Fast Synthesis of Tetra-Aryl-Substituted Aza-BODIPYs

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Abstract. This article presents the fast and easy way to synthesize tetra-aryl-substituted aza-BODIPY dyes. The standard synthesis technique in solution was modified by mechanochemical solid-state grinding and minimizing the solvent amount. These approaches substantially reduced reaction time. Obtained dyes showed moderate fluorescence in near-infrared window in biological tissue and may be further used in areas of biological sensing.

1. Introduction
BODIPY – is a versatile family of fluorescent complexes [1]. Due to their unique structure, they exhibit high quantum yield of fluorescence [2], good photostability [3] and it is relatively simple to modify substituents in a huge variety of ways [4]. That’s why these complexes find application in many areas, especially in sensing [5–10]. However, it is still a problem, that many of new BODIPY modifications absorb and emit light at short wavelengths (500-600 nm), that makes them hardly suitable for real biological application. There are several ways to move BODIPY’s fluorescence and absorption spectra to near-infrared window in biological tissues, but the most promising is to use the family of aza-BODIPY dyes. These compounds contain nitrogen atom in meso-position, that leads to about 100 nm bathochromic shift of both fluorescence and absorption spectra with no fluorescence quantum yield drop [11].

Moreover, the addition of aryl substituents in α and β positions of aza-BODIPY core (Figure 1) may lead to a further bathochromic shift and appearance of sensing properties. Nonetheless synthesis of tetra-aryl-substituted aza-BODIPYs is extremely time-consuming. Therefore we decided to speed up synthesis from several working days[12] (excluding purification time) to some reasonable values.

Fig. 1. General naming of substituents position (on the example of 1st dye) and structures of synthesized in this work Aza-BODIPYs.
2. Experimental

2.1. Synthesis

A common synthetic route involves a variety of organic solvents on every step [13]. The main concept was to replace liquid-phase reactions with solid-state solvent-free mechanochemical reactions and to minimize solvents where possible (Figure 2).

![Synthetic Route Diagram]

Fig. 2. Modified synthetic route to tetra-aryl-substituted aza-BODIPYs.

Although the final modified synthetic route includes all standard intermediates, the chemical operations were changed:

- **Synthesis of chalcones** a is well known [14]. 5 mmol of appropriate aldehyde and 5 mmol of appropriate ketone were mixed in ceramic mortar. 5 mmol of well-grinded NaOH powder was carefully added within 10 minutes. The mixture was grinded and it turned dry and pale-yellow. The reaction was controlled by TLC (SiO₂, ethyl acetate/hexane, 1:2). The mixture was washed with water, dried on air and recrystallized from ethanol.

- **Michael adducts** b were obtained by solid state grinding [15] with surface catalyst: tetra-n-butylammonium bromide (TBAB). The mixture of K₂CO₃ (20 mmol, 4 eq.), TBAB (0.5 mmol, 0.1 eq.) nitromethane (10 mmol, 2 eq.) were grinded in mortar with pestle for 1 minute. Then the chalcone a (5 mmol, 1 eq.) was added and the mixture was grounded for 5 minutes. The white powder turned into pale-yellow gum. The reaction was controlled by TLC (SiO₂, ethyl acetate/hexane, 1:2). The reaction mixture was dissolved in dichloromethane (DCM), washed with water, dried with Na₂SO₄, the solvent was evaporated under reduced pressure. The product b is yellow oil.

- **Aza-dipyrromethenes** c were obtained without any solvent [16]. Michael adduct b (5 mmol, 1 eq.) and NH₄OAc (100 mmol, 20 eq.) were mixed and heated until boiling (220 °C). The mixture was left boiling for 10 minutes. The darkening of the mixture and disappearing of precursor spot on TLC (Al₂O₃, DCM) indicated the completion of the reaction. The mixture was dissolved in a huge excess of water, filtered and purified by chromatography (Al₂O₃, DCM/hexane, 1:4).

The final step of obtaining aza-BODIPYs 1-4 was carried out in minimal amount of solvent. 5 mmol of appropriate aza-dipyrromethene c was added to NEt₃ (4.9 ml, 7 eq), dissolved in 50 ml of DCM and mixed for 30 minutes at room temperature. Then BF₃(OEt)₂ (5.7 ml, 9 eq) was added and the mixture was left stirring for 3 hours). Then the solvent was removed and product was purified by chromatography (Al₂O₃, DCM/hexane, 1:4). Resulting products are dark copper crystals.

2.2 Identification

**BODIPY 1**: IR, ν, cm⁻¹: 3110, 1551, 1512, 1451, 1389, 1281, 1227, 1134, 949, 841, 802, 764, 740, 879.

**1H NMR (CDCl₃)**, δ, ppm. (J, Hz): 8.03-8.01 (m, 4H), 7.95 (d, J = 4.0, 2H), 7.61 (d, J = 4.0, 2H), 7.48-
7.50 (m, 6H), 7.24-7.22 (m, 2H), 6.94 (s, 2H). 11B NMR (CDCl₃), δ, ppm. (J, Hz): 0.74 (t, J = 32.0, 1B).

MALDI-TOF: calculated for ([C₂₈H₁₈BF₂N₃S₂]⁺) m/z = 509.10, found m/z = 510.1280 [M+H]⁺.

**BODIPY 2**: IR, ν, cm⁻¹: 3160, 2920, 2830, 1510, 1471, 1436, 1410, 1276, 1129, 1090, 954, 853, 802, 701. ¹H NMR (CDCl₃), δ, ppm. (J, Hz): 8.38 (d, J = 4.0, 2H), 7.96 (d, J = 4.0, 2H), 7.66 (d, J = 4.0, 2H), 7.59 (d, J = 4.0, 2H), 7.28-7.30 (m, 2H), 7.22-7.24 (m, 2H) 7.07 (s, 2H). ¹¹B NMR (CDCl₃), δ, ppm. (J, Hz): 1.04 (t, J = 32.0, 1B). MALDI-TOF: calculated for ([C₂₄H₁₄BF₂N₃S₄]⁺) m/z = 521.01, found m/z = 522.0528 [M+H]⁺.

**BODIPY 3**: IR, ν, cm⁻¹: 2924, 2855, 1728, 1597, 1512, 1512, 1451, 1389, 1227, 1126, 1096, 1026, 972, 810, 764, 733, 687, 571. MALDI-TOF: calculated for ([C₃₄H₂₆BF₂N₃]⁺) m/z = 525.22, found m/z = 526.6931 [M+H]⁺.

**BODIPY 4**: IR, ν, cm⁻¹: 2924, 2854, 1604, 1512, 1473, 1411, 1296, 1196, 1018, 849, 802, 748, 710, 556. MALDI-TOF: calculated for ([C₃₀H₂₂BF₂N₃S₂]⁺) m/z = 537.13, found m/z = 538.5663 [M+H]⁺.

### 3. Spectral properties

![Normalized absorption (left) and fluorescence (right) spectra of investigated aza-BODIPY dyes 1-4 in DCM.](image)

The shape of absorption and fluorescence spectra were investigated in DCM and are standard for all of investigated compounds (Figure 3). Nonetheless, the substituents influence significantly the spectral properties of dyes.

Table 1. Photophysical properties of investigated compound (λₘₐₓ – wavelength of maximum absorption; λₘₚ – wavelength of maximum fluorescence; Δν – Stokes shift; Φₚ – quantum yield of fluorescence; FWHM - Full width at half maximum)

| Compound | λₘₐₓ, nm | λₘₚ, nm | Δν, nm | Φₚ | FWHM, nm |
|----------|----------|----------|--------|-----|----------|
| 1        | 683      | 718      | 35     | 0.02| 74       |
| 2        | 741      | 756      | 15     | 0.07| 40       |
| 3        | 652      | 677      | 25     | 0.05| 48       |
| 4        | 718      | 728      | 10     | 0.13| 37       |

This influence is of complex nature. First of all, we may see that compound 1 has the lowest quantum yield of fluorescence (0.02) (Table 1) and the highest Stokes shift (35 nm). In contrast, compound 4 has the highest quantum yield (0.13) and the lowest Stokes shift (10 nm). This dependence may indicate that the geometry of 4 change more slightly upon excitation, than the geometry of 1 [17], that leads to decreasing of non-radiative decay rate and follows by increasing of fluorescence quantum yield [18]. We assume that the lability of bulky tolyl substituents in β-positions of BODIPY core is lower than of small thiethyl substituents, however the relatively high polarity of thiethyl substituents (in contrast to nonpolar tolyl groups) in α-positions prevents rotation by interactions with fluorine atoms of BODIPY core [19].
The rigidity of 4 also confirms by the lowest FWHM (37 nm) and the lability of 1 confirms by the highest FWHM (74 nm).

4. Conclusions
In this work we presented the new way of fast synthesis of tetra-aryl-substituted aza-BODIPY dyes. It was shown that mechanochemical approach and minimizing the solvent amount greatly reduce synthesis time, making it possible to obtain new compound in about 1 working day. We may see that the position of fluorescence maxima is influenced by the nature of the substituents. Introduction of electron-donating groups result in bathochromic shift. The more the groups – the higher the shift. Comparison of fluorescence and absorption maxima positions of investigated dyes show that substituents in α-positions have higher influence on maxima positions than substituents in β-positions.

All investigated compounds 1-4 exhibit absorption and fluorescence in near-infrared window in biological tissues, that makes them suitable for further investigation in areas of biological sensing.

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