Synthesis and Theoretical Calculation of *p*-Aminostyryl-BODIPY Derivative: *Trans*-Configuration Selectivity of Knoevenagel Condensation Reaction

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Abstract

BODIPY derivatives have become important molecules because of their spectroscopic and biological properties and they have been found some application fields such as florescent sensors, photosensitizer and cellular imaging. To increase the competence of these fields of BODIPYs, an extension of the conjugation is needed. For this purpose, Knoevenagel condensation reaction is generally performed. During this research, the synthesis of BODIPY **10** was achieved by performing Knoevenagel condensation reaction and resulted in the formation of *trans*-configurated styryl-product. In addition to the synthetic performance, we also examine the fate of the stereoselectivity by DFT calculations.

Keywords: BODIPY, Knoevenagel Condensation Reaction, DFT Calculation

p-Aminostiril-BODIPY Türevinin Sentezi ve Teorik Hesaplamalarının Yapılması: Knoevenagel Kondenzasyon Reaksiyonunun *trans*-Konfigürasyon Seçiciliği

Öz

BODIPY türevi malzemeler göstermiş oldukları biyolojik ve spektroskopik özellikleri açısından önemli moleküller haline gelmiş ve fluoresans sensör, fotoduyarlaştırıcı ve hücre görüntüleme gibi bazı uygulama alanları bulmuşlardır. BODIPY türevlerinin göstermiş olduğu bu özelliklerin yetkinliğini artırmak için yapı üzerindeki konjugasyonun artırılması önem arz etmektedir. Bu amaçla uygulanan en yaygın yöntem Knoevenagel kondenzasyon reaksiyonudur. Bu çalışma çerçevesinde, BODIPY **10** molekülünün sentezi Knoevenagel kondenzasyon reaksiyonu ile gerçekleştirilmiş ve *trans*-konfigurasyona sahip ürün elde edilmiştir. Yapılan bu sentetik çalışmaya ilaveten elde edilen *trans*-seçiciliğin kaynağını anlama adına DFT hesaplamaları yapılmıştır.

Anahtar Kelimeler: BODIPY, Knoevenagel Kondenzasyon Reaksiyonu, DFT Hesaplama

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1. Introduction

BODIPY (4,4-Difluoro-4-bora-3a,4a-diaza-*s*-indacene) derivatives take great attention during the last two decades because of their strong UV-absorption, sharp fluorescence peaks, large extinction coefficients and high quantum yields (Loudet & Burgess, 2007). Because of these properties, BODIPY based fluorophores are used in photodynamic therapy (PDT) applications, ion sensor devices, solar radiation harvesting and biomolecule labeling systems (Kostereli, Ozdemir, Buyukcakir, & Akkaya, 2012; Sozmen et al., 2014). BODIPY core structure has an absorbance wavelength at around 500 nm. Modification of the BODIPY structure with electron-donating or withdrawing groups can change the fluorescence characteristic of BODIPY to the desired direction (Kolemen et al., 2011; Loudet & Burgess, 2007). The bathochromic shift to the longer wavelength is generally explored the point of the BODIPY core and improve the efficiency of some applications such as PDT (Zhu et al., 2012). Extension of the conjugation on the BODIPY core, bathochromically shifts absorption and fluorescence emission bands. Thus, a substation of BODIPY with having π-conjugated systems becomes a more important effort for this purpose. The "Knoevenagel Condensation Reaction" is the most applied method for the π-bonds extension of the BODIPY structure. Knoevenagel condensation reaction is a modified type of aldol condensation reaction. An aldehyde or ketone reacts with activated methyl or methylene groups in the presence of organic amine as the organocatalyst to yield a substituted olefin (Knoevenagel, 1898). For the substitution of BODIPY, Knoevenagel reaction takes place at the position of the most acidic position of the BODIPY core, 3- and 5-
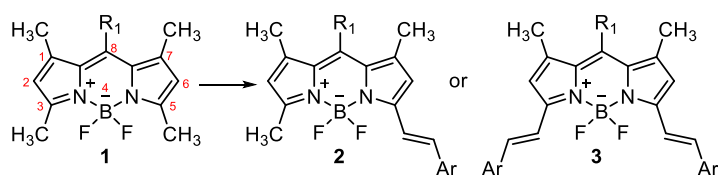
methyl substituent (Loudet & Burgess, 2007)

Figure 1. Knoevenagel Reaction of BODIPY Derivatives

(Figure 1). This type of reaction generally yields in the formation of *trans*-configurated styryl-products. The focus of this study, synthesis a 3-*p*-aminostyryl-BODIPY derivative and examine the fate of the *trans*-configuration product formation by performing the theoretical calculation.

2. Material and Methods
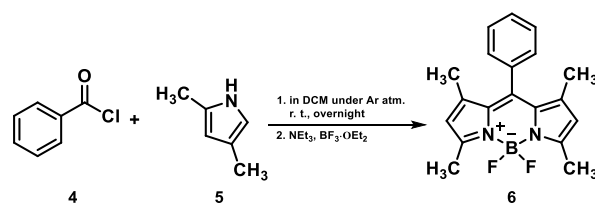
Scheme 1. Synthesis of BODIPY **6**

Synthesis of (E)-3-(2-(benzofuran-2-yl)vinyl)-10-(4-(tert-butyl)phenyl)-2,8-diethyl-5,5-difluoro-1,7,9-trimethyl-5H-5λ⁴,6λ⁴-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinine (6)

1.848 g (2.0 mL, 19.4 mmol, 1.94 eq) of 2,4-dimethylpyrrole (**5**) was dissolved in dry CH_2Cl_2 under the argon atmosphere. To this solution, 1.4 g (1.15 mL, 10.0 mmol, 1 eq) of benzoyl chloride (**4**) was added dropwise over 10 minutes, and then the reaction mixture was stirred overnight. After completion of the reaction, monitoring by TLC, 5 mL of
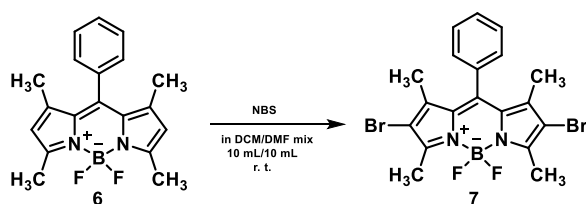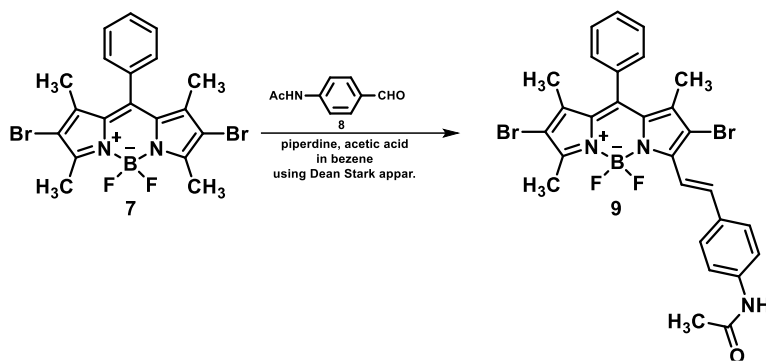

Scheme 2. Synthesis of BODIPY **7**

triethylamine was added, and the reaction was stirred at room temperature for an additional 15 minutes. 5 mL of BF$_3$·OEt$_2$ was added to the reaction mixture. The reaction was completed within 15 minutes, monitored by TLC. Then, the reaction mixture was diluted with ethyl acetate and washed with water and then brine.

Scheme 3. Knoevenagel condensation reaction of BODIPY **7**

Organic layers were combined and dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography over silica gel and eluted with dichloromethane. BODIPY **6** was obtained as a pale brown solid (0.60 g, 19.1%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.61 – 7.38 (m, 1H), 7.39 – 7.23 (m, 1H), 6.00 (s, 1H), 2.58 (s, 2H), 1.40 (s, 2H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 155.4, 143.2, 141.8, 135.0, 131.5, 129.1, 128.9, 128.0, 121.2, 14.6, 14.3. HRMS (ESI): for C$_{19}$H$_{19}$N$_2$BF$_2$ [M] calculated as 304.16616; found as 304.16610. Δ=0.21 ppm (Ekmekci, Yilmaz, & Akkaya, 2008).

Synthesis of 2,8-dibromo-5,5-difluoro-1,3,7,9-tetramethyl-10-phenyl- 5H-4λ4,5λ4-dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinine (7)

281.1 mg (0,87 mmol, 1 eq) of meso-phenyl-BODIPY **6** was dissolved in mixture 20 mL of DCM/DMF (1:1) and added 309.7 mg (1.74 mmol, 2 eq) of *N*-bromosuccinamide. After 1 h, the reaction was completed, monitored by TLC. From the reaction mixture, DCM was

evaporated and the mixture was extracted with water (50 mL) and EtOAc (3 × 50 mL). Then, the organic phase was treated with brine. After that, organic phases were combined and dried
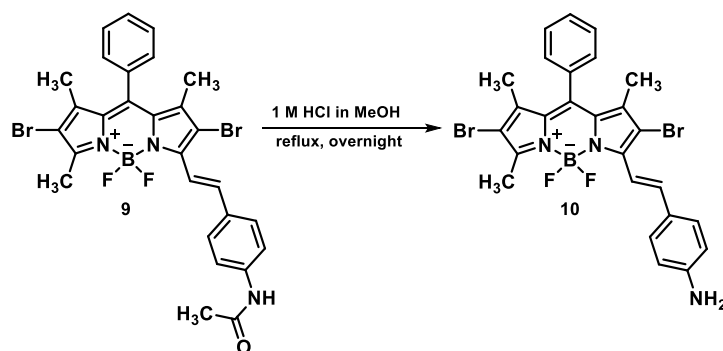
Scheme 4. Deprotection reaction of BODIPY **9**

by MgSO$_4$, and concentrated under reduced pressure. The resulting crude product was purified by column chromatography over silica gel and eluted with hexane/dichloromethane (1:1). BODIPY **7** was obtained as a light pink solid (376 mg, 89.7%). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 – 7.51 (m, 3H), 7.30 – 7.23 (m, 2H), 2.63 (s, 6H), 1.39 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.0, 142.1, 140.7, 134.4, 130.4, 129.6, 129.5, 127.8, 111.8, 13.7, 13.7. HRMS (ESI): for C$_{19}$H$_{17}$N$_2$BFBr$_2$ [M] calculated as 459.98719; found as 459.98744. Δ=0.54 ppm.

Synthesis of 2,8-dibromo-5,5-difluoro-1,3,7,9-tetramethyl-10-phenyl- 5H-4λ4,5λ4-

*dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinine
(9)*

303.3 mg (0.63 mmol, 1 eq) of compound **7** was dissolved in 15 mL benzene and successively added 116.4 mg (0.65 mmol, 1.03 eq) of 4-(acetoxyamino)-benzaldehyde (**8**) under argon atmosphere. After 10 min. 0.5 mL of piperidine and 0.5 mL of acetic acid were respectively added to the reaction medium. The resulting mixture was refluxed by using a Dean-Stark apparatus and monitored by TLC. After the completion of reaction, water (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). Combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified over silica gel by eluting with hexane/EtOAc (5:1). BODIPY **9** was obtained as a green-yellow solid (326.0 mg, 82.6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 16.7 Hz, 1H), 7.70 – 7.49 (m, 8H), 7.36 – 7.24 (m, 4H), 2.68 (s, 3H), 2.22 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 154.7, 141.5, 140.9, 140.4, 138.8, 138.2, 134.6, 132.8, 131.4, 131.2, 129.6, 129.4, 129.0, 128.5, 128.1, 119.7, 117.1, 29.7, 24.7, 13.9, 13.6. HRMS (ESI): for $C_{28}H_{24}N_3BFBr_2O$ [M] calculated as 606.04723; found as 606.04304. Δ=6.91 ppm (Kolemen et al., 2014; Wang, Shiraishi, & Hirai, 2010).

*Synthesis of 2,8-dibromo-5,5-difluoro-1,3,7,9-tetramethyl-10-phenyl- 5H-4λ^4,5λ^4-
dipyrrolo[1,2-c:2',1'-f][1,3,2]diazaborinine
(10)*

125.4 mg (0.2 mmol) of compound **9** was dissolved in15 mL MeOH. 5.0 mL of 1 M HCl was added and the resulting mixture was refluxed overnight. After completion of the reaction, the pH of the solution was adjusted

at 7.0 with $NaHCO_3$. Brine was added to this mixture and extraction was performed with EtOAc (3 × 30 mL). Organic phases were combined, dried with $MgSO_4$ and concentrated under reduced pressure to yield the crude product. The crude product was purified over silica gel by eluting with hexane/EtOAc (2:1). BODIPY **10** was obtained as a greenish solid (86.0 mg, 73.5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 16.6 Hz, 1H), 7.62 – 7.44 (m, 6H), 7.36 – 7.18 (m, 2H), 6.71 (d, J = 8.5 Hz, 2H), 3.95 (s, 2H), 2.67 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 141.8, 141.5, 139.9, 139.3, 139.2, 134.8, 131.5, 130.7, 129.5, 129.4, 129.4, 128.2, 127.3, 115.0, 114.2, 114.1, 114.1, 100.0, 29.7, 13.7, 13.6. HRMS (ESI): for $C_{26}H_{22}N_3BFBr_2$ [M$^+$] calculated as 563.02884; found as 563.02743. Δ=2.5 ppm (Wang et al., 2010).

3. Research Findings

BODIPY derivatives are an important molecule because of having some important abilities mentioned above. As a result, synthetic strategies and biological applications of BODIPY derivatives are widely under investigation in the literature. The scope of this research is the synthesis of novel BODIPY derivative **10** and understand the *trans*-configuration selectivity of the Knoevenagel condensation reaction by performing theoretical calculations. For this purpose, we applied literature synthetic pathway starting from the reaction of benzoyl chloride (**4**) and 2,5-dimethylpyrrole (**5**) to yield BODIPY **6** (Scheme 1).

After synthesis of BODIPY **6**, bromination reaction was taken place by NBS (*N*-bromosuccinamide) in the solvent mixture of DCM (dichloromethane) and DMF (dimethylformamide) at room temperature to
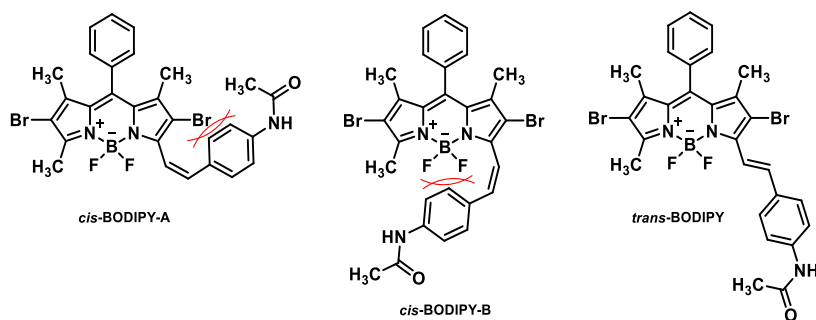
Figure 2. Possible configurations of Knoevenagel reaction of BODIPY **9**

form the compound **7** in good yield. This reaction only gives the dibrominated product **7** in a short time (Scheme 2).

BODIPY derivatives are subjected to some reaction which extends the pi-bond conjugation of the BODIPY core to shift its excitation and emission wavelength to near-IR region overcoming some drawbacks of BODIPY dyes such as penetration problems of during photodynamic therapy (PDT). For this purpose, Knoevenagel condensation reaction is the most applied method to extend the BODIPY conjugation. (Knoevenagel, 1898). During this reaction, an organic secondary amine, generally piperidine, and acid were used as the catalyst. The reaction begins with the abstraction of the acidic proton by amine and follows by the nucleophilic attack on the carbonyl group of aldehyde or ketone activated by the acid catalyst. As the next step, elimination of the water molecule from the adduct takes place and then Knoevenagel reaction results on the formation of the olefin functionality (Scheme 3). At this stage, there are two possible configurations, the *cis*-and *trans*-configured product. For the BODIPY's Knoevenagel reaction, *trans*-configured product is the only product of the stereospecific reaction. Experimental outcomes show the *trans*-configuration by the coupling constant in ^{1}H NMR spectra. For the formation of BODIPY **9**, the coupling constant of the olefinic protons of styryl-group is 16.6 Hz and proves the *trans*-configuration. It is not difficult to estimate the cause of this selectivity. Steric hindrance and repulsion in between bromine atom on the *cis*-BODIPY-A conformation and borane bridge of the BODIPY core of the *cis*-BODIPY-B con-formation with the styryl-unit increase the energy of the transition state of the resulting *cis*-molecule. On the contrary, the *trans*-con-figured product, *trans*-BODIPY conformation, this interaction is not seen. As a result, the total energy of the resulting molecule for the *trans*-configured BODIPY
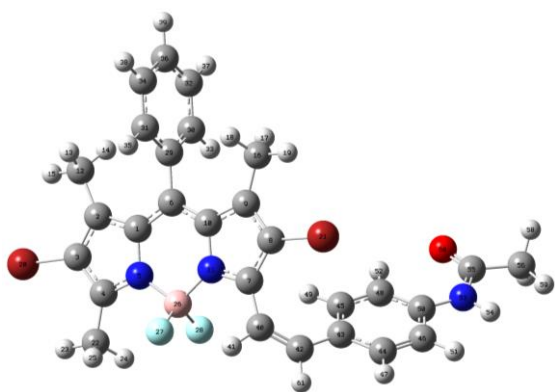

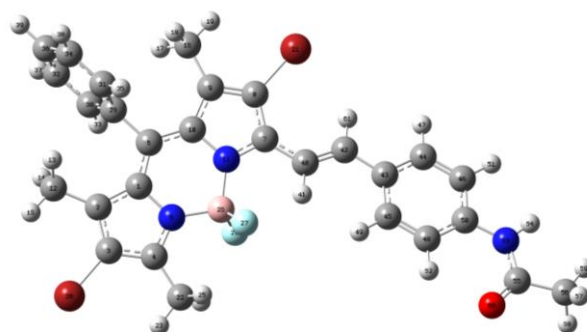Figure 3. Optimized structure of the *cis*-configurated product of BODIPY **9**

Figure 4. Optimized structure of the *trans*-configurated product of BODIPY **9**

has the lower energy and the reaction yields in the formation of *trans*-configurated product as the only product (Figure 2).

To investigate the *trans*-selectivity of Knoevenagel reaction of BODIPY **9**, we applied theoretical calculations. These calculations were performed using Gaussian09 software package. Geometry optimizations of the products were done by using the B3LYP (Becke-3 parameter-Lee–Yang–Parr) hybrid functional and 6-311G(d,p) as the basis set in the gas phase. According to the theoretical calculations, *trans*-configurated isomer has the lower energy than *cis*-configurated one by 6.2 kcal/mol (Table 1). The exclusive

Table 1. DFT Calculation Results (B3LYP/6-311G(D,P))

	cis-BODIPY	*trans*-BODIPY	**ΔH**
a.u. Hartree	-6694,3	-6694,3	0,0
kJ/mol	-17575957	-17575983	-25,8
kcal/mol	-4200757	-4200763	-6,2
*R. E. (kcal/mol)	6,2	0,0	

*R.E.: Relative energy

formation of *trans*-product can be attributed to this energy difference. The geometry optimization results also show the *cis*-configurated is distorted form the planer structure of the BODIPY core. (Figure 3). The dihedral angle of the styryl-group is about 170°. This also affects the delocalization ability of the molecule which needs to sp^2 orbitals of conjugated bonds being in the same plane. On the other hand, *trans*-configurated product has the planer structure which makes the delocalization easier and longer in comparison to the *cis*-product (Figure 4).

After synthesis and theoretical investigation of the acetyl-protected (*p*)-aminostyryl-BODIPY **9** derivative, deprotection reaction was performed in the presence of HCl in MeOH to get the desired product BODIPY **10** in good yield (Scheme 4).

4. Results

The synthesis of the new product BODIPY **10** was performed. In addition to this, Knoevenagel reaction of the BODIPY **9** was investigated by both experimentally and theoretically. Experimentally *trans*-configurated product formation was also explained by the DFT calculations. According to the calculation, the *trans*-configurated product has the lower energy by 6.2 kcal/mol than *cis*-configurated product. The optimized structure of two possible products shows that styryl-group of the *cis*-configurated product is distorted from the planer BODIPY core by 170° whereas the styryl-group of the *trans*-configurated product is on the same plane having longer delocalization with the BODIPY core structure.

5. References

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