine (C=N) is mandatory for efficient synthesis. Recently, Ir(I)-promoted reactions of an alcohol with an activated methylene group in the α-position to a nitrile were demonstrated.[25,26] In general, iridium, especially in a low oxidation state such as +I, shows catalytic activity and is used for annulations[27] and activations of C–H groups.[28] In the case of rhodium in low oxidation state +I, a mechanism has been reported for the annulation to a pyrrolidine ring from an intramolecular alkene coupling with benzimidazole.[29] We also considered whether the opposite C=N-group has an influence when iridium is coordinating to the nitrogen. Therefore we synthesized 2-methyl-3-phenylquinoline **13**, employed it under the same conditions and observed evidence of the synthesis of 1-methyl-4-phenylpyrrolo[1,2-*a*]quinoline **15** as expected in much lower yield. The result of this reaction supports our assumption of an influence of the opposite nitrogen and strengthens the idea of a catalytic pathway. The different behavior of compounds **1** and **13** is depicted in Scheme 2.

Since our initial intention was to create novel homoleptic metal complexes, we designed a reaction with the reactant

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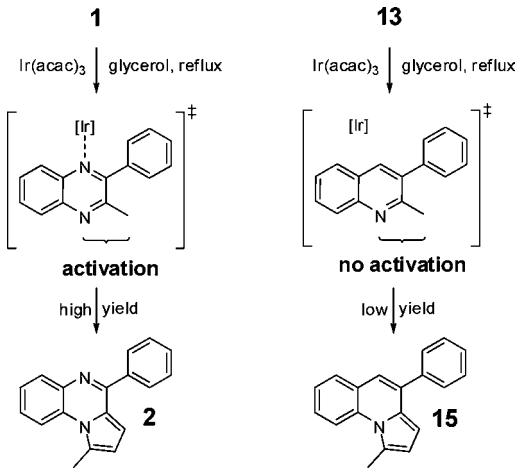
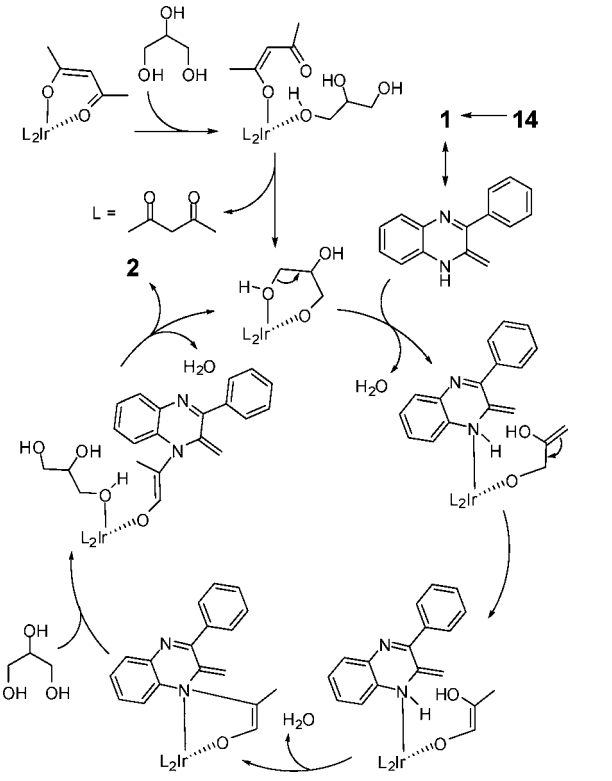
Scheme 2. Depiction of Supposed Influence of Opposite Nitrogen in Compound **1** in Comparison to Compound **13**



Scheme 3. Proposed Preliminary Mechanism



14. We already knew that in case of the unexpected annulation the alkyl group in α-position to the imine remains in the molecule and took into consideration that C−F bonds are thermodynamically stable. Even though Harrak et al.[7] have shown that aromatic C−F bonds can undergo an intramolecular nucleophilic displacement to form pyrrolo[1,2-*a*]quinoxalines we expected the CF_3 group to remain inert. To our considerable surprise we could only isolate the already known quinoxaline **2** in 37% yield with no evidence of any fluorine atom in the structure.

Since the conversion of **14** to **2** was inconsistent with our model, we investigated the reaction more closely. We planned a parallel experiment based on the original setup with reactants **1** and **14**. Both reactions were performed for 76 h at temperatures starting from 160 °C and increasing stepwise every 18−20 h by 10 °C to a final temperature of 190 °C. Samples were taken and analyzed via TLC before increasing the temperature. We found that the reaction with **1** already occurs at 160 °C, whereas **14** needs 180 °C for a clear conversion. Also we noticed an intriguing spot on the TLC of the reaction with **14**, which appeared before final product **2**, vanishing at the same time that **2** was forming. Since the position of the spot corresponded exactly to the retention factor of **1** we analyzed a sample by GC/MS. Indeed, we could prove the presence of **1** in the reaction mixture. Together with the higher temperature needed for conversion of **14** we can assume that a second, as yet unknown, mechanism primarily forms **1** which then converts to **2**. Presumably, the reaction proceeds via an insertion of iridium into the C−F bonds. Very recently, Chan and Leong investigated an iridium CO complex activating an aromatic C−F bond together with water.[30] As proved by our own research, the appearance of a CO molecule in an iridium complex is feasible.[31] From the sum of the presented reactions we propose the preliminary mechanism shown in Scheme 3. Because of the excess of glycerol, one 2,4-pentanedione ligand is exchanged, creating the catalytically active complex. In the following steps, water from glycerol is eliminated, possibly explaining the presence of water in the single crystals of **2**, and finally C−C and C−N bonds are established.

In summary, we have prepared various novel, potentially bioactive, methyl-substituted pyrrolo[1,2-*a*]quinoxalines from 2-alkylquinoxalines via a new route. $Ir(acac)_3$ probably reacts as a catalyst and glycerol represents the carbon source for the annulation of a pyrrole ring. We have proven the structure of our products by complete analysis including two X-ray structures, proposed a preliminary mechanism for the reaction and supported our conjectures by experiments.

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Supporting Information Available. Experimental procedures, spectral and crystallographic data of described compounds, and discussed HPLC, GC/MS, and TLC results. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.