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Synthesis of Double-Bond-Substituted Hemithioindigo Photoswitches

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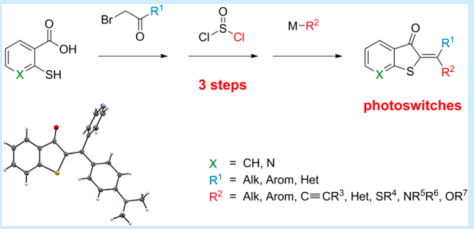
Supporting Information

ABSTRACT: A very short, high yielding, and convergent synthesis with broad substrate scope, enabling access to a very diverse range of hemithioindigos with 4-fold substituted double-bonds, is presented. With this method, carbon as well as nitrogen, oxygen, or sulfur based substituents can easily be introduced, delivering a wide array of novel structural motifs. Irradiation studies with visible light demonstrate proficient photoswitching properties of these chromophores at wavelengths up to 625 nm.



Hemithioindigo (HTI) is a chromophore[1] of very high current interest because of its efficient photoswitching properties[2] in the visible part of the electromagnetic spectrum. For this reason, HTI has attracted increasing attention for applications in biological,[3] supramolecular,[4] or medicinal chemistry[5] as well as in the realms of molecular machines[6] or molecular computing.[7] HTIs consist of a central double-bond, which bears a thioindigo moiety at one end and a so-called stilbene fragment at the other end (Figure 1). The central

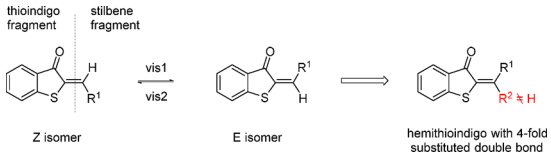


Figure 1. Hemithioindigo chromophore and derivatives with 4-fold substituted double-bond.

double-bond undergoes photoisomerization after irradiation with a suitable wavelength, usually from the thermodynamically stable *Z* to the metastable *E* configuration. The complementary *E* to *Z* photoisomerization takes place after irradiation with longer wavelengths (positive photochromism).

A number of different synthetic schemes are available to obtain HTI chromophores.[8] However, the overwhelmingly prevalent structural motive contains a stilbene fragment with only one, and typically aromatic, substituent. HTIs bearing instead two substituents at that side of the double-bond (i.e., an overall 4-fold substituted double-bond) are known in the literature, but only limited and (in most cases) cumbersome syntheses are available for this scarcely explored class of potential photoswitches. We have used HTIs with 4-fold-substituted double-bonds in the context of light driven molecular motors[6a] and also recently presented a new synthesis to access sterically more hindered derivatives, which showcases the importance of this substitution pattern for advanced functions.[6b]

For the introduction of two carbon-based substituents R^1 and R^2 at the stilbene fragment, most published synthetic schemes rely on condensation reactions between benzothiophenone and either ketones and analogues,[9] electron-poor double-bonds bearing a leaving group,[10] or reverse condensations between oxidized benzothiophenones and enolates or enols.[11] Additionally, very limited and few examples are described employing Friedel−Crafts acylations,[12] ring contraction reactions,[13] rearrangement reactions of *N*-tosylsulfilimines[14] or thiochromanone sulfoxides,[15] addition of diazomethane,[16] or Grignard addition to ketone-substituted hydroxyl-benzothiophenone.[17] However, in all hitherto described cases many synthetic steps are usually required, yields are low, and the scope as well as the functional group tolerance is very limited. The situation is similarly restricted for the introduction of one carbon-based substituent in combination with a heteroatom-substituent, e.g., amine[18] or thioether[18e,19] groups.

In the present work, we describe a short, modular, and high yielding synthesis for 4-fold double-bond substituted HTIs, which provides a vast range of highly interesting substitution patterns. The convergent nature of this synthesis allows facile generation of a multitude of new HTI chromophores and photoswitches with group variation at both molecular fragments. This protocol also allows the easy generation of precursor HTI structures ready for further late-stage functionalization via, e.g., cross-coupling chemistry or peptide conjugation. Apart from carbon-based substituents, introduction of heteroatoms such as oxygen, sulfur, or nitrogen at the central double-bond is also possible in a very convenient and straightforward way (Scheme 1).

Our synthesis commences with inexpensive commercially available starting materials, i.e., different thiosalicylic acids (for introduction of different thioindigo fragments) and α-bromoketones (Scheme 2). A nucleophilic substitution reaction

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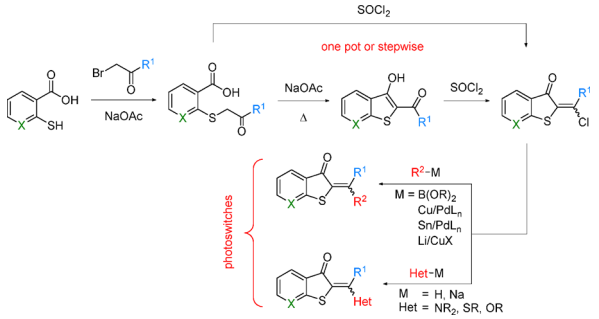
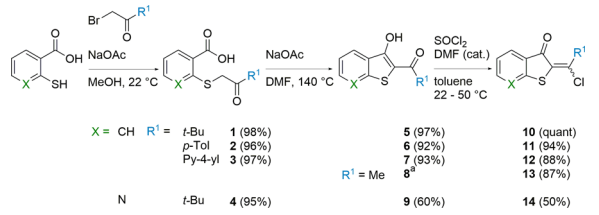
Scheme 1. Synthesis of HTIs with 4-Fold Substituted Double-Bonds



Scheme 2. Synthesis of Chlorinated HTIs 10 to 14



[a]Prepared according to ref 22. All yields are isolated yields.

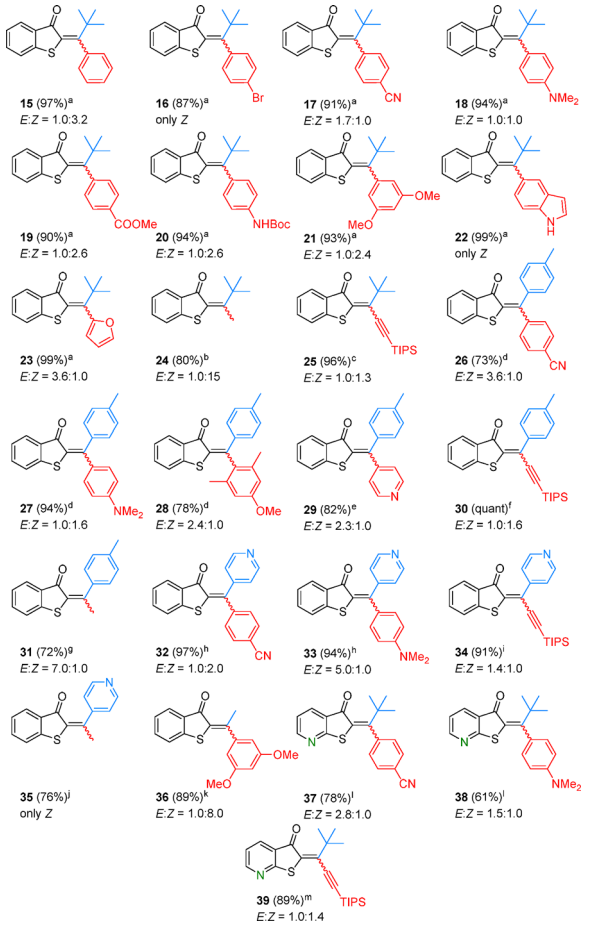


Figure 2. Prepared substituted HTIs **15**–**39**. Conditions: (a) **10**, various boronic acids, $Pd(PPh_3)_4$, K_2CO_3, dioxane/H_2O, 80 °C; (b) **10**, MeLi, CuI, THF, −78 → 23 °C; (c) **10**, (triisopropylsilyl)acetylene, CuI, $PdCl_2(PPh_3)_2$, NEt_3, THF, 60 °C; (d) **11**, various boronic acids, $Pd(PPh_3)_4$, K_2CO_3, dioxane/H_2O, 80 °C; (e) **11**, 4-(tributylstannyl)-pyridine, $Pd(PPh_3)_4$, CsF, CuI, dioxane, 100 °C; (f) **11**, (triisopropylsilyl)acetylene, CuI, $PdCl_2(PPh_3)_2$, NEt_3, THF, 60 °C; (g) **11**, MeLi, CuI, THF, −78 → 23 °C; (h) **12**, various boronic acids, $Pd(PPh_3)_4$, K_2CO_3, dioxane/H_2O, 80 °C; (i) **12**, (triisopropylsilyl)-acetylene, CuI, $PdCl_2(PPh_3)_2$, NEt_3, THF, 60 °C; (j) **12**, MeLi, CuI, THF, −78 → 23 °C; (k) **13**, potassium (3,5-dimethoxyphenyl)-trifluoroborate, APhos Pd G3, dioxane/H_2O, 80 °C; (l) **14**, various boronic acids, $Pd(PPh_3)_4$, K_2CO_3, dioxane/H_2O, 80 °C; (m) **14**, (triisopropylsilyl)acetylene, CuI, $PdCl_2(PPh_3)_2$, NEt_3, THF, 60 °C. All reported yields are isolated yields.

replaces the bromine with the thiol group and provides the corresponding thioethers in excellent yields. In this reaction, the first substituent (R^1) is introduced and can be varied between aliphatic or aromatic character. Addition of NaOAc in DMF leads to facile ring closure and formation of the corresponding 3-hydroxybenzothiophenyl-ketone, a reaction that has been described before for related benzothiophenyl-ketones.[20] Reaction with thionyl chloride readily establishes the HTI chromophore structure with a chloride as the fourth substituent at the double-bond, again in excellent yields. Interestingly, the corresponding regioisomer with the chloride at the benzothiophene ring is not observed under these conditions. These two steps can also be realized in a one-pot reaction without the need to isolate the benzothiophenyl-ketone products while maintaining high yields of the products (e.g., 92% for **10**). The chlorinated HTIs are stable and easy to handle compounds and were, to the best of our knowledge, not described so far. The only related structures bear a carboxylic acid or ester function as R^1 group and could only be obtained under low yielding and harsh reaction conditions.[21]

With chloride as the fourth substituent at the double-bond, the HTIs are now set up for introduction of various substituents R^2 via nucleophilic substitution reactions or cross-coupling chemistry. We exemplify the broad scope of this step by installing a variety of aliphatic, aromatic, acetylenic, or heterocyclic substituents with different electronic and steric character using Suzuki, Sonogashira, or Stille cross-coupling reactions (Figure 2).

As can be seen in Figure 2, these palladium-catalyzed reactions give very high yields, usually beyond 90%, without interference of the particular electronics at the metalated species. Typically mixtures of *E* and *Z* isomers are obtained, which are most likely a result of the thermal- and light-induced isomerizability. Thus, pharmaceutically interesting heterocycle motives such as pyridines (HTIs **29**, **32**, **33**, **34**, and **35**), indole (HTI **22**), or furane (HTI **23**) can be introduced as well as ordinary aromatics bearing nitriles (HTIs **17**, **26**, **32**, and **37**), amines (HTIs **18**, **27**, **33**, and **38**), or methoxy groups (HTIs **21**, **28**, and **36**). Of special interest is the straightforward introduction of protected carboxylic acid and amine functionalities (HTIs **19** and **20**) as they can be used directly for further peptide coupling or other bioconjugation chemistry. Substitution with silyl-protected acetylene (HTIs **25**, **30**, **34**, and **39**) provides a different possibility for further functional group elaboration via, e.g., click-chemistry or cross-coupling reactions. Another interesting aspect is the selectivity of cross-coupling reactions as exemplified by the high yielding introduction of a brominated aromatic substituent in HTI **16**. Apparently the chlorinated precursor HTI **10** is a considerably better electrophile and undergoes oxidative addition faster than the bromide-bearing coupling partner. This allows introducing another halogen functional group with reactivity orthogonal to amide chemistry for further and late-stage cross-coupling chemistry. For chlorinated HTI **10** as well as

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HTIs **19**, **29**, **33**, and **37**, crystal structures were obtained (shown in Figure 4a) facilitating assignment of the double-bond configuration in solution by extrapolating ^{1}H NMR shifts (see Supporting Information). Introduction of aliphatic groups is also straightforward starting from the HTI chlorides by reacting them with, e.g., methyl-cuprates. The corresponding methyl-substituted derivatives are obtained in good yields (HTIs **24**, **31**, and **35** in Figure 2). For the introduction of heteroatom-substituents at the double-bond, the HTI chlorides can be reacted with amines (HTIs **40**, **43**, and **44** in Figure 3), alcohols (HTI **41** in

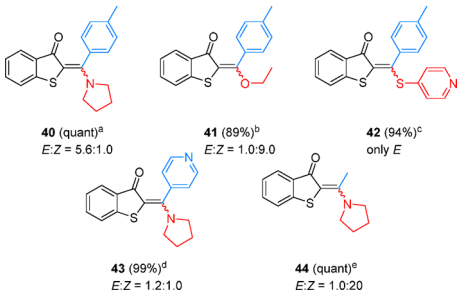

Figure 3. Prepared heteroatom substituted HTIs **40**–**44**. Conditions: (a) **11**, pyrrolidine, dioxane, 23 °C; (b) **11**, NaOEt, EtOH, 23 °C; (c) **11**, pyridine-4-thiol, K_2CO_3, THF, 23 °C; (d) **12**, pyrrolidine, dioxane, 23 °C; (e) **13**, pyrrolidine, dioxane, 23 °C. All yields are isolated yields.

Figure 3), or thiols (HTI **42** in Figure 3). In each case, high yields of the corresponding products are obtained. Crystal structural data were obtained for HTIs **40**, **42**, and **44** (Figure 4a).

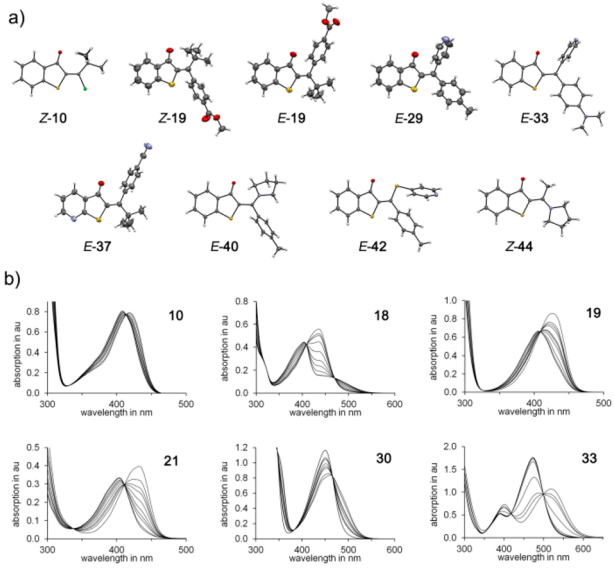

Figure 4. (a) Structures in the crystalline state of HTIs *Z*-**10**, *Z*-**19**, *E*-**19**, *E*-**29**, *E*-**33**, *E*-**37**, *E*-**40**, *E*-**42**, and *Z*-**44**. (b) Absorption changes at different time points during photoisomerization of HTIs **10**, **18**, **19**, **21**, **30**, and **33** in toluene solution.

To showcase the potential of this method to generate actual photoswitches, we have examined the photoswitching properties of all HTIs presented in this work. Apart from a few exceptions (HTIs **23**, **24**, **35**, **40**, **43**, and **44**), all derivatives show good photoswitching properties in the visible part of the spectrum. This can be clearly seen by the spectral changes upon photoirradiation and the clean isosbestic points that are observed (see Figure 4b for the photoswitching of HTIs **10**, **18**, **19**, **21**, **30**, and **33** in toluene as example). First, trends can be established: all HTIs bearing strong electron donating substituents show pronounced red shifts of their absorptions and typically considerable photochromism. If both substituents are electron withdrawing, then photoswitching is not efficient because of the strongly reduced photochromism. Heteroatom substituents also seem to inhibit photoisomerization in most cases.

In summary, we present a novel, concise, and highly efficient method to synthesize HTI photoswitches with 4-fold substituted double-bonds. This method possesses a very broad substrate scope and delivered more than 30 new photoswitches with very different structures and electronic properties. Incorporation of aromatic, heterocyclic, aliphatic, or acetylenic carbon based substituents is similarly straightforward as the introduction of nitrogen, oxygen, or sulfur based residues as the fourth substituent. We also provide a variety of prefunctionalized HTIs for further synthetic elaboration, i.e., brominated and acetylene-substituted derivatives for late stage cross-coupling or click-chemistry reactions and aminated as well as carboxylated derivatives for amide formation or peptide conjugation chemistry. The photoswitching properties under visible light irradiations were examined for all derivatives showing that efficient photoisomerizations take place in almost all cases. A full photophysical and -chemical assessment of these structures is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03574.

Synthetic procedures as well as a full set of characterization data including melting points, ^{1}H NMR, ^{13}C NMR, IR, and (HR)MS, structural analysis in solution and in the crystal, and photophysical data including extinction coefficients and absorption changes during light irradiation (PDF)

Accession Codes

CCDC 1586002–1586010 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or 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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