Chemistry–A European Journal
Research Article
doi.org/10.1002/chem.202400644
Chemistry Europe
European Chemical Societies Publishing
www.chemeurj.org

Hot Paper

Tuning the Emission Properties of 2,1,3-Benzothiadiazoles via Regioselective Substitution

Mauricio Posada Urrutia[a] and Christine Dyrager*[a]

The 2,1,3-benzothiadiazole (BTD) unit is a prominent building block commonly used in various research areas such as optoelectronics and bioimaging. Despite its great versatility, the development of strategies to elaborate BTD has been largely neglected, including exploring its reactivity and understanding how regioselective functionalization can be used to tune the fluorescence emission. Previous focus has primarily been on C4- or C4,C7-substitutions. Here, a series of unsymmetrical mono – and disubstituted BTDs was synthesized and characterized for their photophysical properties. The reaction scope includes all six possible substituent patterns on the BTD benzoid ring (C4-, C5-, C4,C5-, C4,C6-, C4,C7- and C5,C6-substitution), which comprise arrangements that previously been synthetically challenging to access. By introducing a methoxy and/or a phenyl group we demonstrate that the emissive behavior of BTD derivatives strongly depends on the position of the substituent (s). We show that regioselective substitution on BTD can engender long-lived fluorescence and circumvent strong fluorescence quenching in polar protic solvents, which is a limitation of many previously described BTD derivatives.

Introduction

The development of new small organic fluorophores is often a trial-and-error process for synthetic and photophysical chemists. The role that a particular substituent has on the photophysical properties of a fluorophore can be predicted to some extent. However, there are perplexing cases where seemingly inconsequential substitution induces unexpected luminescence or lack thereof. For example, fluorophores based on 7-nitrobenz-2-oxa-1,3-diazole (NBD) exhibit what initially can be perceived as a set of uncommon properties.[1] In derivatives of this structure the nitro substituent does not quench fluorescence (as is commonly the case)[2] but rather predisposes the molecule for charge transfer emission in the presence of an appropriate electron donor.[3] It is therefore imperative to understand the intrinsic behavior of a fluorophore and what role different substituents have on its excited state behavior. The electronic coupling of a substituent, its ability to induce intersystem crossing (ISC), and its potential specific solvent interactions are some of the many ways substitution can alter the luminescence of a particular molecule. Another factor is the position of the substituent, referred to as the "site-effect".[4] Regioisomers can exhibit significantly different photophysical features, as described previously for various modified fluorescent scaffolds (e.g., pyrene, xanthene and carbostyryl).[4–5] Exploring different substituent patterns can therefore be a promising approach for tuning the emission or changing the emissive nature of a fluorophore. However, the prospect for desired regioselective modifications is often limited by the innate reactivity of the fluorophore backbone and/or the absence of appropriate methodologies.

The 2,1,3-benzothiadiazole (BTD) unit (**1**, Figure 1) is a prominent fluorescent scaffold with strong electron-withdrawing ability that facilitates intramolecular charge transfer (ICT), large Stokes shift and redshifted absorption/emission profiles.[6] It is a strong acceptor motif in many donor-acceptor (D–A)

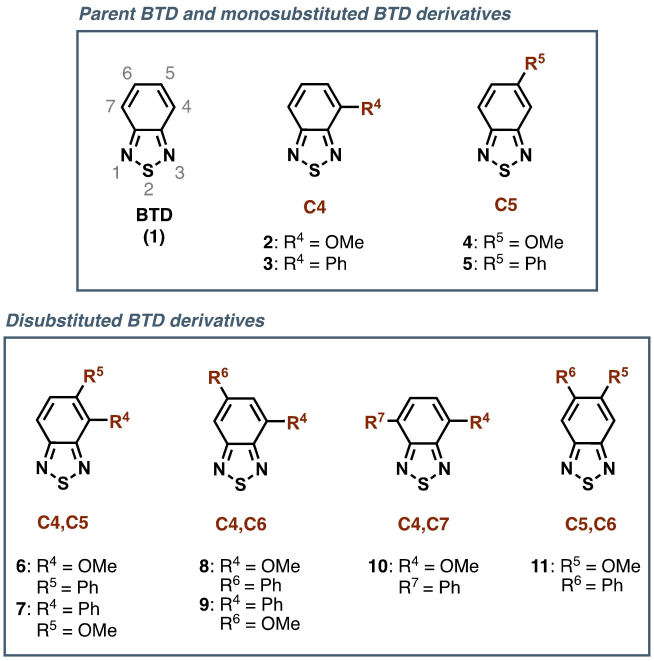


Figure 1. Scope of the synthesized and studied compounds **1**–**11** in this work.

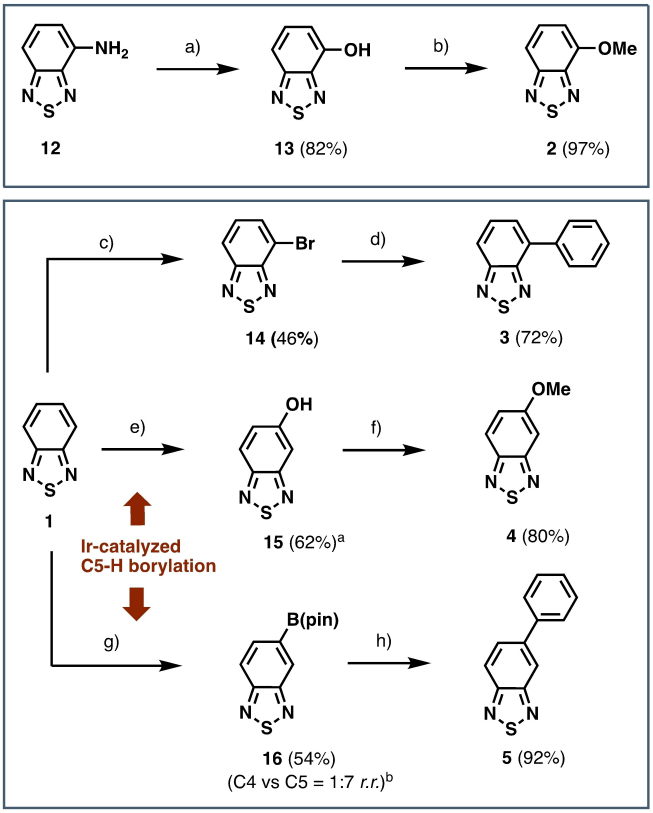
[a] M. Posada Urrutia, Dr. C. Dyrager
Department of Chemistry-BMC, Uppsala University, Box 576, 751 23 Uppsala, Sweden
E-mail: christine.dyrager@kemi.uu.se

Supporting information for this article is available on the WWW under https://doi.org/10.1002/chem.202400644

fluorophores that engender electronic polarization in the excited state. It has therefore found use as a building block in optoelectronic devices,[7] chemical sensors[8] and cellular imaging probes.[6c,d,9] Functionalization of **1** can be achieved by electrophilic aromatic substitution, which commonly gives a mixture of C4- and C4,C7-substituted BTDs.[10] Bromination is regularly used in this aspect (with NBS and H_2SO4,[11] or Br_2 in aqueous HBr) to obtain 4,7-dibromo-BTD that subsequently can be subjected to transition metal-catalyzed arylations and/or alkynylations to obtain π-extended symmetric or unsymmetric products.[12] The presence of directing functionalities, such as amino- and hydroxy groups, in the 4-position of BTD grants access to *ortho*-directed electrophilic aromatic substitutions, while 4-nitrated BTD leads toward *meta* selectivity.[13] By contrast, C5- and C6-substituted BTDs are traditionally obtained by *de novo* synthesis of the thiadiazoloid ring, from pre-derivatized *o*-phenylenediamines and an appropriate sulfur source such as $SOCl_2$.[14] However, the synthesis of applicable aryl diamines can be cumbersome, and this has limited the prospects of investigating the site-effect of many substituents on the photophysical properties of C5- and C6-substituted BTDs. Our group recently reported a strategy that bypasses such *de novo* synthesis via regioselective Ir-catalyzed C5–H borylation of BTD.[15] We showed that 5-boryl BTDs serve as versatile precursors for subsequent manipulation of the BTD core at each of the C4, C5, C6, and C7 positions, including in various π-extending reactions.

Here, we set out to systematically modify each of the positions on the electron-deficient BTD benzenoid ring, with either an electron donating substituent (methoxy), to form a D–A structure, or an aromatic fragment (phenyl group) that extends the π-conjugation. Figure 1 shows the scope of the compounds synthesized and studied in this work (**1**–**11**), focusing on mono – and disubstituted BTD derivatives. These represent all possible arrangements (C4-, C5-, C4,C5-, C4,C6-, C4,C7- and C5,C6-substitution) of the two chosen substituents, which includes substituent patterns that previously been difficult to access. This is the first study that systematically compare the photophysical properties of regioisomeric BTD derivatives. The synthesis presented herein provides a powerful platform from which further (more complex) derivatives of BTD can be made.

C4- and C5-substituted BTD derivatives



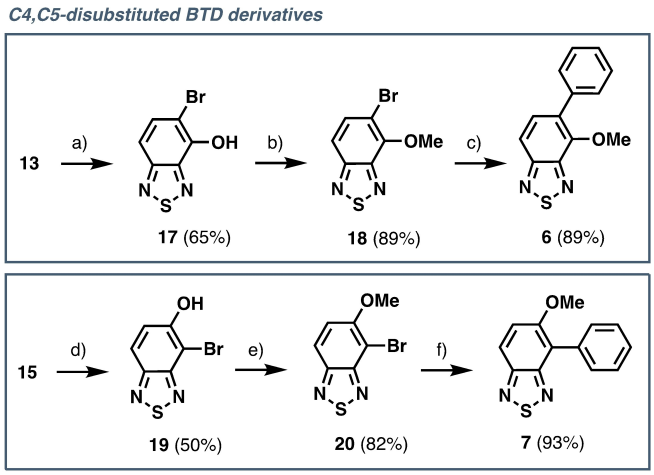
Scheme 1. Synthesis of monosubstituted BTD derivatives **2**–**5**. Reagents and conditions: a) $Na_2S_2O_5$, H_2O, reflux, 16 h. b) NaH, MeI, DMF, r.t., 16 h. c) Br_2, $HBr_{(aq)}$, reflux, 1.5 h. d) $PhB(OH)_2$, PEPPSI-IPr, K_2CO_3, toluene/MeOH (1 : 1 v/v), 80 °C, 2 h. e) i) $B_2(pin)_2$, Me_4Phen, $[Ir(OMe)(COD)]_2$, THF, 80 °C, 1 h, ii) OXONE®, acetone/H_2O (1 : 1 v/v) r.t., 15 min. f) NaH, MeI, DMF, r.t., 16 h. g) $B_2(pin)_2$, Me_4Phen, $[Ir(OMe)(COD)]_2$, THF, 80 °C, 3 h. h) Bromobenzene, $Pd(OAc)_2$, XPhos, K_3PO_4, toluene/H_2O (10 : 1 v/v), 80 °C, 4 h. [a] Purification of the reaction also generated the isolated C4 isomer **13** in 11 % yield. [b] The regioisomer ratio (*r. r.*) was determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard.

Results and Discussion

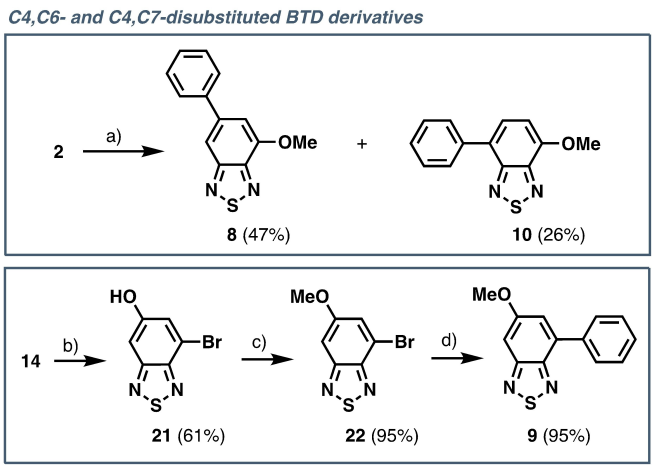
Synthesis

The synthesis of the monosubstituted BTD derivatives **2**–**5** is depicted in Scheme 1. The 4-methoxy BTD derivative **2** was prepared from commercially available 4-amino-BTD (**12**). The amino group was converted via a Bucherer reaction[16] using $Na_2S_2O_5$ to yield **13**. The hydroxy group was then methylated in the presence of MeI and NaH to give **2** in near quantitative yield (97 %). The C4-phenyl derivative **3** was obtained by bromination of the C4-position of BTD (**1**), which gave **14**, followed by Suzuki–Miyaura cross coupling with $PhB(OH)_2$ to afford **3**. The C5-substituted derivatives **4** and **5** were synthesized using regioselective Ir-catalyzed C–H borylation[17] of BTD (**1**).[15] Here, the 5-methoxy BTD derivative **4** could be prepared most efficiently by using a one pot procedure (Ir-catalyzed C–H borylation of **1** with $B_2(pin)_2$ and *in situ* oxidation with OXONE®)[18] to afford 5-hydroxy BTD **15**, followed by *O*-methylation to obtain **4**. The synthetic route starting from **1** also gave 4-hydroxy BTD **13** as a minor product (11 % yield). In a separate reaction, the C5–B(pin) derivative **16** was isolated, albeit with lower yield (54 %) than **15** (62 %), and it was further used to generate 5-phenyl BTD **5** via Suzuki–Miyaura cross coupling with bromobenzene. Compound **16** was also successfully oxidized using OXONE®, which gave 5-hydroxy-BTD **15** (see ESI for details).

The C4,C5-substituted derivatives, **6** and **7**, were prepared from 4- and 5-hydroxy BTD, **13** and **15**, using a three-step reaction sequence; *ortho*-bromination, *O*-methylation and Suzuki–Miyaura cross coupling (Scheme 2). The C5-bromination of 4-hydroxy BTD **13** using NBS was indeed proven to be *ortho*-selective to give **17** but also generated the C5,C7 dibrominated



Scheme 2. Synthesis of the C4,C5-disubstituted BTD derivatives **6** and **7**. Reagents and conditions: a) $^{i}Pr_2NH$, NBS, CH_2Cl_2, r.t., 16 h. b) NaH, MeI, DMF, r.t., 16 h. c) $PhB(OH)_2$, $Pd(OAc)_2$, XPhos, K_3PO_4, toluene/H_2O (10:1 v/v), 80 °C, 5.5 h. d) NBS, toluene, 0 °C for 4 h then r.t. for 2 h. e) NaH, MeI, DMF, r.t., 16 h. f) $PhB(OH)_2$, $Pd(OAc)_2$, XPhos, K_3PO_4, toluene/H_2O (10:1 v/v), 80 °C, 24 h.



Scheme 3. Synthesis of C4,C6- and C4,C7-disubstituted BTD derivatives **8**–**10**. Reagents and conditions: a) i) $B_2(pin)_2$, Me_4Phen, $[Ir(OMe)(COD)]_2$, THF, 80 °C, 2 h. ii) $PhB(OH)_2$, $Pd(OAc)_2$, XPhos, K_3PO_4, toluene/H_2O (10:1 v/v), 80 °C, 20 h. b) i) $B_2(pin)_2$, Me_4Phen, $[Ir(OMe)(COD)]_2$, THF, 80 °C, 16 h. ii) OXONE®, acetone/H_2O (1:1 v/v) r.t., 20 min. c) NaH, MeI, DMF, r.t., 16 h. d) $PhB(OH)_2$, $Pd(OAc)_2$, XPhos, K_3PO_4, toluene/H_2O (10:1 v/v), 80 °C, 18 h.

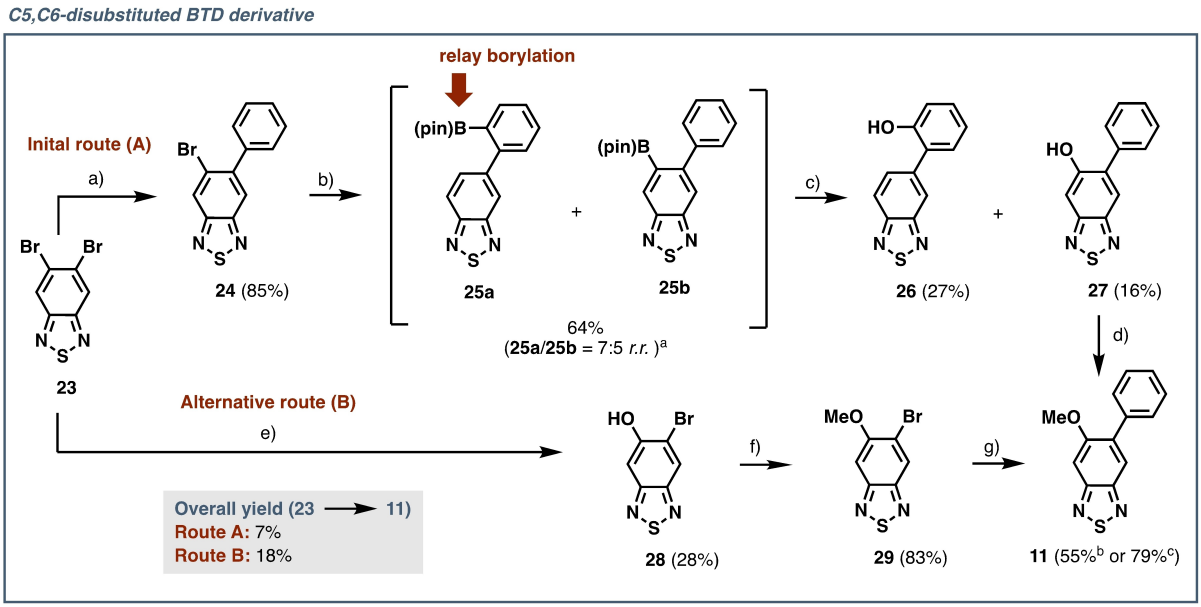
material as a minor product. Addition of diisopropylamine to the reaction resulted in higher monoselectivity giving the *ortho*-substituted product **17** in 65% yield.[19] Bromination at C5, and not C7, to give **17** was unambiguously ascertained by synthesizing 4-bromo-7-hydroxy-BTD and comparing the respective spectroscopic data (see ESI). C4 bromination of 5-hydroxy-BTD **15** to obtain **19** was successfully performed without the addition of diisopropylamine (dibromination was not observed). The selectivity for this reaction can be ascribed to the preference of the C4 position of BTD to undergo electrophilic aromatic substitution. The hydroxy group at C5 is likely to further increase this effect. *O*-methylation of the brominated derivatives, **17** and **19**, gave **18** and **20**, respectively. Finally, the phenyl group was installed via Suzuki–Miyaura cross coupling to afford the regioisomers **6** and **7**.

The synthesis of disubstituted C4,C6 and C4,C7 derivatives, **8**–**10**, is shown in Scheme 3. The 4-methoxy BTD derivative **2** was subjected to Ir-catalyzed C–H borylation conditions with $B_2(pin)_2$, which gave a mixture of the C6 and C7 borylated products. These were directly coupled with $PhB(OH)_2$ to give the C4,C6 and C4,C7 derivatives **8** and **10**. The C4,C6 isomer **9** was prepared in three steps from 4-bromo-BTD **14**. Ir-catalyzed C–H borylation and subsequent oxidation with OXONE® (one pot) gave **21**. Compound **21** was then *O*-methylated in the 6-position to obtain **22** in 95% yield, which further was subjected to Suzuki–Miyaura cross coupling with $PhB(OH)_2$ to give **9**.

The synthesis of non-symmetrical C5,C6-disubstituted BTD derivatives remains as a challenge. In this work, commercially available 5,6-dibromo-BTD **23** was used as a starting material. Our initial strategy (Scheme 4, route A) involved a Suzuki–Miyaura cross-coupling with $PhB(OH)_2$, which gave **24**, followed by a one pot Miyaura borylation and oxidation sequence to generate 5-hydroxy-6-phenyl BTD **27**. However, upon subjecting **24** to Miyaura borylation conditions, a mixture of regioisomers **25a** and **25b** formed (*r.r.* = 7:5; see ESI for details). We ascribe the formation of **25a** to a Pd-mediated 'relay borylation' process previously investigated by Feng and co-workers for the synthesis of vinylic boronates.[20] The isomers **25a** and **25b** were oxidized with OXONE® to the corresponding phenols **26** and **27**. The minor product **27** was *O*-methylated to afford the C5,C6-disubstituted derivative **11**. Various conditions were tested to avoid or reduce the formation of the relay borylation product **25a**. Changing the base (from KOAc to Et_3N or KOPh)[21] or the solvent (from DMF to 1,4-dioxane) did not improve the yield of **25b**. Instead, route B was explored to provide a more straightforward synthesis of **11**. 5,6-Dibromo-BTD **23** was subjected to one pot Miyaura borylation and consecutive oxidation to give **28**, followed by *O*-methylation to obtain **29**. Compound **11** was subsequently generated using Suzuki–Miyaura cross coupling with $PhB(OH)_2$. The overall yield, going from **23** to **11**, increased about 2.5-fold when using the alternative synthetic pathway (route B) instead of the initial strategy (route A). With all desired compounds in hand (**1**–**11**) we moved on to exploring their photophysical properties.

Photophysical Properties

Photophysical data for compound **1**–**11** in toluene and MeOH are summarized in Table 1 and 2. Unsubstituted BTD (**1**) is a poor fluorophore by itself. Its strongest absorption band is seen in the UV region; $\lambda_{Amax} = 310$ nm in MeOH (Figure 2). Excitation into this band results in short-lived weak emission ($\tau \leq 1.3$ ns, $\Phi = 0.01$), which peaks at 394 nm. It should be noted that detailed spectroscopic analyses of **1** have previously been reported in literature.[22] These studies have looked at vapour absorption, in solution absorption, and rigid glasses absorption; fluorescence and phosphorescence emission from rigid glass matrixes; polarized electronic absorption as well as electron magnetic resonance (EPR). Some of these studies also comprise



Scheme 4. Synthesis of the C5,C6-disubstituted derivative **11**. Reagents and conditions: a) $PhB(OH)_2$, Cs_2CO_3, $Pd(PPh_3)_4$, toluene/H_2O (40:1 v/v), 90 °C, 18 h. b) $B_2(pin)_2$, KOAc, $PdCl_2(dppf)$, DMF, 90 °C, 3 h. c) OXONE®, acetone/H_2O (1:1 v/v) r.t., 2 h. d) NaH, MeI, DMF, r.t., 16 h. e) i) $B_2(pin)_2$, KOAc, $PdCl_2(dppf)$, 1,4-dioxane, 90 °C, 16 h. ii) OXONE®, acetone/H_2O (1:1 v/v), r.t., 1 h. f) NaH, MeI, DMF, r.t., 16 h. g) $PhB(OH)_2$, $Pd(OAc)_2$, XPhos, K_3PO_4, toluene/H_2O (10:1 v/v), 80 °C, 18 h. [a] Regioisomer ratio (*r.r.*) determined by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yield starting from compound **27** (Route A). [c] Isolated yield starting from compound **29** (Route B).

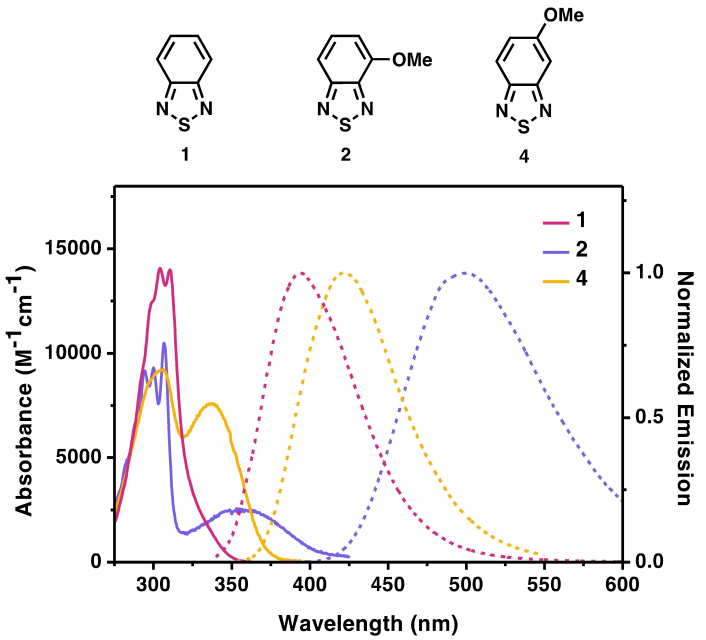
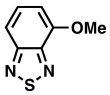
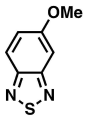
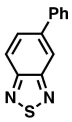
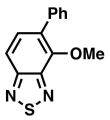
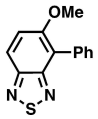
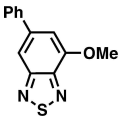
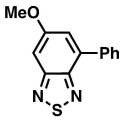
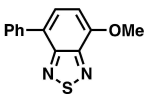
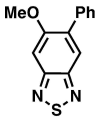


Figure 2. Absorbance normalized to the respective extinction coefficient, (solid line) and normalized emission (dashed line) spectrum of unsubstituted BTD **1** (pink), 4-methoxy-BTD **2** (violet), and 5-methoxy-BTD 4 (yellow) in MeOH.

analyses of analogous heterocycles with Se or O (instead of S as found in **1**). The first electronically allowed $^1\pi\pi^*$ transitions in **1** have been ascribed to $^1A_1 \leftarrow {}^1A_1$ and $^1B_2 \leftarrow {}^1A_1$, where the latter band intensity (found at ~328 nm) partly originate from $^1A_1 \leftarrow {}^1A_1$. The lowest energy band at ~328 nm is weak and hard to resolve. The dominant vibration is a symmetrical (a_1) C4 C5 C3a angle bend with a ring contraction. Meanwhile, B2 vibrations engage in Herzberg–Teller intensity stealing, most likely from the $^1A_1 \leftarrow {}^1A_1$ transition at ~310 nm.

C4 or C5 substitution on **1**, with either a methoxy or phenyl group, changes the structure of the $^1A_1 \leftarrow {}^1A_1$ band, which primarily loses magnitude through intensity stealing (c.f., **1** with **2** and **4**, Figure 2). This further contributes to the intensity of a new band that appears at a longer wavelength (e.g., **2**, $\lambda_{Amax} =$ 360 nm in MeOH). The C4-substituted derivatives **2** and **3**

Table 1. Steady-state photophysical data of compounds **1**–**11** in toluene and MeOH.

Compound	Structure	λ_{Amax} (nm) Toluene/MeOH	λ_{Emax} (nm) Toluene/MeOH	Stokes Shift×10^3 (cm^{-1}) [nm] Toluene/MeOH	ε×10^3 ($M^{-1}\,cm^{-1}$) Toluene/MeOH	Φ[a] Toluene/MeOH
1		307b/310b	385/394	4.5[57][c]/5.1[66][c]	13.6/13.9	0.01/0.01
2		357/360	445/501	5.5[88]/7.8[141]	2.7/2.5	0.56/0.36
3		355/349	441/471	5.7[103]/7.4[122]	4.8/5.1	0.48/0.63
4		338/337	391/421	4.0[53]/5.9[84]	9.2/7.6	0.03/0.03
5		325/323	400/432	5.8[75]/7.6[109]	30.2/12.3	0.05/0.06
6		353/353	484/533	7.7[101]/9.6[180]	3.0/3.2	0.29/0.21
7		370/368	468/503	5.7[98]/7.3[135]	5.4/4.9	0.44/0.50
8		360/362	451/501	5.6[91]/7.7[139]	4.2/4.6	0.39/0.44
9		355/355	442/469	5.6[87]/6.9[114]	7.4/6.4	0.06/0.09
10		388/389	504/548	5.9[116]/7.5[159]	4.5/4.4	0.64/0.10
11		326/333	397/424	4.6[71]/6.5[91]	19.5/15.1	0.08/0.12

[a] Fluorescence quantum yields (Φ) were determined with λ_{ex} = 360 nm relative to quinine sulfate in 0.1 M aq. H_2SO_4 (Φ = 0.54) or λ_{ex} = 450 nm relative to fluorescein in 0.1 M aq. NaOH (Φ = 0.95). [b] The value corresponds to the most pronounced transition in the absorption spectrum. The most redshifted transition can be found at *circa* 328 nm. [c] Calculation based on the transition at ~328 nm.

exhibit a clearer vibrational progression for the $^1A_1 \leftarrow {}^1A_1$ band than **1** (c.f., **1** with **2**), while the vibrational structure is lost upon C5 substitution (c.f., **1** with **4**). The latter hints at a different electronic origin to these transitions or possibly specific solvent-solute interactions.[23] However, there seems to be substantial electronic coupling between the BTD unit and substituents at C5. The degree of loss of the vibrational progression is hard to quantify but it is evident that compounds that retain the pseudo-BTD-like vibrational structure (at ~300 nm) exhibit more redshifted λ_{Amax}. For example, λ_{Amax} for the C4- and C5-substituted regioisomers **2** and **4** are 360 and 337 nm, respectively, in MeOH. The emission maxima for **2**–**5**

Table 2. Time-dependent photophysical data for compound **1**–**11** in toluene and MeOH.

	$\tau^{[a]}$ (ns) Toluene/MeOH	$k_{rad}\times10^7$ (s^{-1}) Toluene/MeOH	τ_0 (ns) Toluene/MeOH
1	$\leq$1.3/$\leq$1.3	0.77/0.77	130/130
2	21.1/32.4	2.6/1.1	38/90.0
3	6.5/16.6	7.4/3.8	13.6/26.3
4	$\leq$0.8/$\leq$0.8	3.8/3.8	26.7/26.7
5	$\leq$0.8/$\leq$0.8	6.3/7.5	16/13.3
6	31.6/24.9	0.92/0.84	109/119
7	11.1/26.7	4.0/1.9	25.2/53.4
8	14.1/38.1	2.8/1.2	36.2/86.6
9	1.4/3.5	4.2/2.6	24/38.7
10	19.1/7.6	3.4/1.3	29.8/76.3
11	1.1/$\leq$0.8	7.3/15.0	13.8/6.7

[a] Emission lifetimes (τ) were determined using time-correlated single photon counting (TCSPC) measurements (see ESI for details).

(391–501 nm) increase with solvent polarity, suggesting that the excited states are stabilized by polar solvents. The emission also reveals large Stokes shifts that range between 4000–7800 cm^{-1}. A methoxy substituent at C4 lead to a larger redshift in the emission than a phenyl group (**2** and **3**: $\lambda_{Emax}=501$ and 471 nm, respectively, in MeOH), while the opposite is seen at C5 (**4** and **5**: $\lambda_{Emax}=421$ and 432 nm, respectively, in MeOH). The molar extinction coefficients (ε) are also significantly affected by the position of the substituents, as reflected by the different intensities of the lowest energy bands (c.f., **2** and **4**, Figure 2). The C5-substituted derivatives have markedly higher molar absorptivity than the C4-substituted isomers (e.g., $\varepsilon=2500$ vs 7600 $M^{-1}cm^{-1}$ for **2** and **4** in MeOH). Compound **5**, with a phenyl at C5 displays the largest ε in the series (30,200 $M^{-1}cm^{-1}$ in toluene and 12,300 $M^{-1}cm^{-1}$ in MeOH). The substantial disparity in ε in the two different solvents for **5** further strengthens the observation that substitutions at C5 have a different set of interactions with the solvent compared to the C4-substituted isomers.

The fluorescence quantum yields (Φ) follow the opposite trend to ε; C4 substitution give higher quantum yields than C5 substitution. Compound **5**, which has a phenyl group at C5 has a quantum yield of 0.05 in toluene and 0.06 in MeOH. In comparison, the C4-substituted regioisomer **3** has a tenfold higher quantum yield. It also boasts the highest Φ value in the whole series measured in MeOH ($\Phi=0.48$ and 0.63, in toluene and MeOH, respectively). The C4 methoxylated derivative **2** has a similar emissive efficiency but exhibits supressed emission in MeOH ($\Phi=0.56$ and 0.36, in toluene and MeOH, respectively). Quenching in polar protic solvents is a recurrent behaviour for BTD-based D–A fluorophores, which almost exclusively are substituted in the C4 or C4,C7 positions.[24] This quenching effect is commonly attributed to hydrogen bonding ability of substituents, which usually lead to an increase of k_{nr} and non or weakly emissive excited states.[25] Compounds that exhibit charge separation in the excited state (e.g., from ICT) are also associated with quenching and non-radiative processes. However, these have a fundamentally different k_{rad} and k_{nr} decay. Polar protic media can further aid in the stabilization of charge-separated complexes contributing to these quenching effects.[26]

Further insight into the effect upon different emissive outcomes of C4 vs. C5 substitution could be obtained by returning to the spectroscopic behaviour of the parent BTD unit **1**. Monosubstitution at C4 (as in **2**) breaks the symmetry observed in **1**. Critically C4 substitution seems to play a strong role in the C4 C5 C3a angle bend previously discussed by Hollas and co-workers, which is key in the electronic transitions of **1**. Substitution at C4 leads to increased "allowedness" of the weak transition seen at 328 nm in **1**. As mentioned above, this transition is also partly bathochromically shifted to longer wavelengths (see **2**, Figure 2). We recently observed that C4-aurated BTDs exhibit a related behavior.[27] Long fluorescence lifetime of **2** ($\tau=32.4$ ns in MeOH) and large quantum yield in toluene and MeOH ($\Phi=0.56$ and 0.36, respectively) imply low geometrical distortion of the excited state. The excited state has few modes through which it can decay non-radiatively, that ultimately stabilize the Frank–Condon state (leading to large Stokes shifts). We further hypothesize that the excited state has poor overlap with the ground state wavefunction since it originates from a weakly allowed symmetry breaking vibration mode and thus acquires an extended lifetime. Accordingly, **2** and **3** (in which symmetry is broken by a C4 substituent) have long fluorescence lifetimes (e.g., **2**: $\tau=32.4$ ns in MeOH), while the C5-substituted derivatives, **4** and **5**, have short-lived emission (e.g., **4**: $\tau\leq0.8$ ns in MeOH). Several publications report the lifetime of BTD-based fluorophores, but there has been little to no discussion around these values and how they can be modified or even tuned.[28] Often it has been observed that the lifetimes depend on solvent polarity and whether the solvent is protic or aprotic. Demand for the ability to tune fluorescence lifetimes in fluorophore design is growing. For example, long-lived emission allows for lower detection of unwanted autofluorescence, which is commonly present in biological samples.[29] In addition, fluorophores with lifetimes that significantly differ in solvents of different polarity can be used as environment-sensitive probes.[30]

Photophysical trends for the disubstituted BTD derivatives **6**–**9** are not immediately obvious. In general, they have similar features as the monosubstituted congeners, such as solvent-dependent emission maxima and large Stokes shifts. The C4,C6-disubstituted **8** and **9** serve as another example of how significant the position of the substituents can be to the overall photophysical properties. Compound **8**, with a methoxy at C4 and a phenyl group at C6, has an order of magnitude longer lifetimes than **9**, where the substitution is reversed ($\tau=38.1$ for **8** and 3.5 ns for **9**, in MeOH). Also, the quantum yields of **8** are five to six times higher than for **9** (e.g., $\Phi=0.44$ and 0.09, respectively, in MeOH). The different behaviours of **8** and **9** resemble the effects seen for the monosubstituted BTDs (**2**–**5**). Here, the position of the donor motif dominates the emissive character as the properties primary match those of the methoxy substituted **2** and **4**. Accordingly, compounds **8** and **2** have

long lifetimes ($\tau = 38.1$ and 32.4 ns, respectively, in MeOH) and similar quantum yields ($\Phi = 0.44$ and 0.36, respectively, in MeOH), which implies that methoxy substitution at C4 plays a strong role in the emissive nature of the excited state of **8**. The *meta*-relationship of the substituents on the benzoid ring can be invoked as a possible explanation as the substituents do not a have direct electronic impact on each-other. Similarly, compounds **4** and **9** have short lifetimes (e.g., $\tau \leq 0.8$ and 3.5 ns, respectively, in MeOH) and low quantum yields ($\Phi = 0.09$ and 0.03, respectively, in MeOH). This also indicates that the excited state behaviour of **9** is dominated by the methoxy substitution at C5. In this case, it causes rapid non-radiative decay, short lifetimes, and diminished quantum yields. The absorption and emission spectra for **8** and **9** (Figure 3) show that the vibrational progression for the $^1A_1 \leftarrow ^1A_1$ band is lost due to substitution in the 6-position (equivalent to C5 substitution, discussed above) and that the emission for **8** is more redshifted than **9** ($\lambda_{Emax} = 501$ vs. 469 nm in MeOH) in virtue of the methoxy substitution at C4.

By analogy to **8**, the *ortho*-substituted **6** and **7** exhibit a set of photophysical properties that can be considered more desirable. Both compounds show extended lifetimes ($\tau = 24.9$ ns for **6** and 26.7 ns for **7** in MeOH) and the emission remain relatively unquenched in MeOH ($\Phi = 0.21$ for **6** and 0.50 for **7**). The effect of C4-substitution seem to be dominant for these derivatives as similar emissive properties are seen for the mono-C4-substituted **2** and **3**. However, compound **6** exhibits a slightly lower quantum yield in comparison with **7**, which might be due to a stronger D–A character of the system facilitated by the methoxy group at C4. Compound **6** also has the largest Stokes shift of all the studied derivatives (7700 cm^{-1} in toluene and 9600 cm^{-1} in MeOH). Compounds **6**–**8** serve as a proof-of-concept that regioselective substitution on BTD can prevent fluorescence quenching, as commonly seen for BTD derivatives in polar solvents.

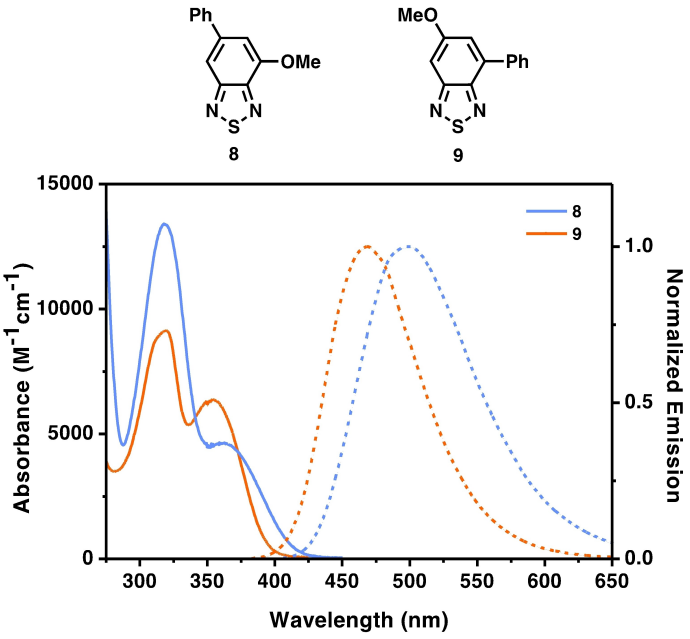


Figure 3. Absorbance normalized to the respective extinction coefficient (solid line) and emission (dashed line) spectrum of 4-methoxy-6-phenyl-BTD **8** (blue) and 4-phenyl-6-methoxy-BTD **9** (orange) in MeOH.

As expected (in accordance with the discussion above), the emission of the C4,C7 derivative **10** is highly dependent on the polarity of the solvent. It displays a high quantum yield in toluene ($\Phi = 0.64$) but is severely quenched in MeOH ($\Phi = 0.10$) where it loses 85% of the emission efficiency. It is the only derivative in the series that exhibits markedly higher lifetime in toluene than in MeOH ($\tau = 19.1$ and 7.6 ns, respectively). It also displays the most redshifted absorption and emission profiles in the series, which manifests a higher level of conjugation throughout the system than for the other derivatives. The C5,C6 regioisomer **11** displays the opposite behaviour; it has the lowest absorption wavelength and emission maxima of the disubstituted BTDs (**6**–**11**) and the quantum yield is not markedly solvent-dependent ($\Phi = 0.08$ and 0.12, respectively, in toluene and MeOH). The effect of C5 substitution also generates short-lived emission for **11** as well as high molar extinction coefficients ($\varepsilon = 19.5$. and 15.1×10^3 $M^{-1}cm^{-1}$ in toluene and MeOH, respectively).

Lippert–Mataga (L–M) analysis and correlation between the Stokes shift and Reichardt's $E_T(30)$ solvent polarity parameter showed positive solvatochromism in the excited state for all the derivatives **1**–**11** (ESI, Figure S1–11). Using Reichardt's $E_T(30)$ solvent polarity parameter gave a better linear fit but some compounds still showed low R^2 values (e.g., **4** and **11**, see ESI Figure S4 and S11). The relatively small slopes, which are near identical in the series, indicate that the excited species are equally stabilized by the solvent. We therefore assume that ICT does not have a predominant role in the observed steady state emissive nature of the compounds, which further can be supported by the fact that the emission of many compounds in the series do not quench in MeOH.

To better understand the time-dependant photophysical properties of **1**–**11**, a Strikler–Berg (SB) analysis[31] was done (for details see ESI). For compound **1**, it is unlikely that a simple SB analysis can accurately represent its excited state behaviour and lifetime as its $S_0 \rightarrow S_1$ transition originates from a partially symmetry forbidden transition that is weakly allowed. The natural lifetime (τ_0) for **1** is an upper bound estimation dependant on the true value of the fluorescence lifetime. Due to the very short radiative lifetimes of some compounds (**1**, **4**, **5**, and **11**) the experimentally determined radiative decay rates represent a lower bound for their true value. Relatively good agreement of the experimental and theoretically predicated values of k_{rad} and τ were observed for the monosubstituted derivatives **2** and **3**. However, the predicted values for the disubstituted derivatives with a phenyl at C5 or C6 (**6**, **8** and **11**) were significantly mismatched. For these, shorter lifetimes and faster radiative decay rates were predicted. This difference indicates that these compounds lack efficient non-radiative pathways from their excited states during relaxation. For all compounds, the SB relationship was able to predict relative increases or decreases in lifetime between toluene and MeOH. The exact origin and nature of the long natural lifetimes seen for many of the fluorophores in this work is unknown.

Conclusions

Mono- and disubstituted BTD-based regioisomers with methoxy and/or phenyl motifs were synthesized and characterized for their photophysical properties. Steady-state and time-resolved measurements revealed that the emission properties of these are highly dependent on the position of the substituent(s). The mono-C4-substituted derivatives exhibit long-lived emission due to breaking of the symmetry in the core BTD unit. In contrast, C5 substitution is detrimental for both fluorescence lifetimes and quantum yields. The regioisomeric effects were more pronounced upon methoxylation than arylation and the position of the methoxy group further dominates the excited state behavior for the disubstituted derivatives. For example, all C4-methoxylated BTDs displayed long fluorescence lifetimes and moderate to high quantum yields – regardless of arylation at C5 or C6. Notably, these arylations played an important role to secure high emission efficiency in MeOH. This demonstrates that C4,C5- and C4,C6-substituted BTDs, with a strong donor motif in the C4 position, can shift away from pure D–A or ICT character and circumvent fluorescence quenching in polar protic solvents. To the best of our knowledge, this is the first study that systematically investigates the regioisomeric effect on the emission of BTD. Our synthetic approach to generate all possible substituent patterns on BTD is highly modular. It comprises borylated, hydroxylated, and brominated intermediates that are amenable to a wide diversity of synthetic transformations. We foresee that this work breaks ground for expanding the chemical and photophysical space of BTD-based luminophores.

Supporting Information

The authors have cited additional references within the supporting information.[22g,32]

Acknowledgements

This work was supported by the Swedish Research Council Dnr: 2018-03524. The study made use of the NMR Uppsala infrastructure, which is funded by the Department of Chemistry – BMC and the Disciplinary Domain of Medicine and Pharmacy at Uppsala University. We thank Dr. Nidhi Kaul for valuable input on the photophysics and, Dr. Susanna Kunz and Dr. Lukasz T. Pilarski for proof-reading the manuscript.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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Manuscript received: February 16, 2024
Accepted manuscript online: April 15, 2024
Version of record online: May 22, 2024