Title

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

Journal

Organic Letters, 17(23)

ISSN

1523-7060

Authors

Palazzo, Teresa A
Patra, Digambara
Yang, Joung S
et al.

Publication Date

2015-12-04

DOI

10.1021/acs.orglett.5b02680

Peer reviewed

HHS Public Access

Author manuscript

Org Lett. Author manuscript; available in PMC 2016 December 04.

Published in final edited form as:

Org Lett. 2015 December 4; 17(23): 5732–5735. doi:10.1021/acs.orglett.5b02680.

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

Teresa A. Palazzo[‡,[a]], **Digambara Patra**[Δ,[b]], **Joung S. Yang**[Ψ,[a]], **Elsy El Khoury**[Ψ,[b]], **Mackenzie G. Appleton**[Ψ,[a]], **Makhluf J. Haddadin**[Δ,[b]], **Dean J. Tantillo**[*,[a]], and **Mark J. Kurth**[*,[a]]

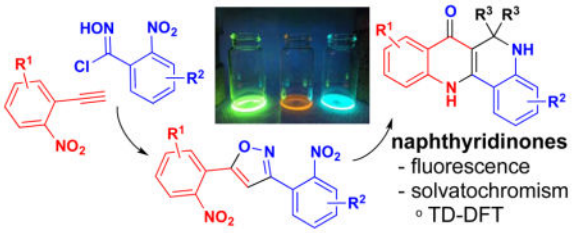
[a]Department of Chemistry, University of California, Davis, One Shields Avenue, Davis CA 95616

[b]Department of Chemistry, American University of Beirut, Beirut, Lebanon

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 λ_{max} of excitation for DBNs with varying electronic character.

Graphical abstract



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 positioin,

[*]Corresponding Authors: mjkurth@ucdavis.edu and djtantillo@ucdavis.edu.

[‡]T.A.P. is the primary author.

[Δ]D.P. and M.J.H. contributed equally.

[Ψ]J.S.Y., M.G.A., and E.E.K. contributed equally.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

The authors declare no competing financial interest.

Supporting Information

Supporting information for this manuscript (including experimental, computational, and crystallographic details) is available online at www.ACS.org.

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 chage in the polarity of the medium.” [5] It has been demonstrated that solvatochromic materials make intruiging 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 additon 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,2b,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-iodo-2-nitrobenzene and 2-nitro-benzaldehyde precursors (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 electron-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 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 ineffectively react with intermediate **4**.

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 one equivalent of **4a** (as determined by LCMS).

The structure of **8** was unambiguously verified by X-ray crystallography (Figure 2). Interestingly, the *N,N-trans* diastereomer 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 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→π* 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} for compound **5a**. 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 Supporting Information).[20] Although these correlations are not strong, they do indicate a reproduceable trend in the data: a redshift in the $\lambda_{max}^{excitation}$ observed when non-polar 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 $\lambda_{max}^{excitiation}$ for these heterocycles. DBNs that have both the potential to bind biological targets and to express useful optical properties may find application as tools for probing and visualizing the polarity of various biological environs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

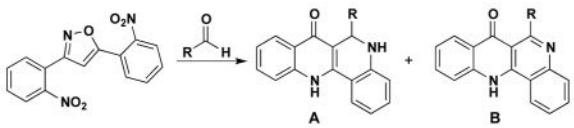
The authors dedicate this work in memory of Esther M. Kurth (Baum Harmon Mercy Hospital), a wonderful and gracious mentor. Financial support provided by the NIH (DK072517 and GM089153), the NSF (XSEDE program), and the Tara K. Telford Fund (fellowship to T.A.P.). We thank Department of Chemistry/University of California, Davis scientists Dr. Kelli M. Farber, Dr. Keith C. Coffman, and Dr. Chris S. Hamann for insightful discussions as well as Dr. Marilyn M. Olmstead and Mr. Jeremy D. Erickson for their assistance in preparing the crystallographic data for publication.

References

1. a) Galloway WRJD, Isidro-Llobet A, Spring DR. Nat Commun. 2010; 1:1–13. [PubMed: 20975674] b) Schreiber SL. Science. 2000; 287:1964–1968. [PubMed: 10720315] c) Burke MD, Schreiber SL. Angew Chem Int Ed. 2004; 43:46–48.d) Tan DS. Nat Chem Biol. 2005; 1:74–84. [PubMed:

16408003] e) Spandl RJ, Bender A, Spring DR. Org Biomol Chem. 2008; 6:1149–1158. [PubMed: 18362950]

2. a) Jensen S, Torssell KBG. Acta Chem Scand. 1995; 49:53–56.b) Sakamoto T, Kondo Y, Uchiyama D, Yamanaka H. Tetrahedron. 1991; 28:5111–5118.c) Coffman KC, Duong V, Bagdasarian AL, Fettinger JC, Haddadin MJ, Kurth MJ. Eur J Org Chem. 2014; 34:7651–7657.d) Piccionello AP, Buscemi AGS, Vivona N, Pace A. J Org Chem. 2010; 75:8724–8727. [PubMed: 21080723] e) Coffman KC, Hartley TP, Dallas JL, Kurth MJ. ACS Comb Sci. 2012; 14:280–284. [PubMed: 22352295]
3. Coffman KC, Palazzo TA, Hartley TP, Fettinger JC, Tantillo DJ, Kurth MJ. Org Lett. 2013; 15:2062–2065. [PubMed: 23557405]
4. a) Avetisyan AA, Aleksanyan IL, Ambartsumyan LP. Russ J Org Chem. 2007; 43:1052–1057.b) Li G, Zhu D, Xue L, Jiang H. Org Lett. 2013; 15:5020–5023. [PubMed: 24040756] c) Moszew J, Bala M, Sledziwska E. Pol J Chem. 1996; 4:621–628.d) Moszew J, Sledzieweska E. Bull Acad Pol Sci Ser. 1964; 7:447–450.e) Moszew J, Zankowska-Jasinka W. Bull Acad Pol Sci Ser. 1964; 7:455–458.
5. McNaught, AD.; Wilkinson, A. IUPAC Compendium of Chemical Terminology, 2nd ed. (the “Gold Book”). Blackwell Scientific Publications; Oxford: 1997. XML on-line corrected version: http://goldbook.iupac.org (2006) created by Nic, M., Jirat, J., Kosata, B., updates compiled by Jenkins, A
6. a) Cohen BE, McAnaney TB, Park ES, Jan YN, Boxer SG, Jan LY. Science. 2002; 296:1700–1703. [PubMed: 12040199] b) Sun KM, McLaughlin CK, Lantero RA, Manderville. J Am Chem Soc. 2007; 129:1894–1895. [PubMed: 17256942] c) Silva MAD, Seoud OAE, Areas EPG. J Mol Struct. 2007; 841:51–60.d) Yamaguchi EDR, Wang C, Fukazawa A, Taki M, Sato Y, Sasaki T, Ueda M, Sasaki N, Higashiyama T, Yamaguchi S. Angew Chem Int Ed. 2015; 54:4539–4543.
7. Miolo G, Moro S, Venaldi D, Caffieri S, Guiotto A, Dall’Acqua F. Il Farmaco. 1999; 54:551–561. [PubMed: 10510852]
8. Cecchetti V, Fravolini A, Sabatini S, Tabarrini O, Xin T. Eur J Med Chem. 1998; 33:899–903.
9. Johnson DS, Choi C, Fay LK, Favor DA, Repine JT, White AD, Akumme HC, Fitzgerald L, Nicholls K, Snyder BJ, Whetzel SZ, Zhang L, Serpa KA. Bioorg Med Chem Lett. 2011; 21:2621–2625. [PubMed: 21353774]
10. a) Bloomfiel DG, Partridge MW, Vipond HJ. J Chem Soc C. 1970; 19:2647–2653.b) Moszew J, Sulko S. Zeszyty Nauk Uniw Jagiel, Ser Nauk Chem. 1962; 7:151–160.c) Moszew J, Zankowska-Jasinka W. Bull Acad Pol Sci Ser. 1964; 6:403–406.d) Anet R. Can J Chem. 1959; 37:43–47.e) Mysona M. Rocz Chem. 1952; 26:44–50.f) Sutko S. Rocz Chem. 1951; 25:174–182.g) Kermack WO, Storey NE. JChem Soc. 1951; 0:1389–1392.h) de Diesbach H, Klement O. Helv Chim Acta. 1941; 24:158–173.i) Hope E, Anderson JS. J Chem Soc. 1936:1474–1478.j) Backeberg OG. J Chem Soc. 1933; 0:390–391.k) Jensen S, Torssell KBG. Acta Chem Scan. 1995; 49:53–56.
11. Guggenheim KG, Butler JD, Painter PP, Lorsbach BA, Tantillo DJ, Kurth MJ. J Org Chem. 2011; 76:5803–5812. [PubMed: 21650164]
12. Allen AC, Stevenson ML, Nakamura SM, Ely RA. J Forensic Sci. 1992; 37:301–322.
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. Only in the case of benzaldehyde was a resolvable spectrum yet not completely pure sample obtained for the **B** analog (<10% yield; the **A** analog, 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/6-31G(d,p) in the gas phase and 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.

15. a) Mataga, N.; Kubota, T. Molecular Interactions and Electronic Spectra. Marcel Dekker; New York: 1970. p. 371-410.b) Liptay, W. Excited States. Lim, EC., editor. Academic Press; New York: 1974. p. 129-229.
16. a) Jacquemin D, Perpete EA, Scuseria GE, Ciofini I, Adamo C. J Chem Theory Comput. 2008; 4:123–135. [PubMed: 26619986] b) Laurent AD, Jacquemin D. Int J Quantum Chem. 2013; 113:2019–2039.c) Patra D, Palazzo TA, Malaeb NN, Haddadin MJ, Tantillo DJ, Kurth MJ. J Fluoresc. 2014; 24:1285–1296. [PubMed: 24910112]
17. Frisch MJ, et al. Gaussian09, Revision B.01. 2009Gaussian, IncWallingford CT(for full *Gaussian09* reference please see the Supporting Information).
18. a) Becke ADJ. J Chem Phys. 1993; 98:1372–1377.b) Becke ADJ. J Chem Phys. 1993; 98:5648–5652.c) Lee C, Yang W, Parr RG. Phys Rev B. 1988; 37:785–789.d) Stephens PJ, Devlin FJ, Chabalowski CF, Frisch MJ. J Phys Chem. 1994; 98:11623–11627.e) Tirado-Rives J, Jorgensen WL. J Chem Theory Comput. 2008; 4:297–306. [PubMed: 26620661]
19. a) Kelly CP, Cramer CJ, Truhlar DG. J Chem Theory Comput. 2005; 1:1133–1152. [PubMed: 26631657] b) Manerich AV, Olson RM, Kelly CP, Cramer CJ, Truhlar DG. J Chem Theory Comput. 2007; 3:2011–2033. [PubMed: 26636198] c) Manerich AM, Cramer CJ, Truhlar DG. J Phys Chem B. 2009; 113:6378–6396. [PubMed: 19366259]
20. Solvent specific correlations can be found in the Supporting Information. In the case of non-polar 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).

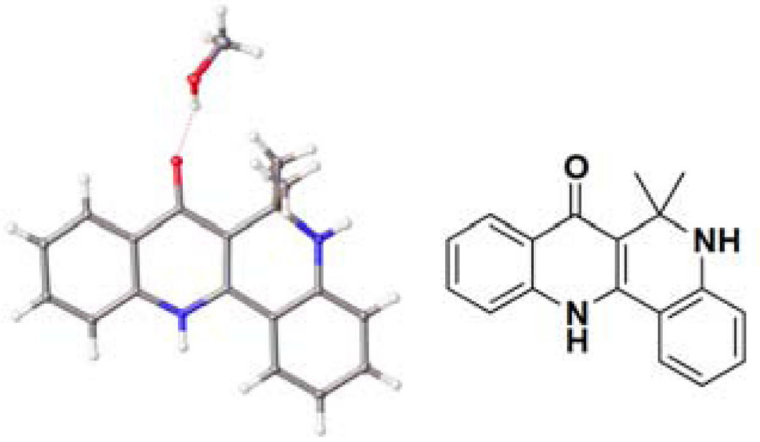


Figure 1.

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

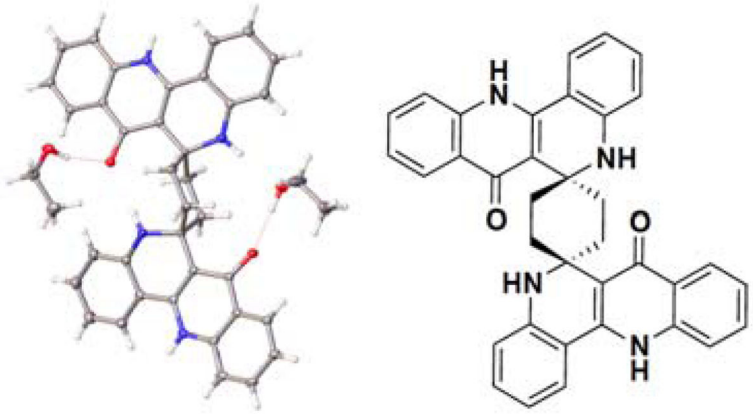


Figure 2.
Thermal ellipsoid plot (30% probability) of **8** with a final R value of 5.99% (monoclinic space group $P2_1/c$).

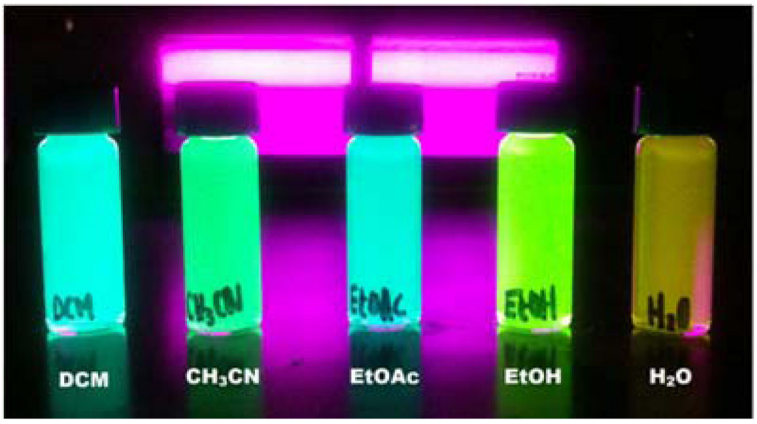


Figure 3.

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).

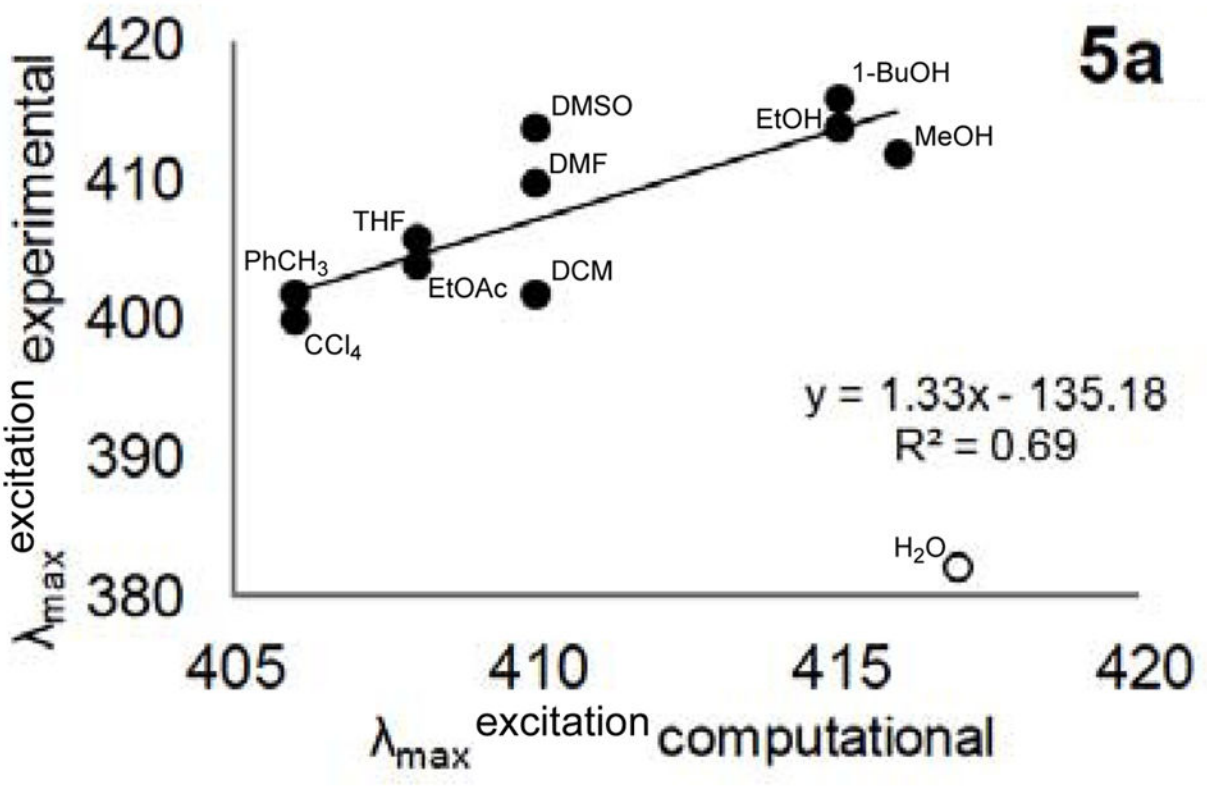
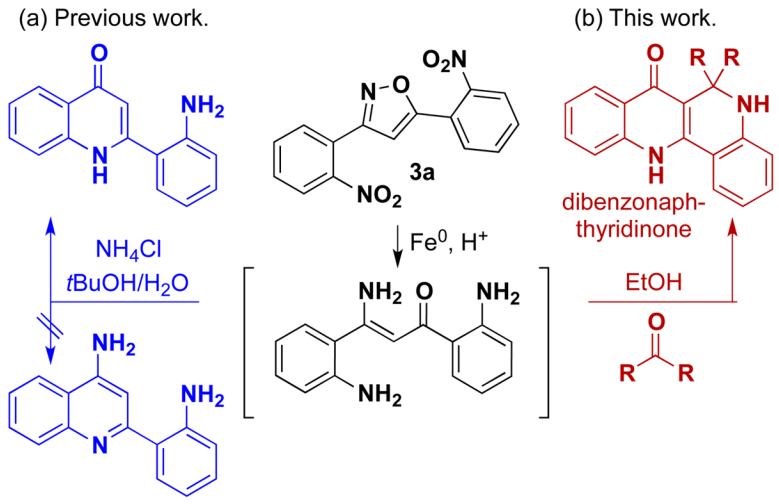


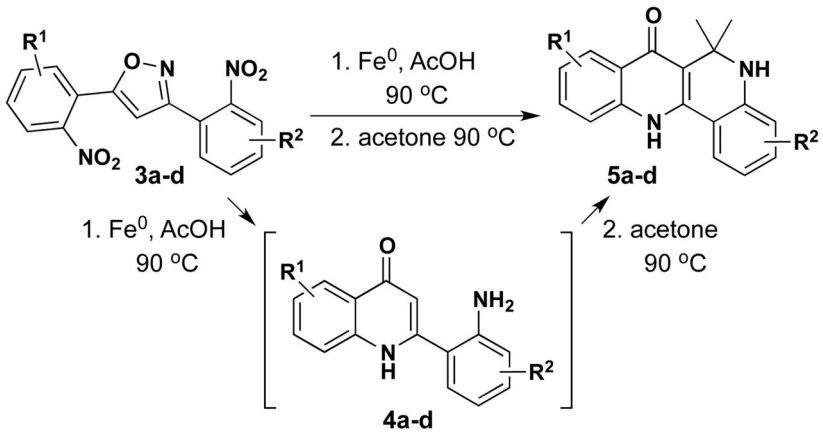
Figure 4.

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.



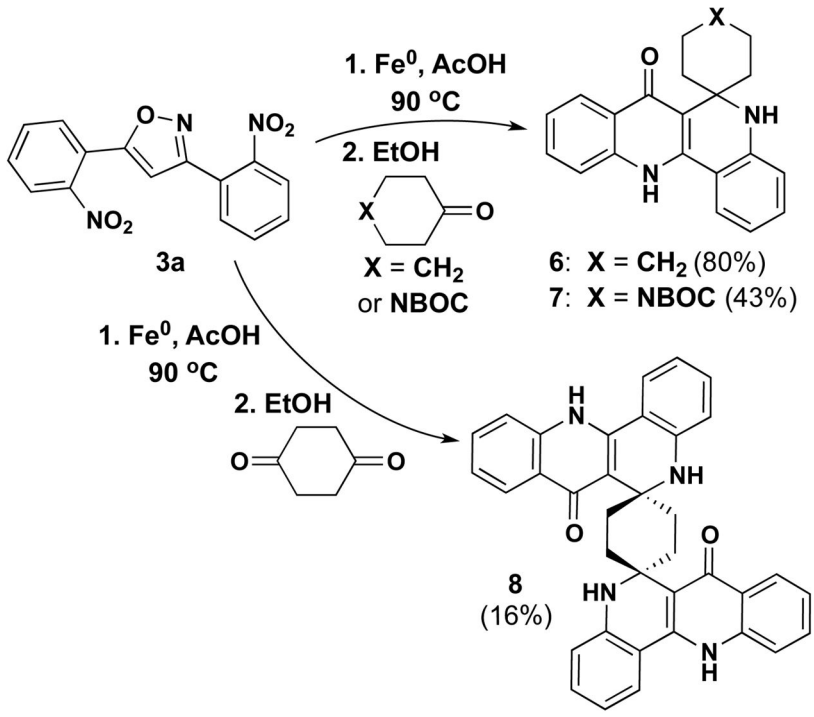
Scheme 1.

Previous[(a)] and current[(b)] reductive 3,5-bis-*o*-nitro-phenyl substituted isoxazole methodology.



Scheme 2.

Reduction of isoxazoles **3a**–**d** to quinolinones **4a**–**d** followed by condensation with acetone delivers DBNs **5a**–**d**.

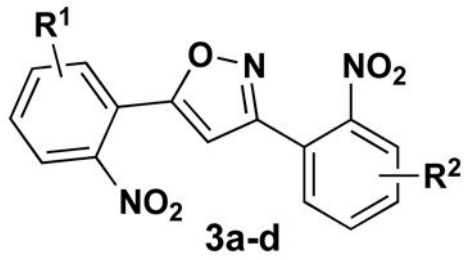


Scheme 3.

Reduction of isoxazole **3a** followed by addition of various electrophiles to yield **6**, **7** and **8**.

Table 1

Substituents and yields for alkyne/nitrile oxide 1,3-dipolar cycloadditions yielding isoxazoles **3a–d**.



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

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

Table 3

Electrophile limitations in reactions of intermediate **4**.

electrophile	**concluding result**
acetophenone 2-pentanone	trace product via LCMS-intractable
benzaldehyde propionaldehyde 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