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Blue-Light Photocleavable Protecting Groups Based on Benzothiadiazole Scaffolds

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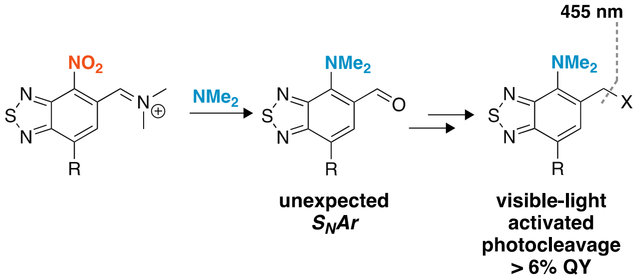
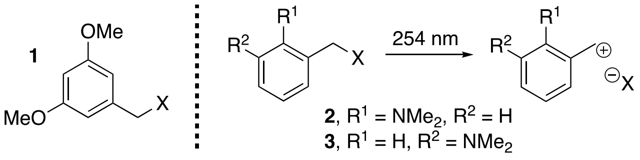
Supporting Information

ABSTRACT: An unexpected nucleophilic aromatic substitution lead to a novel benzothiadiazole scaffold that bore the functional group pattern associated with benzyl-type photocleavable protecting groups. The new molecules display efficient photochemical release of leaving groups with blue light. The performance of both ortho- and meta-substituted derivatives was probed through both structural manipulation and computational metrics to improve performance.



The reactivity of molecules in their ground and excited states differ due to changes in bond length and electronic distribution. A key example of this phenomenon is the "meta-ortho effect".[1] Electron-donating groups are generally understood to activate the ortho- and para-positions of a benzene ring in ground-state reactions (e.g., S_EAr). Upon photoexcitation, however, electron density redistributes to the ortho- and meta-positions, imparting different reactivity in the excited state. An archetype of this chemistry is the 3,5-dimethoxybenzyl system (**1**, Scheme 1), which only undergoes cleavage of the C–X benzyl bond upon photoexcitation with ultraviolet light due to a buildup of electron density at positions meta to the OMe groups, which causes elimination of the leaving group X.[1−3]

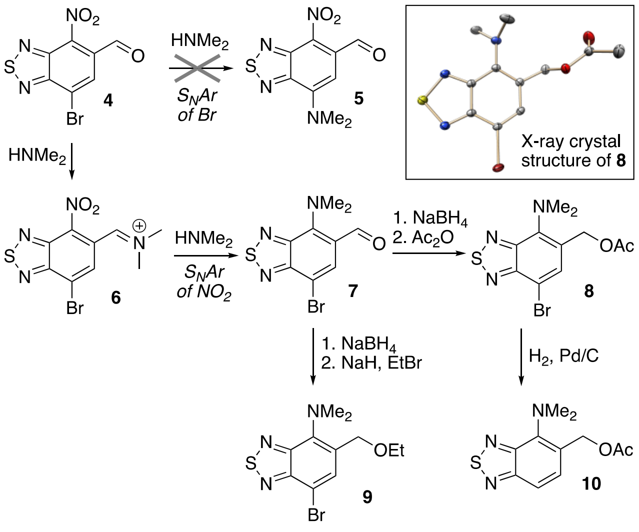
Scheme 1. Photocleavable Protecting Groups Based on the Meta-Ortho Effect



This reactivity is mirrored in the more strongly donating NMe_2 analogues (**2** and **3**).[4] These derivatives have not received much attention when compared to their OMe cousins. Indeed, even though the meta-ortho effect was established for OMe derivatives in the 1960s,[5] it has only been in the last 10 years that the NR_2 analogues have received considerable attention.[4,6−13] However, meta-substituted derivatives related to **3** can display quantum yields of release as high as 0.45 at 254 nm.[4]

Our lab has been studying the excited state properties of push−pull benzothiadiazole dyes.[14] During one particular synthetic route (Scheme 2), we sought to synthesize a push−pull scaffold through installation of an electron-donating group into **4** via S_NAr en route to **5**. We were surprised to observe that the NO_2 substituted in preference to the Br to give **7**. Substitution of NO_2 during S_NAr has been observed previously,[15] and we speculated that putative *in situ* formation of a dimethyl iminium ion (**6**) makes attack at NO_2 more favorable than attack at Br. We noted that the substitution pattern in the unexpected product **7** was similar to established "benzyl-type" photocleavable protecting groups (such as **2**),

Scheme 2. Surprising Substitution



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which lead us to probe the potential for photochemical reactivity in the context of the meta-ortho effect. Accordingly, **7** was elaborated into **8** and **9** for testing, where **8** was unambiguously characterized via X-ray crystallography (Scheme 2).

The absorbance of both **8** and **9** was in the visible (blue) with similar λ_{max} values (Figure 1). We irradiated both compounds individually at 455 nm in methanol using an LED source and, gratifyingly, observed photocleavage of the leaving groups, as predicted by the meta-ortho effect. The quantum yield of release (Table 1) aligned with the leaving group ability of the X substituent, where OAc appeared to cleave more efficiently than OEt for both ortho-derivatives **8** and **9**. It is noteworthy that these results conflict with previous reports that found that ortho-derivative **2** cleaved alcohol leaving groups more efficiently than carboxyl leaving groups.[4] This behavior does not appear to be the case for **8** and **9**.

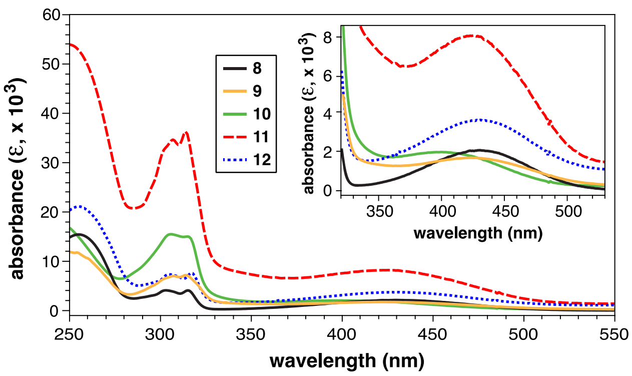


Figure 1. Absorbance spectra of photocleavable protecting groups **8**–**12** in MeOH.

Table 1. Quantum Yield of Photochemical Bond Cleavage

compound	isomer	leaving group	quantum yield of release Φ[a]	ε × Φ[b]
8	ortho	OAc	0.028 ± 0.004	60
9	ortho	OEt	0.015 ± 0.003	25
10	ortho	OAc	0.067 ± 0.001	133
11	meta	OAc	0.061 ± 0.001	483
12	meta	OEt	0.040 ± 0.001	144
1	meta	OAc	0.100 ± 0.001[c]	
2	ortho	OAc	0.26 ± 0.04[d]	
3	meta	OAc	0.080 ± 0.020[d]	

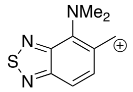
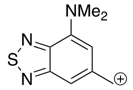
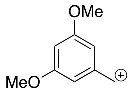
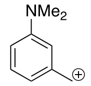
[a] Quantum yields were determined in CD_3OD relative to a BODIPY standard at 455 nm. See Supporting Information for details. [b] The ε corresponds to the λ_{max} (see Table S1 for details). [c] Previously reported[5] in dioxane:H_2O (1:1). [d] Previously reported[4] in CH_3CN:H_2O (1:4).

The magnitude of the quantum yield of release of leaving group from **8** and **9** compares favorably with ortho-substituted derivatives related to **2**.[4] It is noteworthy, however, that **8** and **9** can be excited with blue light and display an order of magnitude higher quantum yield for release compared to other photocleavable protecting groups based on coumarin or BODIPY that operate by a similar mechanism.[16−18]

The presence of a bromine atom in **8** was an artifact of the unanticipated substitution of the NO_2 group in **4**. Indeed, 4-bromo-*N*,*N*-dimethylaniline is known to undergo photochemical scission of the C−Br bond.[19] This potential side reactivity could limit the quantum yield of release for **8**. We therefore sought to probe what effect the bromine might have on the photochemical release of OAc by synthesizing **10**. We were able to reduce the Br using hydrogenation while keeping the benzyl-OAc moiety intact. Subsequent irradiation led to a doubling of the quantum yield of release for **10** compared to **8** (Table 1), indicating that the bromine did have an effect on the efficiency bond-cleaving reaction.[20,21]

To identify other avenues to improve the efficiency of photochemical bond cleavage, we employed a computation prediction tool that has been benchmarked against known photocleavable protecting groups (Table 2).[22] Briefly, the S_0−S_1 vertical energy of the cationic reactive intermediate following heterolytic bond cleavage serves as a simple yet effective predictor of favorable heterolysis of the benzyl group following photoexcitation.[22] A computed S_0−S_1 energy gap below ∼50 kcal/mol is understood to have a higher likelihood for direct heterolysis via an accessible conical intersection between the S_0 and S_1 states. By this metric, the ortho-substituted photocage **10** was predicted to display poor performance toward heterolytic photochemical bond cleavage (Table 2, entry 1, S_0−S_1 values above 50 kcal/mol). Of course, the fact that **10** does undergo photocleavage (Table 1) and that the computed S_0−S_1 energy gap for **10** was only slightly higher than established "meta-ortho effect" photocleavable protecting groups **1** and **3** (Table 2, entries 4 and 5) indicated that this particular computational tool was only a rough estimation (or that **10** may proceed via a different mechanism that does not require a conical intersection such as adiabatic cleavage to produce excited state products that then relax to the ground state).[22]

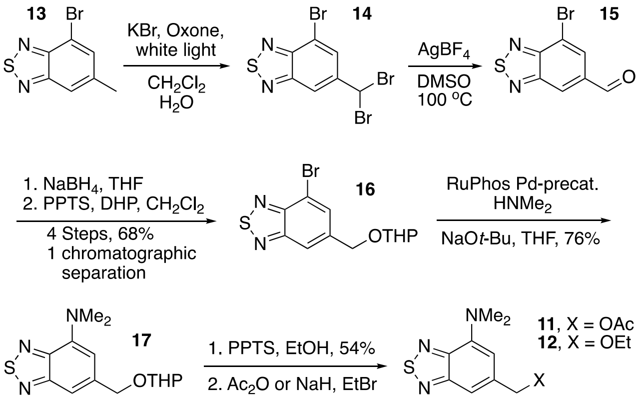
Table 2. Computed Metrics of Ortho- and Meta-Derivatives[a]

entry	cationic intermediate		S_0-S_1 vertical energy (kcal/mol)
1		From **10**	61.7
2		From **11** or **12**	15.7
3		From **1**	42.9[22]
4		From **3**	35.0[22]

[a] S_0−S_1 calculated using TD-rB3LYP/6-311+g(2d,p)//rB3LYP/6-31g(d) following the reported protocol.[22]

Notably, however, a meta-substitution pattern between the NMe_2 group and the benzyl moiety (Table 2, entry 3) was predicted to have a considerably lower S_0−S_1 energy gap than established photocleavable protecting groups **1** and **3**. Thus, the meta-isomer was predicted to have an accessible conical intersection to permit efficient photocleavage. This result drove us to synthesize meta-derivatives **11** and **12** (Scheme 3).

Scheme 3. Synthesis of Meta-Isomers 11 and 12



White-light irradiation of **13** in the presence of KBr and oxone generated a mixture of the dibrominated (**14**) and monobrominated products (not shown).[23] NMR analysis of the crude mixture showed a ratio of 2:1 of di- to monobrominated product, both of which react with $AgBF_4$ to yield aldehyde **15** as the single product.[24] Reduction of aldehyde **15** and protection of the subsequent alcohol as a THP ether produced **16** in a 68% yield over 4 steps. Protection of the alcohol was required to realize productive yields of **17** via Pd-catalyzed C−N cross-coupling.[25] Finally, deprotection of the THP group and installation of either the acetate or ethoxy leaving group provided the meta-derivatives **11** and **12** for testing.

As anticipated, the absorbance of both **11** and **12** was comparable to that of **8**−**10** (Figure 1). Similarly, both **11** and **12** were irradiated at 455 nm in methanol using an LED source to test for photocleavage behavior. The meta-derivatives (Table 1, entries 4 and 5) displayed an approximate doubling of the quantum yield of release of leaving group relative to the brominated ortho-derivatives (Table 1, entries 1 and 2) for both acetate and alkoxy leaving groups. However, as already discussed above for **10**, the increase in quantum yield for the meta-derivatives could be ascribed to the absence of a bromine atom in **11** and **12** relative to **8** and **9**. Indeed, removal of the bromine for ortho-derivatives **10** lead to a similar doubling in quantum yield compared to **8** (Table 1).

Thus, the comparison between **10** and **11** (Table 1) was the most illuminating because both derivatives lack a bromine atom and only differ in terms of their substitution pattern. Accordingly, the quantum yield for both **10** and **11** were almost identical. These data allow us to evaluate the performance prediction described in Table 2. The computational tool used in Table 2 attempts to estimate the energy gap between the ground and excited state of the cationic intermediate following bond heterolysis. In principle, the smaller this energy gap, the greater the propensity for direct photocleavage due to a nearby conical intersection.[22] Based on the data presented here, the computational metric may well be able to predict competent photocleavable protecting groups for structures with S_0−S_1 energy gaps ~50 kcal/mol. However, based on the similar quantum yield of **10** and **11**, some caution is warranted in the quantitative comparison and prediction of enhanced photocleavage efficiency based on smaller S_0−S_1 energy gaps. This finding is by no means an indictment of the computational metric as the method provides a simple and rapid prediction of performance, where the quantitative description of excited-state energy surfaces requires time-intensive computational approaches (e.g., CASSCF).

We report a novel photocleavable protecting group based on the benzothiadiazole scaffold, which arose via an unexpected nucleophilic aromatic substitution reaction. The new protecting groups are activated with visible blue light and appear to behave according to the so-called "meta-ortho effect" to cleave a bond at the benzyl position with release of a leaving group. The molecules described here display quantum yields of release that are 10-fold higher than other photocages based on chromophores that absorb visible light and operate by a similar mechanism.[16−18] The efficiency of release corresponds to the leaving group ability at the benzyl position. Finally, this work provides evidence that a previously reported computational tool can inform the design of new photoactivatable probes through a qualitative prediction of properties. Future efforts will focus on strategies to further improve the quantum efficiency of release as well as structural strategies to red-shift the absorbance of this new class of photocleavable protecting groups.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04268.

> Synthetic procedures, compound characterization, ^1H and ^{13}C NMR, HRMS, and quantum yield procedures and data (PDF)

Accession Codes

CCDC 1967940 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Zimmerman, H. E. The Meta-Ortho Effect in Organic Photochemistry; Mechanistic and Exploratory Organic Photochemistry. *J. Phys. Chem. A* **1998**, *102*, 7725−7725.

(2) Pincock, J. A. Photochemistry of Arylmethyl Esters in Nucleophilic Solvents: Radical Pair and Ion Pair Intermediates. *Acc. Chem. Res.* **1997**, *30*, 43−49.

(3) Zimmerman, H. E. The Meta Effect in Organic-Photochemistry - Mechanistic and Exploratory Organic-Photochemistry. *J. Am. Chem. Soc.* **1995**, *117*, 8988−8991.

(4) Skalamera, D.; Blazek Bregovic, V.; Antol, I.; Bohne, C.; Basaric, N. Hydroxymethylaniline Photocages for Carboxylic Acids and Alcohols. *J. Org. Chem.* **2017**, *82*, 12554−12568.

(5) Zimmerman, H. E.; Sandel, V. R. Mechanistic Organic Photochemistry 0.3. Excited State Solvolyses. *J. Am. Chem. Soc.* **1963**, *85*, 915−922.

(6) Winter, A. H.; Falvey, D. E.; Cramer, C. J.; Gherman, B. F. Benzylic Cations with Triplet Ground States: Computational Studies of Aryl Carbenium Ions, Silylenium Ions, Nitrenium Ions, and Oxenium Ions Substituted with Meta Pi Donors. *J. Am. Chem. Soc.* **2007**, *129*, 10113−9.

(7) Wang, P.; Zhou, L.; Zhang, X.; Liang, X. Facilitated Photochemical Cleavage of Benzylic C-O Bond. Application to Photolabile Hydroxyl-Protecting Group Design. *Chem. Commun.* **2010**, *46*, 1514−6.

(8) Perrotta, R. R.; Winter, A. H.; Falvey, D. E. Photochemical Heterolysis of 3,5-Bis(Dimethylamino)Benzyl Alcohols and Esters: Generation of a Benzyl Cation with a Low-Energy Triplet State. *Org. Lett.* **2011**, *13*, 212−5.

(9) Zhou, L.; Yang, H.; Wang, P. Development of Trityl-Based Photolabile Hydroxyl Protecting Groups. *J. Org. Chem.* **2011**, *76*, 5873−81.

(10) Wang, P.; Lu, W.; Devalankar, D.; Ding, Z. Photochemical Formation and Cleavage of C-N Bond. *Org. Lett.* **2015**, *17*, 170−2.

(11) Wang, P.; Lu, W.; Devalankar, D. A.; Ding, Z. Structurally Simple Benzyl-Type Photolabile Protecting Groups for Direct Release of Alcohols and Carboxylic Acids. *Org. Lett.* **2015**, *17*, 2114−7.

(12) Wang, P.; Devalankar, D. A.; Lu, W. Photochemical Cleavage of Benzylic C-N Bond to Release Amines. *J. Org. Chem.* **2016**, *81*, 6195−200.

(13) Ding, X.; Wang, P. Photochemical Cleavage of Benzylic C-O Bond Facilitated by an Ortho or Meta Amino Group. *J. Org. Chem.* **2017**, *82*, 7309−7316.

(14) Thooft, A.; Cassaidy, K.; VanVeller, B. A Small Push-Pull Fluorophore for Turn-on Fluorescence. *J. Org. Chem.* **2017**, *82*, 8842−8847.

(15) Youngs, W. J.; Tessier, C. A.; Bradshaw, J. D.; Senskey, M. D. Aryl Nitro Group Substitution by Primary and Secondary Amines. *Tetrahedron Lett.* **1995**, *36*, 6217−6220.

(16) Atta, S.; Jana, A.; Ananthakirshnan, R.; Narayana Dhuleep, P. S. Fluorescent Caged Compounds of 2,4-Dichlorophenoxyacetic Acid (2,4-D): Photorelease Technology for Controlled Release of 2,4-D. *J. Agric. Food Chem.* **2010**, *58*, 11844−51.

(17) Goswami, P. P.; Syed, A.; Beck, C. L.; Albright, T. R.; Mahoney, K. M.; Unash, R.; Smith, E. A.; Winter, A. H. Bodipy-Derived Photoremovable Protecting Groups Unmasked with Green Light. *J. Am. Chem. Soc.* **2015**, *137*, 3783−6.

(18) Klan, P.; Solomek, T.; Bochet, C. G.; Blanc, A.; Givens, R.; Rubina, M.; Popik, V.; Kostikov, A.; Wirz, J. Photoremovable Protecting Groups in Chemistry and Biology: Reaction Mechanisms and Efficacy. *Chem. Rev.* **2013**, *113*, 119−91.

(19) Freccero, M.; Fagnoni, M.; Albini, A. Homolytic Vs Heterolytic Paths in the Photochemistry of Haloanilines. *J. Am. Chem. Soc.* **2003**, *125*, 13182−90.

(20) Slanina, T.; Shrestha, P.; Palao, E.; Kand, D.; Peterson, J. A.; Dutton, A. S.; Rubinstein, N.; Weinstain, R.; Winter, A. H.; Klan, P. Search of the Perfect Photocage: Structure-Reactivity Relationships in Meso-Methyl Bodipy Photoremovable Protecting Groups. *J. Am. Chem. Soc.* **2017**, *139*, 15168−15175.

(21) Kamkaew, A.; Lim, S. H.; Lee, H. B.; Kiew, L. V.; Chung, L. Y.; Burgess, K. Bodipy Dyes in Photodynamic Therapy. *Chem. Soc. Rev.* **2013**, *42*, 77−88.

(22) Buck, A. T.; Beck, C. L.; Winter, A. H. Inverted Substrate Preferences for Photochemical Heterolysis Arise from Conical Intersection Control. *J. Am. Chem. Soc.* **2014**, *136*, 8933−8940.

(23) Moriyama, K.; Takemura, M.; Togo, H. Direct and Selective Benzylic Oxidation of Alkylarenes Via C-H Abstraction Using Alkali Metal Bromides. *Org. Lett.* **2012**, *14*, 2414−7.

(24) Ganem, B.; Boeckman, R. K. Silver-Assisted Dimethylsulfoxide Oxidations - Improved Synthesis of Aldehydes and Ketones. *Tetrahedron Lett.* **1974**, *15*, 917−920.

(25) Bruno, N. C.; Niljianskul, N.; Buchwald, S. L. N-Substituted 2-Aminobiphenylpalladium Methanesulfonate Precatalysts and Their Use in C-C and C-N Cross-Couplings. *J. Org. Chem.* **2014**, *79*, 4161−6.

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