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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-1H-cyclopenta[b]quinoxaline-1-ones with 2-aminobenzaldehyde yield, unexpectedly, 8H-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] is 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 (–COCH₂–) moiety at C2 of a quinoxaline would access a number of hetero-cycles ligated to the quinoxaline ring system. A series of steps involving a Beirut reaction^{6a} (1 → 2-4) followed by Polonovski rearrangement⁶ (2-4 → 5-7), base

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‡Dedicated to Professor Musa Z. Nazer of the University of Jordan on his 75th birthday.

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

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).

Somewhat surprisingly, saponification of hydroxy-quinoxaline **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 *t*-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

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 quinolino-quinoxalinone **18** (50%, orange). The ¹H-NMR of **17** indicated 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 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).

Mechanistic steps to explain the formation of these unexpected products (**17** and **18**) is 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 cyclopentadienone-like intermediate [**21**]. This intermediate does 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**.

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 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*]cyclo-hepta[2,3-*b*]quinoxaline (**22**, 74%), 12,14,15-trihydroquinolino[2,3-*c*]-

cyclohepta[2,3-*b*]quinoxline (**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, and quinoxalinoquinoxaline 1,4-dioxides. The work presented here also underscores how 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).

Supplementary Material

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Acknowledgments

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

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

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Scheme 5.