Regioselective mono and homo/hetero dihalogenation of the benzothioxanthene monoimide

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Abstract: Through the preparation and characterization of five new derivatives, the regioselective mono and di, homo and hetero, halogenation of the benzothioxanthene (**BTXI**) core is demonstrated herein. All structurally solved by X-ray crystallography, these complementary functionalized building blocks open doors to the design of new symmetrical and asymmetrical π-conjugated systems based on this promising but still under-explored rylene.

Introduction

Over the past decades, the naphthalene (**NDI**) and perylene (**PDI**) diimides have emerged as reference building blocks in the field of organic electronics due to their excellent thermal and photochemical stability, synthetic tunability as well as specific electrochemical and high charge transport properties (Figure 1).[1-6] Although belonging to the imide-containing rylene family, the benzothioxanthene monoimide (**BTXI**) has not triggered such research interest, until recently.[7]

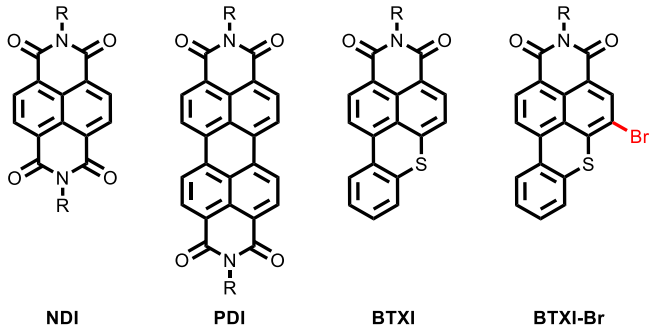


Figure 1. Structures of naphthalene diimide (**NDI**), perylene diimide (**PDI**), benzothioxanthene monoimide (**BTXI**) and the brominated derivative **BTXI-Br**.

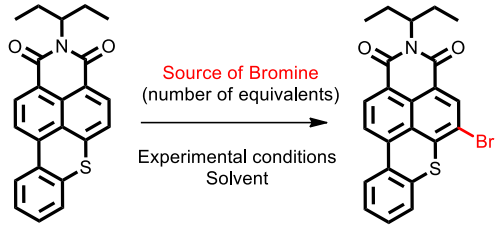
Synthesized in the 70's and solely functionalized on the *N*-position for post-grafting and/or solubility purposes,[8-12] we indeed recently demonstrated the selective mono-bromination (Figure 1, **BTXI-Br**) and use of this new promising block to prepare new π-conjugated systems *via* conventional palladium catalyzed cross-coupling reactions for organic photovoltaic applications.[13-15] As a step towards new design principles, and therefore potential applications, we report herein a systematic halogenation study of the **BTXI** block to afford complementary mono- and di-halogenated derivatives.

Results and Discussion

Hence, and from our early reported procedure,[13] where the **BTXI** was efficiently mono-brominated in the presence of 1.1 equivalents of bromine (Table 1, entry 1), we started to investigate the reactivity of additional and safer sources of bromine atoms.

To that end, the reactivity of the cheap and well-known *N*-bromosuccinimide (NBS) was first evaluated. It turned out that regardless of the reaction time (from few minutes to hours), temperature (room temperature or reflux) and nature of the solvent (chloroform or *N*,*N*-dimethylformamide), the entirety of the starting material was systematically recovered (Table 1, entries 2-5). However, while activating the NBS with *p*-toluenesulfonic acid in ethanol barely improved the conversion (Table 1, entry 6),[16] it was found that mechanochemistry can be an interesting tool to prepare the target **BTXI-Br** in high yield (Table 1, entry 7).[17] However, this solvent-free method requires a large excess of reactant (12 equivalents) to reach a full conversion of the starting material (Table 1, entry 9).

Table 1. Experimental conditions evaluated in this study to mono-brominate the **BTXI**. R.T. = room temperature.



BTXI **BTXI-Br**

Entry	Source of Bromine atom	Number of equivalents	Solvent	Experimental conditions	Synthetic Yield of isolated BTXI-Br
1	Bromine (Br_2)	1.1	dichloromethane	R.T.; overnight	93%
2	*N*-bromosuccinimide	4.0	*N*,*N*-dimethylformamide	R.T.; overnight	0%
3	*N*-bromosuccinimide	4.0	chloroform	R.T.; overnight	0%
4	*N*-bromosuccinimide	4.0	*N*,*N*-dimethylformamide	reflux; overnight	0%
5	*N*-bromosuccinimide	4.0	chloroform	reflux; overnight	0%
6	*N*-bromosuccinimide	4.0	ethanol	*p*-toluenesulfonic acid; microwave; 100 °C 15 minutes	11%
7	*N*-bromosuccinimide	3	no solvent	ball-milling; 1 hour	33%
8	*N*-bromosuccinimide	6	no solvent	ball-milling; 1 hour	60%
9	*N*-bromosuccinimide	12	no solvent	ball-milling; 1 hour	99%
10	Dibromoisocyanuric acid	1.1	*N*,*N*-dimethylformamide	R.T.; overnight	95%
11	Pyridinium tribromide	1.1	dichloromethane	R.T.; overnight	47%
12	Pyridinium tribromide	1.1	dichloromethane	microwaves, 100 °C; 1 hour	52%
13	Pyridinium tribromide	2.2	dichloromethane	microwaves, 100 °C; 1 hour	94%

In contrast, this was not the case for the dibromoisocyanuric acid since only 1.1 molar equivalents of this strong bromine source were indeed necessary to efficiently convert the **BTXI** into the target compound. Moreover, it is important to note that the reaction occurs under very mild conditions, *i.e.*, at room temperature and overnight (Table 1, entry 10). However, considering the relative high price of this reagent, the use of a cheaper one but still known to be a strong and solid source of bromine was finally assessed, namely the pyridinium tribromide. When engaged under the previously described mild conditions, *i.e.*, 1.1 equivalents at room temperature and overnight (Table 1, entry 11), a maximum conversion of 50% was reached (47% isolated), corresponding to a mixture of the target **BTXI-Br** and the starting material (**BTXI**). In an attempt to improve the reactivity, the conventional oil bath was directly replaced by microwave irradiations (Table 1, entry 12). Unfortunately, a well-balanced blend of **BTXI-Br** and **BTXI** was once

again recovered even after one hour of stirring at 100 °C. According to these observations, it was decided to double the amount of brominating agent (Table 1, entry 13) resulting in a full conversion, thus suggesting that the quantity of the pyridinium tribromide was the limiting parameter.
On the other hand, characterization of the crude by mass spectrometry also revealed the presence of a minor product attributed to a dibrominated species. As an important building block for a multi functionalization of the **BTXI** core, the second insertion of a bromine atom was naturally investigated. To do so, the amount of pyridinium tribromide was significantly increased to 5, 10 and even 20 equivalents under the same heating conditions (Table 2, entries 1-3). It turned out that using a large excess of this brominating agent indeed generated a dibrominated species but with a maximum yield of 12%, the major product still being in these conditions the mono derivative, ie, the **BTXI-Br**.

Hence, owing to its high reactivity, 2.2 equivalents of dibromoisocyanuric acid were subsequently added to a solution of **BTXI** (Table 2, entry 4). After 16 hours under reflux and the total consumption of the starting material, only one spot migrated on the thin layer chromatography (TLC), corresponding, after purification, to a dibrominated compound. With a resulting yield of *ca*. 32%, the quantity of brominated agent was increased to 5.0 equivalents (Table 2, entry 5). In these conditions, although only a single dibrominated derivative was recovered from the purification, the synthetic yield dropped to 18%, resulting from the higher amount of polar by-products stuck at the start of the chromatography column.

Consequently, the **BTXI** was finally exposed to an increasing quantity of bromine and the solutions were refluxed overnight (Table 2, entries 6-8). While, in all cases, the starting material was systematically consumed, the full conversion into a dibrominated derivative was only reached with 20 equivalents (Table 2, entry 8).

All isolated **Br-BTXI-Br** products were analyzed by ^{1}H NMR revealing a perfect superimposition of their spectra, thus confirming, in consistency with the TLC (same R_f = 0.6 in toluene), the generation of the same and unique dibrominated compound regardless of the nature of the brominating agent. Luckily, single crystals were successfully grown revealing the exact grafting of the second bromine atom at the 11 position as depicted in Figure 2.

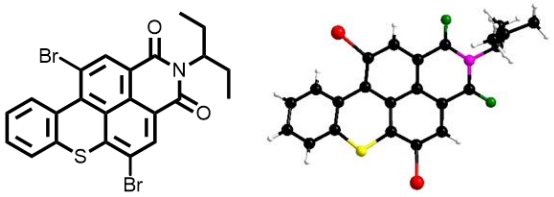
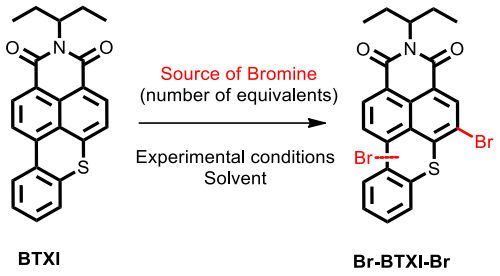


Figure 2. Molecular structure of the **Br-BTXI-Br** obtained by X-ray diffraction.

In parallel, the iodination of the **BTXI** was also investigated to extend the range of functionalization and reactivity (Table 3).

Table 2. Experimental conditions evaluated for the preparation of a dibrominated **BTXI**.



Entry	Source of Bromine atom	Number of equivalents	Solvent	Experimental conditions	Synthetic yield of BTXI/BTXI-Br and Br-BTXI-Br
1	Pyridinium tribromide	5.0	dichloromethane	microwaves, 100 °C; 1 hour	0%/93%/5%
2	Pyridinium tribromide	10.0	dichloromethane	microwaves, 100 °C; 1 hour	0%/85%/11%
3	Pyridinium tribromide	20.0	dichloromethane	microwaves, 100 °C; 1 hour	0%/83%/12%
4	Dibromoisocyanuric acid	2.2	*N,N*-dimethylformamide	reflux.; overnight	0%/0%/32%
5	Dibromoisocyanuric acid	5.0	*N,N*-dimethylformamide	reflux.; overnight	0%/0%/18%
6	Bromine	5.0	dichloromethane	reflux; overnight	0%/78%/19%
7	Bromine	10.0	dichloromethane	reflux; overnight	0%/23%/73%
8	Bromine	20.0	dichloromethane	reflux; overnight	0%/0%/98%

Mild and green conditions, reported by Gohier and coworkers,[16] using *N*-iodosuccinimide in ethanol with a catalytic amount of *p*-toluenesulfonic acid, were first investigated (Table 3, entry 1). Stirring the reaction mixture overnight at 60 °C successfully led to the formation of a new compound. Once isolated in good yield by column chromatography, the latter was subsequently analyzed by mass spectrometry and NMR experiments revealing the presence of a single iodine atom grafted on the constituting naphthyl moiety of **BTXI**, the exact position of which was, once again, solved by single crystal X-ray diffraction (Figure 3).

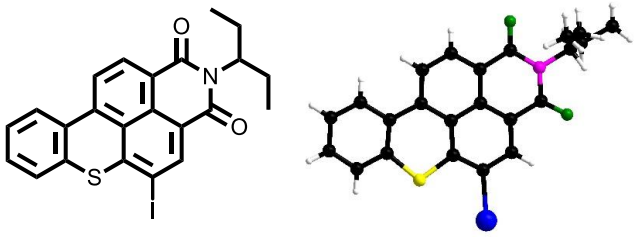
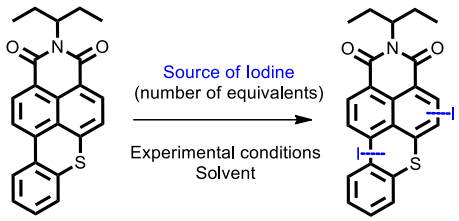


Figure 3. Molecular structure of the **BTXI-I** obtained by X-ray diffraction.

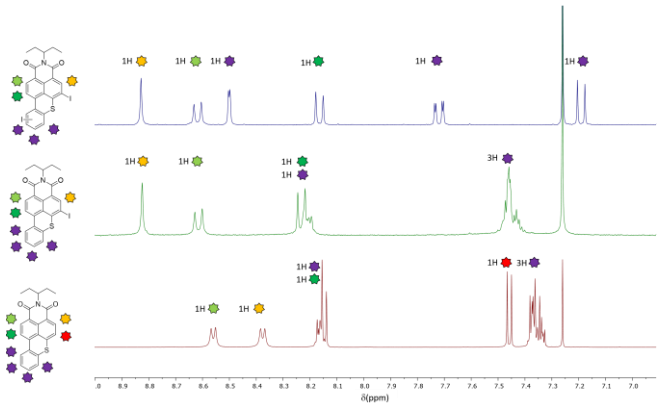
Table 3. Experimental conditions for the synthesis of the mono- and di-iodinated **BTXI** based derivatives (**BTXI-I** and **I-BTXI-I**). R.T. = room temperature.



Entry	Source of Iodine atom	Number of equivalents	Solvent	Experimental conditions	Synthetic yield of BTXI/BTXI-I and I-BTXI-I
1	*N*-iodosuccinimide	2.0	ethanol	*p*-toluenesulfonic acid; 60 °C.; overnight	30%/67%/0%
2	*N*-iodosuccinimide	2.0	ethanol	*p*-toluenesulfonic acid; microwave, 100 °C; 1 hour	12%/80%/0%
3	*N*-iodosuccinimide	4.0	ethanol	*p*-toluenesulfonic acid; microwave, 100 °C; 1 hour	0%/100%/0%
4	Iodine/Iodic acid	2.5/cat.	acetic acid:sulfuric acid:water:$CHCl_3$ (1:0.02:0.2:0.08 /v:v:v:v)	R.T.; overnight	0%/67%/3%
5	Iodine/Iodic acid	2.5/cat.	acetic acid:sulfuric acid:water:$CHCl_3$ (1:0.02:0.2:0.08 /v:v:v:v)	90 °C; overnight	0%/38%/19%

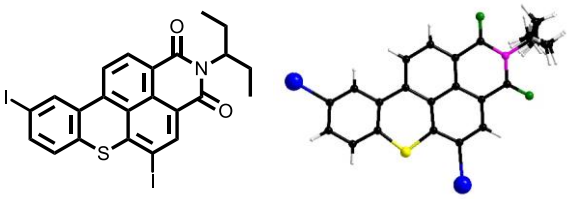
As for **BTXI-Br**, the iodination occurs on the rylene core at the β-position with regards to the sulfur atom. In addition to changing the heating method (Table 3, entry 2), the full conversion of the **BTXI** in this new derivative, namely **BTXI-I,** was only achieved by increasing the quantity of *N*-iodosuccinimide (Table 3, entry 3). Interestingly, though a large excess of this reagent was used, no multi-halogenated compound was detected in the crude. In an attempt to generate such species, a stronger method based on the use of the iodic acid/iodine couple in a mixture of acetic and sulfuric acid, water and chloroform was considered and evaluated. After 16 hours of stirring at room temperature, TLCs highlighted the formation of two compounds (Table 3, entry 4). Once purified by simple column chromatography, the major product was found to be the above mentioned mono-iodinated **BTXI** (**BTXI-I**) while the second, isolated with a low yield, corresponds to a di-iodinated derivative. In stark contrast with **Br-BTXI-Br** where both bromine atoms are localized on the naphthyl ring, ^{1}H NMR experiments of the new **I-BTXI-I** suggested a functionalization of the constituting phenyl ring (Figure 4, purple tagged protons).

Figure 4. Comparison of **BTXI**, **BTXI-I** and **I-BTXI-I** ^{1}H NMR spectra recorded at room temperature in deuterated chloroform.



While the integrity of the naphthyl constituting protons were recovered when comparing the spectra of both **BTXI-I** and **I-BTXI-I**, the multiplet centered at ca. 7.45 ppm, that comprises three hydrogen atoms, splits into a doublet (at 7.19 ppm) and a doublet of doublets (at 7.72 ppm) of one proton each. Moreover, the characteristic doublet centered at 8.5 ppm of **I-BTXI-I**, also attributed to a phenyl proton, appears significantly deshielded (compared to its **BTXI-I** analogue) thus supporting a close-by halogenation. Single crystal X-ray diffraction later confirmed these suppositions, thus revealing the exact position of the second iodine atom, corresponding to a functionalization in *para* of the sulfur atom (Figure 5).

Figure 5. Molecular structure of the **I-BTXI-I** obtained by X-ray diffraction



In a further attempt to improve the conversion into this new bis-functionalized derivative, the temperature of the reaction was increased to 90 °C for 24 h (Table 3, entry 5). While a larger amount of **I-BTX-I** was indeed isolated, these conditions also led to more unidentified and mostly insoluble by-products. Hence, to take it to the next level, these reactions were finally complementarily combined to afford hetero- and regiospecific dihalogenated derivatives (Scheme 1).

To do so, **BTXI-Br** was successfully iodinated in acidic conditions in the presence of iodic acid and iodine. As for **I-BTXI-I**, the iodine atom was found to be localized on the phenyl ring in *para* position with respect to the sulfur atom as evidenced by ^{1}H NMR and single crystal X-ray diffraction (**I-BTXI-Br**, Figure 6). In parallel, **BTXI-I** was first exposed to 20 equivalents of bromine. After reflux overnight, TLCs revealed the total consumption of the starting compound and generation of a single compound. However, once isolated and characterized, the latter turned out to be the dibrominated **Br-BTXI-Br**. Consequently, to avoid the halogen exchange reaction, the excess of bromine was replaced by only 1.1 equivalents of dibromoisocyanuric acid. First highlighted by TLCs, a new compound, whose R_f was found to be different from that of the **Br-BTXI-Br**, was successfully isolated in good yield after the total consumption of the starting material and purification of the crude. Mass spectrometry confirmed the presence of both a bromine and an iodine atom on this new **BTXI** derivative and ^{1}H NMR suggested a functionalization on the naphthyl

ring as for **Br-BTXI-Br** (see SI). Luckily, crystals of good quality were successfully grown and analyzed by X-ray diffraction confirming both hypothesized structures (Figure 6).

Scheme 1. Regioselective hetero dihalogenated derivatives reported herein.

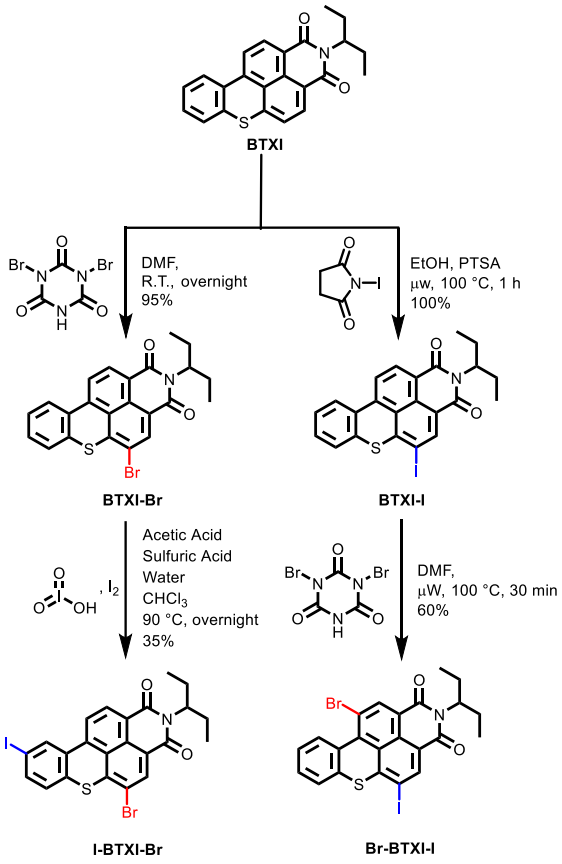
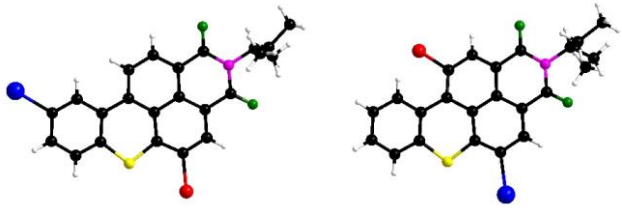


Figure 6. X-ray structures of **I-BTXI-Br** (left) and **Br-BTXI-I** (right).



Conclusion

In conclusion, the regioselective dihalogenation of the **BTXI** core is demonstrated herein. As a result, five new derivatives were successfully prepared, isolated and characterized. Depending on the nature and source of the halogen atom, different positions on the rylene core are now fully and, above all, selectively accessible for post grafting purposes, thus opening doors to new designs of functional π-conjugated BTXI based molecules and polymers.

Experimental Section
Supporting Information

Acknowledgements
Authors thank the MATRIX SFR of the University of Angers. J.M.A.C. and P.S.M. thanks the European Union's Horizon 2020 research and innovation program under Marie Sklodowska Curie Grant agreement No.722651 (SEPOMO). The Région Pays de la Loire is also acknowledged for the grant of C. D. (Projet étoile montante SAMOA). The authors are also grateful to ANR (SADAM ANR-16-CE07-0015-01) for financial support and the PDF grant of L.A.G.

Keywords: selective halogenation • benzothioxanthene • organic chemistry • rylene

References
1. Feng, J.; Jiang, W.; Wang, Z., Synthesis and Application of Rylene Imide Dyes as Organic Semiconducting Materials. *Chemistry – An Asian Journal* 2018, *13* (1), 20-30.
2. Sun, M.; Müllen, K.; Yin, M., Water-soluble perylenediimides: design concepts and biological applications. *Chemical Society Reviews* **2016,** *45* (6), 1513-1528.
3. Zhang, F.; Ma, Y.; Chi, Y.; Yu, H.; Li, Y.; Jiang, T.; Wei, X.; Shi, J., Self-assembly, optical and electrical properties of perylene diimide dyes bearing unsymmetrical substituents at bay position. *Scientific Reports* **2018,** *8* (1), 8208.
4. Kozma, E.; Catellani, M., Perylene diimides based materials for organic solar cells. *Dyes and Pigments* **2013,** *98* (1), 160-179.
5. Würthner, F.; Saha-Möller, C. R.; Fimmel, B.; Ogi, S.; Leowanawat, P.; Schmidt, D., Perylene Bisimide Dye Assemblies as Archetype Functional Supramolecular Materials. *Chemical Reviews* **2016,** *116* (3), 962-1052.
6. Liu, Z.; Wu, Y.; Zhang, Q.; Gao, X., Non-fullerene small molecule acceptors based on perylene diimides. *Journal of Materials Chemistry A* **2016,** *4* (45), 17604-17622.
7. Andrés Castán, J. M.; Abad Galán, L.; Li, S.; Dalinot, C.; Simón Marqués, P.; Allain, M.; Risko, C.; Monnereau, C.; Maury, O.; Blanchard, P.; Cabanetos, C., Nitration of benzothioxanthene: towards a new class of dyes with versatile photophysical properties. *New Journal of Chemistry* **2020,** *44* (3), 900-905.
8. Grayshan, P. H.; Kadhim, A. M.; Perters, A. T., Heterocyclic derivalives of naphthalene-1,8-dicar boxylie anhydride. Part III. Benzo[k,l] thioxanthene-3,4-dicarboximides. *Journal of Heterocyclic Chemistry* **1974,** *11* (1), 33-38.
9. Kadhim, A. M.; Peters, A. T., A new intramolecular cyclisation reaction—I: Novel synthesis of benzo(k,1)thioxanthene-3,4-dicarboxylic anhydride and derived dyestuffs. *Tetrahedron* **1974,** *30* (14), 2245-2249.
10. Danko, M.; Chmela, Š.; Hrdlovič, P., Synthesis, photochemical stability and photo-stabilizing efficiency of probes based on benzothioxanthene chromophore and Hindered Amine Stabilizer. *Polymer Degradation and Stability* **2006,** *91* (5), 1045-1051.
11. Mao, P.; Qian, X.; Zhang, H.; Yao, W., Benzothioxanthene dyes as fluorescent label for DNA hybridization: synthesis and application. *Dyes and Pigments* **2004,** *60* (1), 9-16.
12. Zhang, W.; Chen, M.; Ling Wu, Y.; Tanaka, Y.; Juan Ji, Y.; Lin Zhang, S.; He Wei, C.; Xu, Y., Formation and stabilization of the telomeric antiparallel G-quadruplex and inhibition of telomerase by novel benzothioxanthene derivatives with anti-tumor activity. *Scientific Reports* **2015,** *5* (1), 13693.
13. Josse, P.; Li, S.; Dayneko, S.; Joly, D.; Labrunie, A.; Dabos-Seignon, S.; Allain, M.; Siegler, B.; Demadrille, R.; Welch, G. C.; Risko, C.; Blanchard, P.; Cabanetos, C., Bromination of the benzothioxanthene Bloc: toward new π-conjugated systems for organic electronic applications. *Journal of Materials Chemistry C* **2018,** *6* (4), 761-766.

14. Payne, A.-J.; Rice, N. A.; McAfee, S. M.; Li, S.; Josse, P.; Cabanetos, C.; Risko, C.; Lessard, B. H.; Welch, G. C., Donor or Acceptor? How Selection of the Rylene Imide End Cap Impacts the Polarity of π-Conjugated Molecules for Organic Electronics. *ACS Applied Energy Materials* **2018,** *1* (9), 4906-4916.
15. Dayneko, S. V.; Hendsbee, A. D.; Cann, J. R.; Cabanetos, C.; Welch, G. C., Ternary organic solar cells: using molecular donor or acceptor third components to increase open circuit voltage. *New Journal of Chemistry* **2019,** *43* (26), 10442-10448.
16. Grolleau, J.; Frère, P.; Gohier, F., Clean and Efficient Iodination of Thiophene Derivatives. *Synthesis* **2015,** *47* (24), 3901-3906.
17. Bose, A.; Mal, P., Electrophilic aryl-halogenation using N-halosuccinimides under ball-milling. *Tetrahedron Letters* **2014,** *55* (13), 2154-2156.