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Synthesis of New BODIPY Analogs

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Abstract

This report examines the synthesis of new ligands based upon dipyrazolylmethane and diindazolylmethane. The goal of these modifications is to increase the acidity of the proton on the methyl carbon to allow for deprotonation. The ligands synthesized were dipyrazolylphenylmethane and diindazolylphenylmethane, as well as modifications of the latter. The products were analyzed by NMR spectroscopy and one crystal structure was obtained of diindazolylphenylmethane.

1. Introduction

BODIPY compounds are based upon modification of a 4,4- difluoro-4-bora-3a,4a-diaza-s-indacene core (Figure 1).[1] The molecules have a variety of uses ranging from biomolecular labels[2] to photodynamic therapy due to their fluorescence.[3] Much research has been performed based upon modifying the BODIPY core to achieve desirable properties.

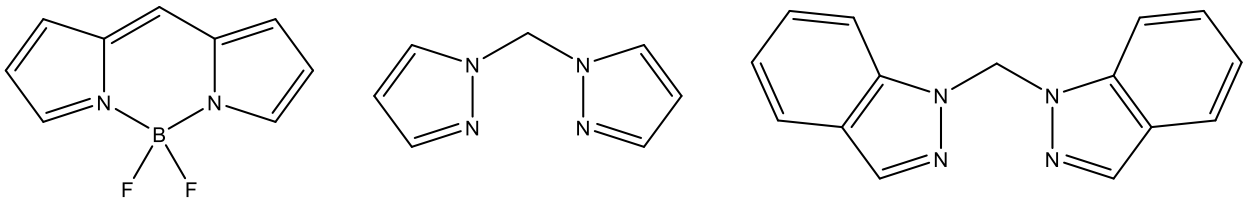


Figure 1: BODIPY core (left), dipyrazolylmethane (center), diindazolylmethane (right).

There are many derivatives of the BODIPY core molecule, however nearly all use the pyrrole based core as opposed to the pyrazole based core.[2] Some work has been done on a pyrazole analog.[4] This report seeks to expand on this research by synthesizing modified versions of the dipyrazolylmethane synthesized previously. Of most interest in this project is modifications of the diindazolylmethane in order to increase the acidity of protons on the methane carbon. These modifications include addition of phenyl groups to the methane carbon to increase the stability of the carbanion intermediate.

2. Experimental

General Information: All reagents and starting materials were purchased from commercial vendors and used without further purification. NMR spectra were recorded on a 300 MHz spectrometer, chemical shifts were given in ppm relative to residual solvent

resonances (^{1}H NMR spectra). X-ray data were collected from a Bruker CCD-based diffractometer with dual Cu/Mo microfocus optics.

Attempted synthesis of dipyrazolylphenylmethane (**1**)

A mixture of 2 equivalents of pyrazole (0.200 g, 2.94 mmol) and 10 equivalents of benzyl chloride (2.365 g, 18.68 mmol) were mixed in toluene with $NBuHSO_4$ (50. mg) and NaOH (5.00 g) in 5 mL water and refluxed for 24 hours. The desired product was not able to be isolated.

Attempted alternative synthesis of dipyrazolylphenylmethane (**1**)

A mixture of 2 equivalents of pyrazole (0.895 g, 13.1 mmol), 1 equivalent of benzaldehyde dimethyl acetal (1.000 g, 6.571 mmol), and 1/20 equivalents of p-toluenesulfonic acid were refluxed in toluene using a Dean-Stark apparatus according to a literature synthesis.[5] The desired product was not able to be isolated.

Synthesis of diindazolylphenylmethane (**2**)

A mixture of 2 equivalents of indazole (2.000 g, 16.90 mmol), 1 equivalent of benzaldehyde (0.898 g, 8.46 mmol), 1/20 equivalents of zinc chloride (0.0576 g), and 5 Å molecular sieves were refluxed for 24 hours in dichloromethane. The solution was filtered and allowed to evaporate. Crystals were obtained and characterized by NMR and X-ray crystallography (**Figures 2, 3**). NMR spectrum and X-ray data were obtained by Briana Schrage. ^{1}H NMR ($CDCl_3$, ppm) 7.15 (4 H), 7.40 (5 H), 7.55 (2 H), 7.72 (2 H), 8.11 (2 H), 8.53 (1 H).

Synthesis of diindazolylperfluorophenylmethane (**3**)

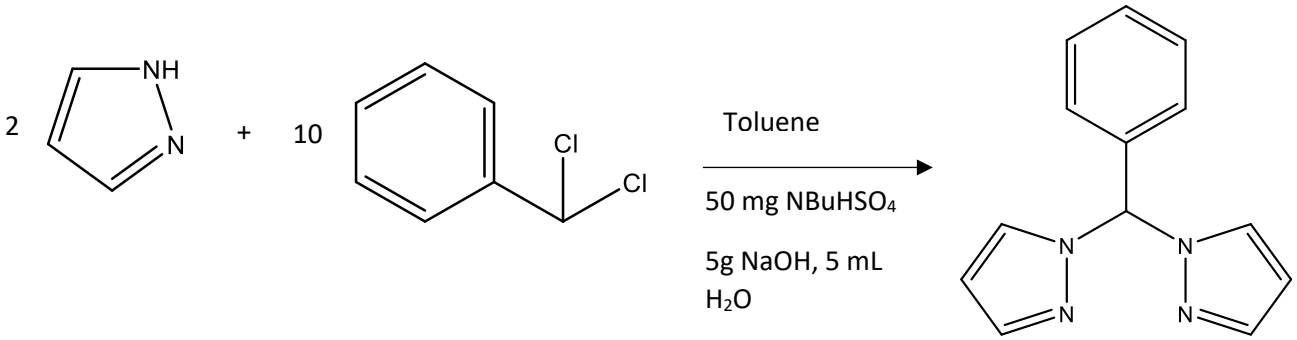
A mixture of 2 equivalents of indazole (2.000 g, 16.9 mmol), 1 equivalent of perfluorobenzaldehyde (1.660 g, 8.467 mmol), 1/20 equivalents of zinc chloride (0.0576 g), and 5 Å molecular sieves were refluxed for 24 hours in dichloromethane. The solution was filtered and allowed to evaporate. Characterization showed a mixture of starting materials suggesting the synthesis was unsuccessful.

Synthesis of diindazolyl-p-chlorophenylmethane (**4**)

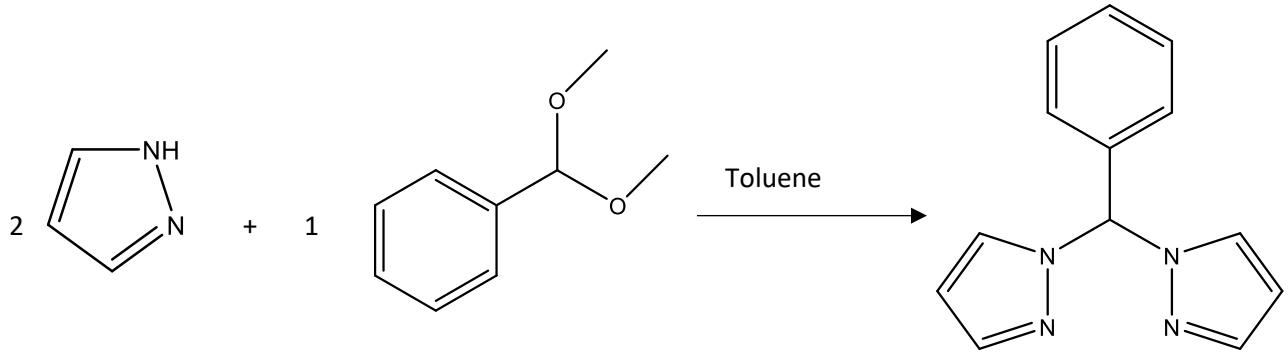
A mixture of 2 equivalents of indazole (0.200 g, 1.69 mmol), 1 equivalent of p-chlorobenzaldehyde (0.119 g, 0.847 mmol), 1/20 equivalents of zinc chloride (5.8 mg), and 5 Å molecular sieves were refluxed for 24 hours in dichloromethane. The solution was filtered and allowed to evaporate. Characterization showed a mixture of starting materials and desired product. Further purification is required to isolate the desired product.

3. Results and Discussion

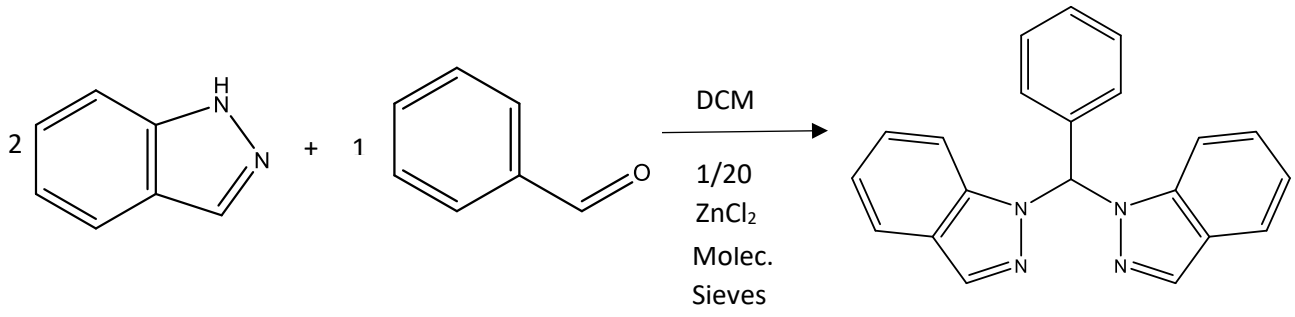
A total of five syntheses were attempted in this experiment. These were the syntheses of dipyrazolylphenylmethane from benzyl chloride as well as from benzaldehyde dimethyl acetal (Schemes 1, 2), diindazolylphenylmethane (Scheme 3), diindazolylperfluorophenylmethane (Scheme 4), and diindazolyl-p-chlorophenylmethane (Scheme 5).



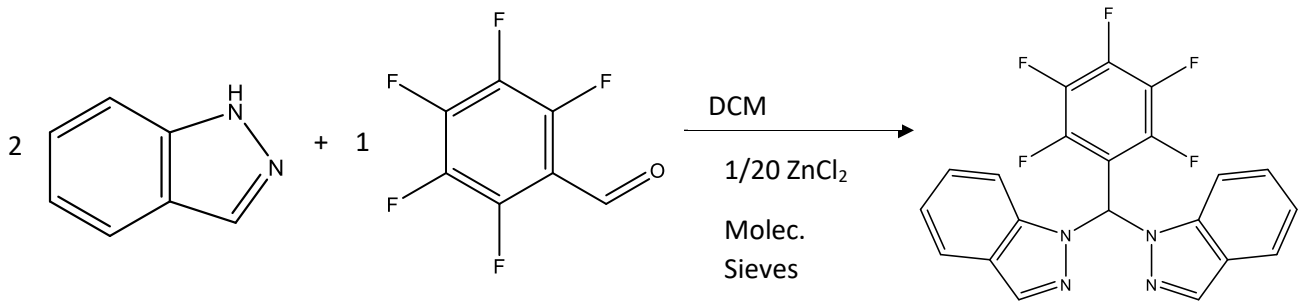
Scheme 1: Synthesis of **1**, pyrazole (left), benzyl chloride (middle), dipyrazolylphenylmethane (right).



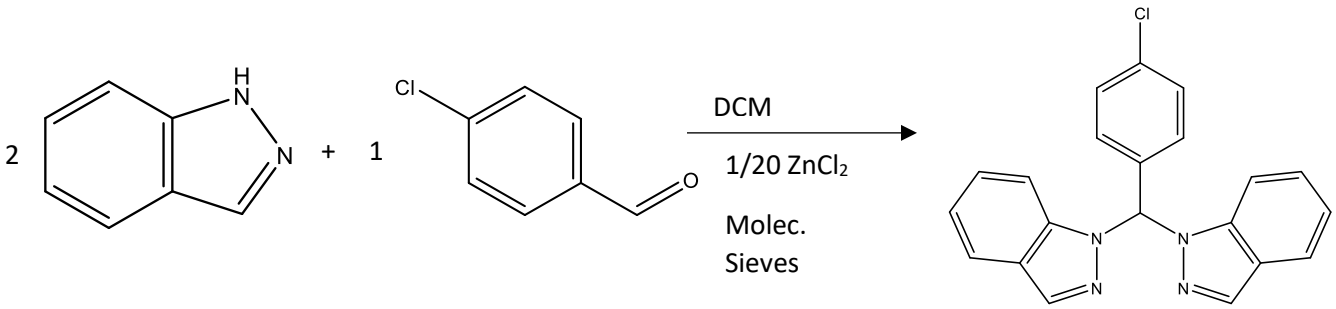
Scheme 2: Synthesis of **1**, pyrazole (left), benzaldehyde dimethyl acetal (center), dipyrazolylphenylmethane (right).



Scheme 3: Synthesis of **2**, indazole (left), benzaldehyde (center), diindazolylphenylmethane (right).



Scheme 4: Synthesis of **3**, indazole (left), perfluorobenzaldehyde (center), diindazolylperfluorophenylmethane (right).



Scheme 5: Synthesis of **4**, indazole (left), p-chlorobenzaldehyde (center), diindazolyl-p-chlorophenylmethane (right).

The syntheses performed in this report achieved a range of success. The reactions attempted with pyrazole were not isolated in this experiment, although **2** has been previously reported.[5] One potential reason for the inability to isolate this compound may be due to limited reaction time, thus preventing the reaction from running to completion. The indazole based reactions saw more success, including isolation of **2** and potentially isolation of **4**. The reason for the lack of characterization and further purification of **4** was due to lack of time to continue the experiment. Further experimentation is required to isolate and fully characterize this

compound. Interestingly, despite a similar reaction mechanism to synthesis of **2**, compound **3** was unable to be obtained, and characterization revealed only starting materials.

Compound **2** was characterized by ^{1}H NMR and X-ray crystallography in Figures **2** and **3**. The solvent used for the NMR spectra was $CDCl_3$. These suggest that the synthesis and isolation of **2** was successful. The crystal structure of this compound has not been previously recorded.[5]

Further research can be performed to attempt complexation of the isolated compound with metals or BF_3. Deprotonation could also be attempted through reaction with a strong base which is not a nucleophile. Finally, more modifications of the dipyrazolylmethane and diindazolylmethane ligands could be synthesized, which potentially could increase acidity of the methyl proton(s).

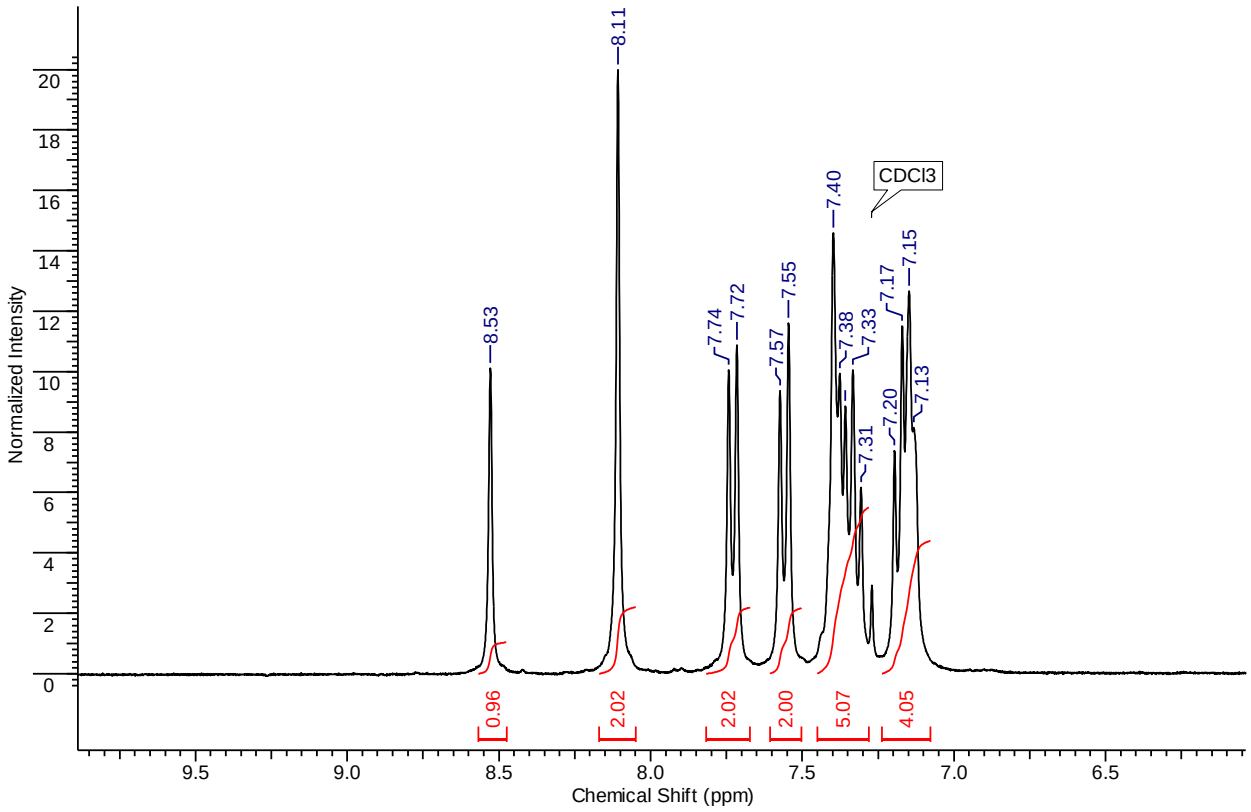


Figure 2: ^{1}H NMR spectrum of **2**. $CDCl_3$ was used as the solvent.

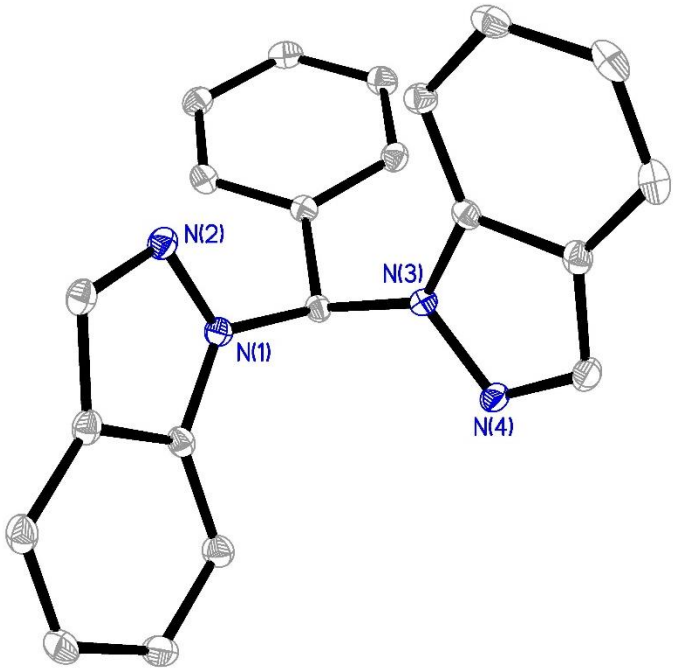


Figure 3: X-ray crystal structure obtained of compound **2**. Table 1 contains data and parameters regarding the measurement. Hydrogen atoms omitted for clarity.

Compound	**Bisindazole_benzaldehyde**
Emp. form	$C_{21}H_{16}N_4$
Form. weight	324.38
Crystal system	monoclinic
Space group	P21/n
a/ Å	10.297(11)
b/ Å	12.315(14)
c/ Å	13.049(14)
α(°)	90
β(°)	101.703(15)
γ(°)	90
Volume ($Å^3$)	1620.00(5)
Z	4
Dc (Mg/m^3)	1.330
μ (mm^{-1})	0.081
F(000)	680
Reflections collected	16370
Data/Restraints/Parameters	4014 / 0 / 226
GOF on F^2	1.035
R1 (on F_o^2, $I > 2\sigma(I)$)	0.0490
wR2 (on F_o^2, $I > 2\sigma(I)$)	0.1054
R1 (all data)	0.0747
wR2 (all data)	0.1180

Table 1: X-ray data collection and structure parameters for compound **2**.

4. Conclusions

Pyrazole and indazole based compounds were used to create a modified BODIPY core. The pyrazole based compound (**1**) could not be isolated. More success was found with the indazole based compounds, including characterization by NMR and X-ray crystallography of compound **2**. Synthesis of **3** was unsuccessful, and **4** achieved mixed results and requires more experimentation. Further research is required to attempt deprotonation and complexation of these compounds.

(1) Ulrich, G.; Ziessel, R.; Harriman, A. *Minireviews* **2008**, 1184–1201.

(2) Ziessel, R.; Harriman, A. *New J. Chem.* **2007**, No. January, 496–501.

(3) Kamkaew, A.; Lim, S. H.; Lee, H. B.; Kiew, L. V.; Chung, L. Y.; Burgess, K. *Chem Soc Rev* **2013**, *42* (1), 1–26.

(4) Gazafy, A. *Exploring New BODIPY Derivatives*; Akron, 2017.

(5) Ballesteros, P.; Elguero, J. *Inst. Química Médica* **1985**, *41* (24), 5955–5963.

Appendix 1

Safety Considerations

Proper safety guidelines were observed at all times in the lab. This includes wearing proper PPE (Personal Protective Equipment) as well as following any and all additional rules set by Dr. Ziegler. PPE worn in the lab includes eye protection and gloves. Additionally, long pants and closed toe shoes were to be worn at all times in the lab. No reagents were to be removed from the lab at any time. All reactions took place inside of a fume hood.