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Unusual Friedlander Reactions: A Route to Novel Quinoxaline-Based Heterocycles

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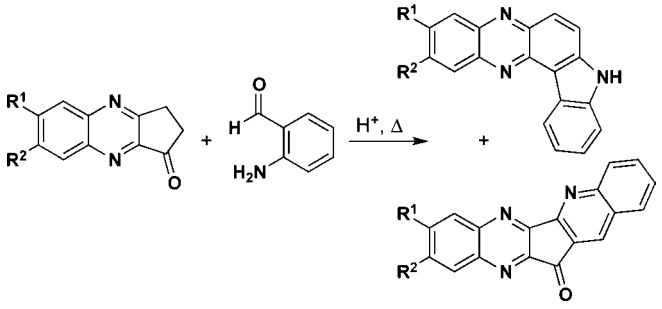
ABSTRACT



Acid catalyzed Friedlander reactions of a number of 2,3-dihydro-1*H*-cyclopenta[*b*]quinoxaline-1-ones with 2-aminobenzaldehyde yield, unexpectedly, 8*H*-indolo[3,2-*a*]phenazine and quinolino[2,3-*c*]cyclopentadienone[2,3-*b*]quinoxalines, the structures of derivatives of which were confirmed by X-ray crystallography. Easy routes to novel quinoxaline-based indoles, quinolones, and quinoxaline-1,4-dioxides are reported, and proposed mechanisms for the unexpected products are discussed.

Indoloquinoxalines are well-known heterocycles generally prepared through the reaction of *o*-phenylenediamine with isatin.[1] In contrast, quinoxaline-based quinolines and quinoxaline-1,4-dioxides are either rare or unknown in the chemical literature.[2] Recent reviews of the biological activities of indoles, quinolines, and quinoxalines point out their medicinal chemistry importance.[3] Indeed, quinoxalines and their 1,4-dioxides have shown activity as anticancer, antifungal, antibacterial, and anti-inflammatory agents.[4] The biological effects of quinoxalines as inhibitors of platelet-derived growth factor receptor tyrosine kinase [PDGF-RTK] are of particular interest, and several were reported to be superior in this regard to quinolines and indoles.[5]

The objective of the work reported here was to develop synthetic routes to novel quinoxaline-based indoles, quinolines, and quinoxaline-1,4-dioxides. We envisaged that introduction of a ketomethylene ($-COCH_2-$) moiety at

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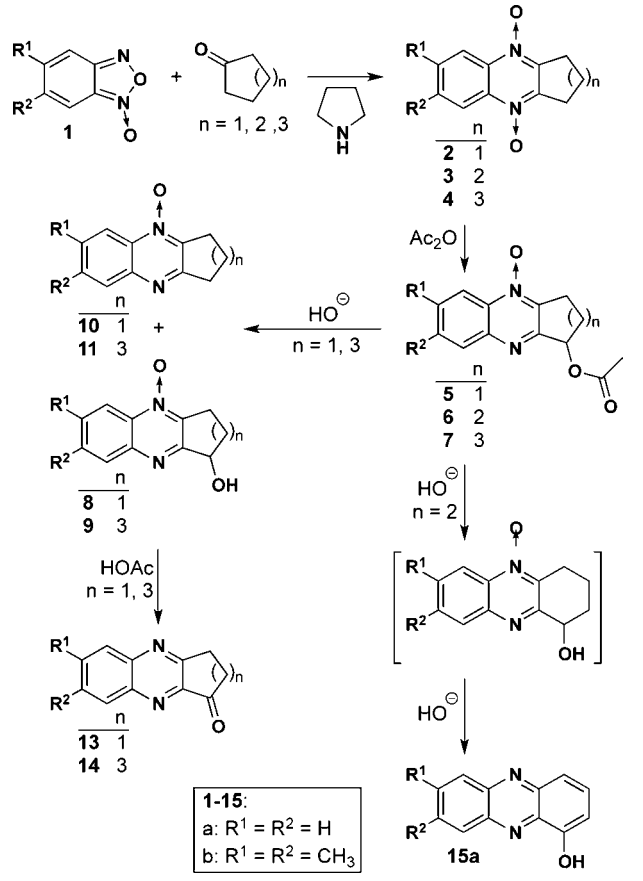
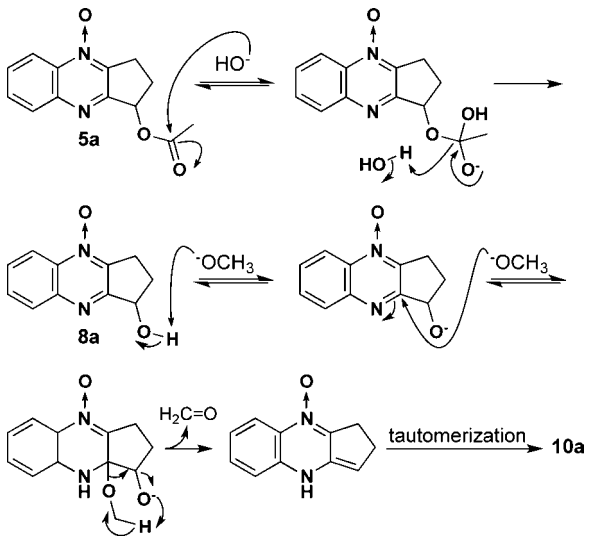
C2 of a quinoxaline would access a number of heterocycles ligated to the quinoxaline ring system. A series of steps involving a Beirut reaction[6a] (**1** → **2**–**4**) followed by Polonovski rearrangement[6] (**2**–**4** → **5**–**7**), base hydrolysis (**5**/**7** → **8**/**9**), and HOAc-mediated oxidation/reduction (**8**/**9** → **13**/**14**) gives the expected 1*H*-cyclopolymethylene-[*b*]quinoxaline-1-one starting materials for this study. In contrast, **6** leads to **12**, which undergoes two consecutive base-mediated tautomerizations followed by a N^1,N^4-dehydration and air oxidation of the resulting 5,10-dihydrophenazine intermediate to yield 1-hydroxyphenazine (**15a**; Scheme 1).

Scheme 1



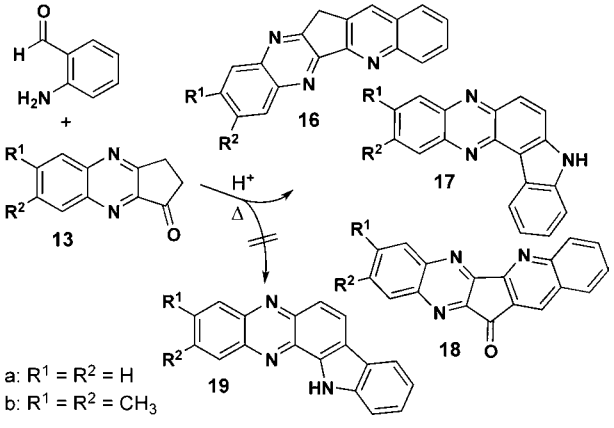
Somewhat surprisingly, saponification of hydroxyquinoxaline **5** or **7** leads unexpectedly to quinoxaline *N*-oxide **10** or **11**, respectively, in modest yields (**10**, 27%; **11**, 24%). While the exact details of how these unique dehydroxylation reactions proceed are not clear, we speculate that methanol plays a pivotal role because this reaction does not take place in *tert*-butyl alcohol/KOH. We propose a methoxide-based mechanism for this reaction (Scheme 2), but a radical mechanism cannot be excluded. This speculation is analogous, in its initial steps, to the recent mechanism proposed by Bjorsvik et al. for the deoxygenation of *N*-heteroarene *N*-oxides.[7]

Scheme 2



Having secured quinoxalino ketone **13**, we attempted the Friedlander reaction[6a] of it with 2-aminobenzaldehyde under acid catalysis; **13** decomposes under basic conditions. We were surprised to find that the expected quinolinoquinoxaline **16** (yellow) was formed (Scheme 3), but in only trace amounts, and that the major products were indolophenazine **17** (20%, yellow) and quinolinoquinoxalinone **18** (50%, orange). The ^{1}H NMR of **17** indicated

Scheme 3



that a rearrangement had taken place as the spectrum showed two sharp doublets at 8.00 and 8.16 ppm, which evidenced only 1,2-splitting and, therefore, independence from other neighboring protons. Initial mechanistic consideration suggested that the structure of **17** might be

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indolophenazine **19**; however, X-ray crystallography (Figure 1) left no doubt that this indolophenazine has structure **17**. In addition to indolophenazine **17**, quinolinoquinoxaline **18** was also formed as confirmed by X-ray crystallography (Figure 2).

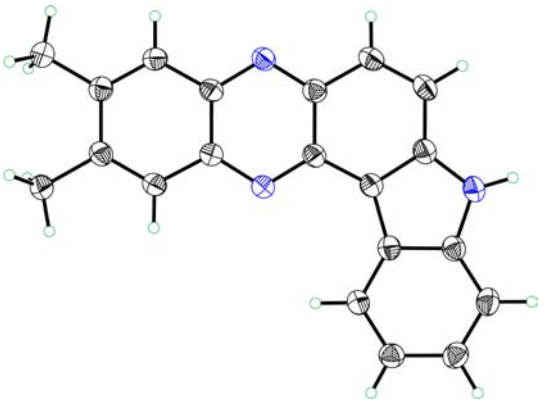


Figure 1. X-ray crystallography of 2,3-dimethyl-8*H*-indolo-[3,2-*a*]-phenazine (**17**).

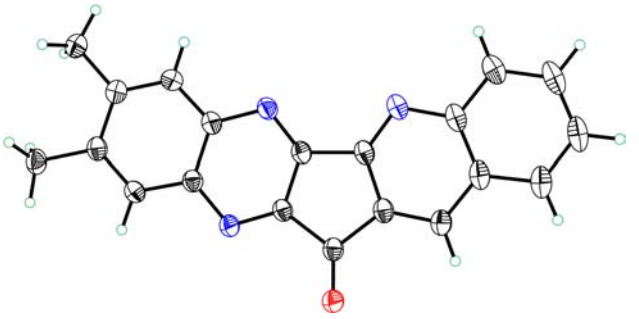
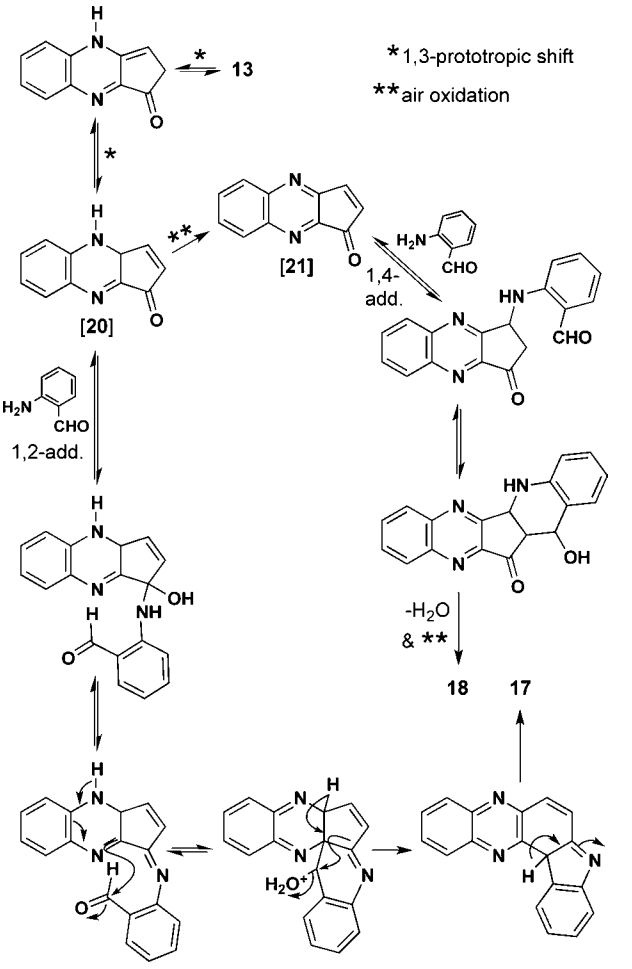


Figure 2. X-ray crystallography of 3,4-dimethylquinolino[2,3-*c*]-cyclopentadienone[2,3-*b*]quinoxalines (**18**).

Mechanistic steps to explain the formation of these unexpected products (**17** and **18**) are presented in Scheme 4. We suggest that both arise from common intermediate [**20**], which is formed from **13** through two consecutive 1,3-prototropic shifts, the second of which is induced by conjugation with the carbonyl group. The relative higher yield of quinolinoquinoxaline **18** (50% vs 20% for **17**) can be rationalized on the basis that intermediate [**20**] undergoes oxidative (air) aromatization of the dihydroquinoxaline moiety to produce the highly reactive cylcopentadieneone-like intermediate [**21**]. This intermediate performs a 1,4-addition of 2-aminobenzaldehyde followed by aldol condensation, dehydration, and air oxidation to give quinolinoquinoxaline **18**. A competing 1,2-addition of 2-aminobenzaldehyde onto the carbonyl group of intermediate [**20**] followed by aldol condensation and a rearrangement eventually leads to indolophenazine **17**.

Scheme 4

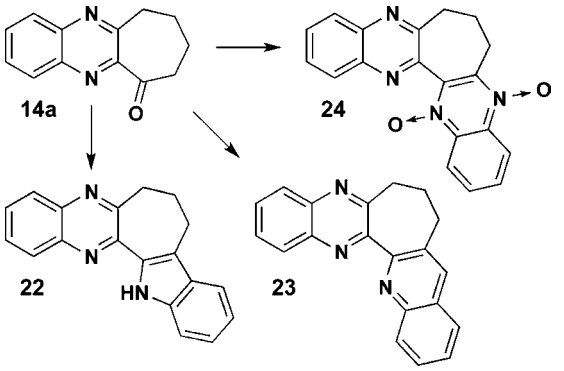


This unique rearrangement in a Friedlander-like reaction is unprecedented, constituting a simple and direct method for the synthesis of the novel parent ring system as well as substituted indolophenazines **17a**/**b** from keto quinoxaline **13a**/**b**. Moreover, the second products of this reaction, quinolinoquinoxalines **18a**/**b**, are also previously unknown heterocycles.

As outlined in Scheme 5, we next turned our focus to the synthesis of novel quinoxaline-based indolo-, quinolino-, and quinoxalino-1,4-dioxides from **14**. It should be added that although quinoxaline **14** can be synthesized from **9** (77% yield; Scheme 1), it can also be prepared directly from **7** under base catalysis (KOH/MeOH) in 40% yield. Reaction of quinoxaline **14** with phenylhydrazine (Fischer indole reaction[6a]), 2-aminobenzaldehyde (Friedlander reaction[6a]), and benzofuran oxide (Beirut reaction[6a]) yielded 12,13,14-trihydroindolo[2,3-*c*]cyclohepta[2,3-*b*]-quinoxaline (**22**, 74%), 12,14,15-trihydroquinolino[2,3-*c*]cyclohepta[2,3-*b*]quinoxaline (**23**, 68%), and 13,14,15-trihydroquinoxalino[2,3-*c*]cyclohepta[2,3-*b*]quinoxaline 1,6-dioxide (**24**, 65%), respectively, in good yields.

In conclusion, we have synthesized a variety of novel heterocycles, which include indolophenazines, quinolinoquinoxalinones, indoloquinoxalines, quinolinoquinoxalines,

Scheme 5



and quinoxalinoquinoxaline 1,4-dioxides. The work presented here also underscores how the C-ring size in Polonovski rearrangement products dramatically affects the outcome of their subsequent base-mediated hydrolysis reactions (**5/7** → **8/9** vs **6** → [**12**] → **15a**; Scheme 1). A similar C-ring dichotomy is noted in the Friedlander reactions of **13** (→ **17/18**; Scheme 3) vs **14** (→ **23**; Scheme 5).

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Supporting Information Available. Full experimental details and characterization data (^{1}H NMR, ^{13}C NMR, IR, and LC/MS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.