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# Dibenzonaphthyridinones: Heterocycle-to-Heterocycle Synthetic Strategies and Photophysical Studies

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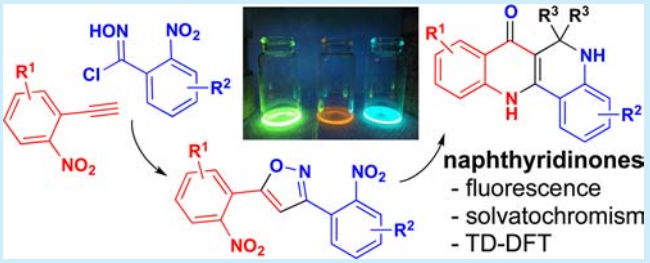
Supporting Information

**ABSTRACT:** A heterocycle-to-heterocycle strategy is presented for the preparation of highly fluorescent and solvatochromic dibenzonaphthyridinones (DBNs) via methodology that leads to the formation of a tertiary, spiro-fused carbon center. A linear correlation between the results of photophysical experiments and time dependent density functional theory calculations was observed for the $\lambda_{max}$ of excitation for DBNs with varying electronic character.




The importance of late-stage skeletal diversification of small molecule libraries is well established,[1] and previous work has demonstrated the utility of heterocycle-to-heterocycle transformations as valuable tools for implementing this strategy.[2] Most recently, we have shown that an isoxazole core (such as in isoxazole **3a**; Scheme 1) can be selectively converted into 4-aminoquinolines, 3-acylindoles (not depicted here), and 4-quinolinones based on the location of a 2-nitrophenyl substituent (e.g., at the C3, C4, or C5 position, respectively) on the isoxazole, which is then subjected to reductive conditions.[3] Of particular relevance to the work reported here, 3,5-bis-*o*-nitrophenyl substituted isoxazoles (e.g., **3a**) were shown to undergo reductive transformation selectively yielding a 4-quinolinone, and not the 4-aminoquinoline (Scheme 1a).[3] In an extension of this initial finding, we now show that 3,5-bis-*o*-nitrophenyl substituted isoxazole reduction in the presence of an added ketone can deliver dibenzonaphthyridinones (DBNs, Scheme 1b). Furthermore, while others have studied the optical properties of DBNs (and related structures),[4] we present new synthetic methodology for constructing these highly fluorescent and solvatochromic materials as well as experimental and theoretical exploration of their optical properties.

Solvatochromism is defined in the IUPAC Gold Book as "the pronounced change in position and sometimes intensity of an electronic absorption or emission band accompanying a change in the polarity of the medium."[5] It has been demonstrated that solvatochromic materials make intriguing biomarkers, which allow for tracking of a material *in vitro*, and also provide information about the polarity of the region where the tracked molecule resides.[6]

In addition to their photophysical properties, DBNs have also been studied for their biological activities. For example, DBNs have been shown by Miolo et al. to be DNA intercalators,[7] and Checcheti et al. have studied their application as modified quinolinone based antibacterials.[8] Arylpiperazinyl naphthyridinones have been reported by Johnson et al. to have utility in the treatments of bipolar disorder and schizophrenia.[9] Thus, DBNs are ripe targets for synthetic strategies that promote rapid structural and functional diversification to facilitate further activity studies. While isoxazole-based reductive quinolinone synthetic methods have been reported by us and others,[2a,b,3] previous synthetic methodologies to DBNs rely on commercially available substituted quinolinone starting materials and acid mediated condensations with aminobenzoic acids to afford the targeted molecular frameworks.[2b,10] The methodology reported here uses a fundamentally different approach to producing DBNs that starts with aryl iodides and readily synthesized aryl oximes. The key 3,5-bis(*o*-nitrophenyl)-isoxazole intermediates **3a**–**d** were synthesized starting from the appropriately substituted 1-

**Scheme 1. Previous (a) and Current (b) Reductive 3,5-Bis-*o*-nitrophenyl Substituted Isoxazole Methodology**

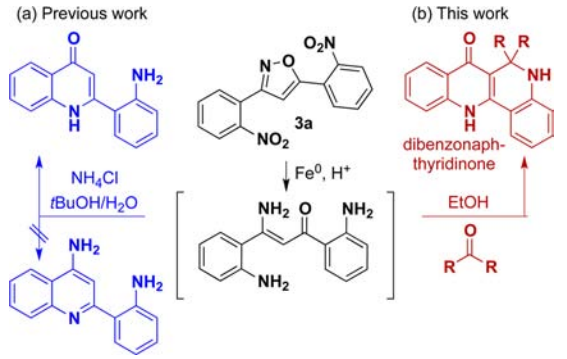



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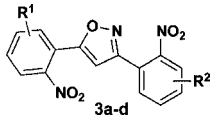
**Table 1. Substituents and Yields for Alkyne/Nitrile Oxide 1,3-Dipolar Cycloadditions Yielding Isoxazoles 3a−d**




| compound | $R^1$ | $R^2$ | yield (%) |
|---|---|---|---|
| **3a** | H | H | 76 |
| **3b** | H | 4-Cl | 40 |
| **3c** | 4-OMe | H | 43 |
| **3d** | 4-OMe | 5-Cl | 20 |

iodo-2-nitrobenzene and 2-nitrobenzaldehyde precursors (Table 1; see the Supporting Information for full details).[3,11]

Isoxazoles **3a−d** were then reduced using $Fe^0$ in neat acetic acid at 90 °C to ultimately give **5a−d**, but in low yields.[12] It was determined that the reduction to **4a−d** and subsequent condensation can be carried out in a one-pot "domino" fashion, wherein acetone is added at the start of the reduction reaction. However, under these conditions the yield remained low. Fortunately, neat acetone dissolution of crude **4a−d** from the worked up reduction reaction followed by heating to 90 °C (8 h, sealed tube) delivered **5a−d** in moderate to excellent yields (Scheme 2 and Table 2). The combination of electron-rich and

**Scheme 2. Reduction of Isoxazoles 3a−d to Quinolinones 4a−d Followed by Condensation with Acetone Delivers DBNs 5a−d**

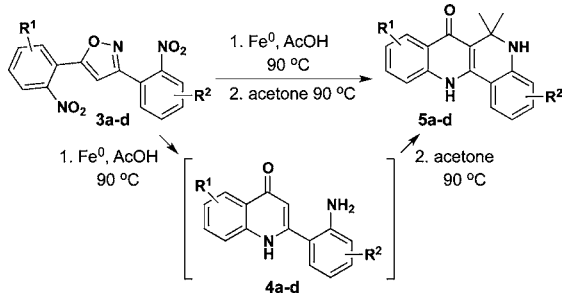



**Table 2. Substituents and Yields for DBNs 5a−d**

| compound | $R^1$ | $R^2$ | yield (%) |
|---|---|---|---|
| **5a** | H | H | 89 |
| **5b** | H | 4-Cl | 80 |
| **5c** | 4-OMe | H | 92 |
| **5d** | 4-OMe | 5-Cl | 33 |

-poor substituents in **3d** likely contributes to the low yield of **5d** (push−pull delocalization would be expected to decrease the reactivity of **4d**). The structure of compound **5a** was unambiguously assigned by X-ray diffraction (Figure 1).

A thorough workup of the **3** → **4** reaction prior to heterocyclization with non-acetone ketones (→ **5a**) is critical, as any carryover iron species and acetic acid lead to in situ formation of acetone,[12] which then competes with the added ketone. Indeed, following removal of all iron species/acetic acid, both cyclohexanone and *N*-boc-piperidinone successfully condensed with intermediate **4a** leading to DBNs **6** and **7** (Scheme 3).

While several additional ketones (most notably acetophenone), aldehydes,[13] and 1,1-dihaloalkanes were examined as

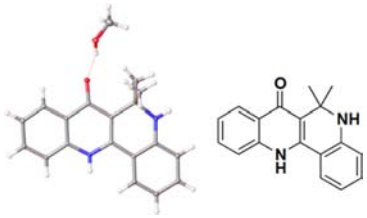
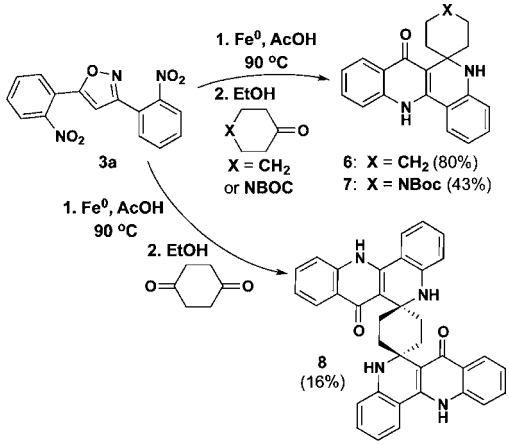



**Figure 1.** Thermal ellipsoid plot (30% probability) of **5a** with a final *R* value of 3.35% (monoclinic space group $P2_1$).

**Scheme 3. Reduction of Isoxazole 3a Followed by Addition of Various Electrophiles To Yield 6, 7, and 8**




added electrophiles in the reaction with **4**, the products were, in each case, observable in the crude reaction mixture via LCMS but not isolable in pure form. For example, after workup and column chromatography, the product from the acetophenone reaction was obtained in ∼10% yield and was still impure as judged by $^1$H NMR analysis. Table 3 provides representative examples of electrophiles that do not react effectively with intermediate **4**.

**Table 3. Electrophile Limitations in Reactions of Intermediate 4**

| electrophile | concluding result |
|---|---|
| acetophenone<br>2-pentanone | trace product via LCMS; intractable |
| benzaldehyde<br>propionaldehyde<br>formaldehyde | mixture of products; intractable (see footnote 13) |
| $CH_2I_2$ | trace product via LCMS; intractable |
| acetyl chloride | amide from reaction with **4**; determined via LCMS |

Lastly, the quinolinone → DBN heterocyclization reaction was also conducted with 1,4-cyclohexanedione in an attempt to isolate the bis-heterocyclization product. While the reaction afforded desired product **8** in low yield (16%, Scheme 3), it was intriguingly obtained as a single diastereomer. The remainder of the crude reaction mixture was composed of 4-quinolinone intermediate **4a**, and the condensation product, of 1,4-cyclohexanedione with only 1 equiv of **4a** (as determined by LCMS).

The structure of **8** was unambiguously verified by X-ray crystallography (Figure 2). Interestingly, the *N,N-trans* diaster-



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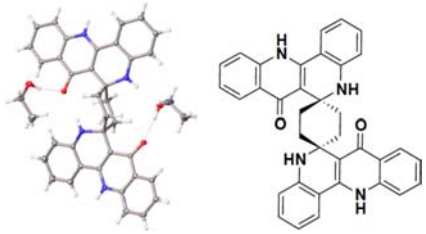

**Figure 2.** Thermal ellipsoid plot (30% probability) of **8** with a final $R$ value of 5.99% (monoclinic space group $P2_1/c$).

eomer obtained in this bis-heterocyclization reaction possesses an intramolecular hydrogen bond in the solid state (Figure 2), which is precluded in the *N,N-cis* diastereomer. This difference perhaps partially explains the observed diastereoselectivity as this hydrogen bond may stabilize the transition state structure leading to **8**. In a thermodynamic sense, the *N,N-trans* diastereomer is 12.4 kcal/mol lower in energy than the *N,N-cis* counterpart as determined by density functional theory (DFT) calculations,[14] indicating that the *N,N-trans* species is also the thermodynamic product.

Having observed fluorescence and solvatochromism with these DBNs during the course of this investigation (Figure 3), we also

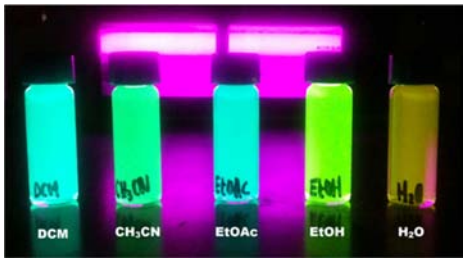


**Figure 3.** Compound **5a** in five different solvents (ranging from relatively nonpolar DCM to highly polar $H_2O$) under long wavelength UV light (365 nm) displaying intense solvatochromism (photo taken with 3 megapixel camera; color unaltered).

explored their photophysical properties. Four compounds (**5a**–**d**) were chosen as candidates for experimental and theoretical study, as they collectively represent electronically neutral (**5a**), skewed (**5b**/**5c**), and push–pull (**5d**) systems. By employing these four systems, this study spanned a range of electronic combinations and thus allowed determination of the relative significance of electronic effects on this system's photophysical properties. The $\lambda_{max}^{excitation}$, $\lambda_{max}^{emission}$, Stokes shift, fluorescence efficiency, and fluorescence lifetime for each of these four DBNs in various solvents can be found in the Supporting Information. An n → $\pi^*$ transition in the visible region (e.g., **5a**: 382–416 nm experimental; 406–417 nm calculated) is proposed as the $\lambda_{max}^{excitation}$ responsible for the variable $\lambda_{max}^{emission}$ observed. The $\lambda_{max}^{excitation}$ and $\lambda_{max}^{emission}$ are dependent upon their environment, as evidenced by the observed solvatochromism of these DBNs (Figure 3). It is noteworthy that a red shift in $\lambda_{max}^{excitation}$ is observed for each compound **5a**–**d** as the polarity of the solvent increases. Moreover, when considering the **5a**–**d** compound series in a given solvent, push–pull compound **5d** always displayed the largest red shift in $\lambda_{max}^{excitation}$ relative to the neutral species **5a** (note: the magnitude of the $\lambda_{max}^{excitation}$ shift increases as solvent polarity increases). The fluorescence lifetimes for these DBNs are also increased in more polar solvents, most so in DMSO (2.02 ns in $CCl_4$ vs 12.05 ns in DMSO). These observed increases in lifetime are attributed to explicit solvent interactions that selectively stabilize the excited state.[15] The longest lifetime observed was 12.05 ns for **5a** in DMSO.

The relative fluorescence efficiency was also sensitive to solvent environment and was highest in THF and lowest in water. Lippert–Mataga plots were generated to correlate the Stokes shift to the orientation polarizability of the various solvents (for a summary of all photophysical properties in all solvents, see the Supporting Information). The $\lambda_{max}^{emission}$ of **5a** shifts a striking 3623 $cm^{-1}$ in $CCl_4$ (460 nm) versus water (552 nm). The largest Stokes shift observed was 8062 $cm^{-1}$ (552 nm) for compound **5a** in water. Lastly, these experimental results were compared to calculations performed using time dependent-density functional theory (TD-DFT), which is effective at predicting and replicating the photophysical properties of cyclic azacyanines and other cyclic conjugated heterocyclic systems.[16] The UV–vis spectra of **5a**–**d** were computed for structures optimized with *Gaussian09*[17] using B3LYP/6-31+G(d,p)[18] and the SMD implicit solvent model.[19] Excluding water, which is difficult to model due to explicit solute–solvent interactions,[16] linear correlations between computed and experimental data were developed [**5a** $R^2$ = 0.69 (see Figure 4); **5b** $R^2$ = 0.68; **5c** $R^2$ = 0.64; **5d** $R^2$ = 0.43 (see

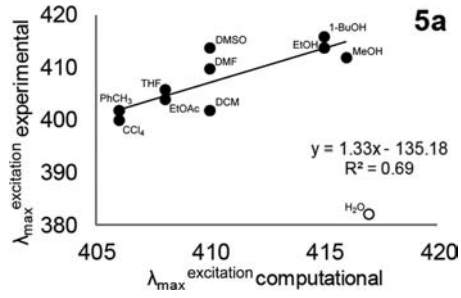


**Figure 4.** Correlation of experimental and computed $\lambda_{max}^{excitation}$ for **5a**. The $R^2$ value shown was determined without inclusion of the data point for water.

Supporting Information)].[20] Although these correlations are not strong, they do indicate a reproduceable trend in the data: a red shift in the $\lambda_{max}^{excitation}$ observed when nonpolar to polar solvents are considered.

In summary, a new route to dibenzonaphthyridinones (DBNs) has been developed, and the photophysical properties of these compounds were evaluated both experimentally and computationally. The reported DBNs are highly solvatochromic with $\lambda_{max}^{emission}$ varying by as much as 3623 $cm^{-1}$ in $CCl_4$ versus water. The lifetime of fluorescence of these DBNs is also highly solvent dependent, varying over a range of 10 ns based on solvent polarity, with shorter lifetimes in nonpolar solvents. Lastly, we have shown that TD-DFT provides reasonable predictions of the $\lambda_{max}^{excitation}$ for these heterocycles. DBNs that have the potential to both bind biological targets and express useful optical properties, which may find application as tools for probing and visualizing the polarity of various biological environs.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02680.

Experimental and computational details (PDF)
Crystallographic data for **5a** (CIF)
Crystallographic data for **8** (CIF)



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### Author Contributions

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### Notes

The authors declare no competing financial interest.

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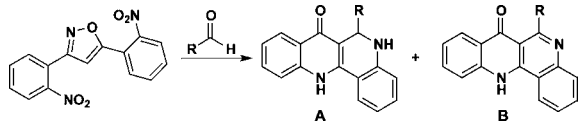
(13) Aldehydes, while reactive with **4**, produce two products, the dihydro species **A** plus the oxidized aromatic species **B**, and these mixtures proved very difficult to resolve/purify; consequently, attempts to obtain spectra of publication quality resulted in very low yields. In the case of benzaldehyde, a resolvable spectrum yet impure sample of the B analogue was obtained (<10% yield). The A analogue, while detected in the crude reaction mixture, was not isolated in pure form. Though several aliphatic aldehydes (including formaldehyde) were attempted, the product mixtures proved to be intractable.




(14) The *N,N-cis* and *N,N-trans* diastereomers were optimized using B3LYP/6-31+G(d,p) in the gas phase and were determined to be minima on the basis of results from frequency calculations. Free energies are presented in kcal/mol. For additional details, references to computational methods, atomic coordinates, and energies, see the Supporting Information.

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(20) Solvent specific correlations can be found in the Supporting Information. In the case of nonpolar solvents (e.g., $CCl_4$), excellent correlations between experiment and theory are obtained using the SMD solvation model ($R^2$ = 0.90 for $CCl_4$). In the case of polar or protic solvents, this correlation is not observed, as the SMD model is inherently unable to predict explicit solvent interactions ($R^2$ = 0.00 for EtOH).




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