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Synthesis of rigid photoswitchable hemithioindigo ω-amino acids

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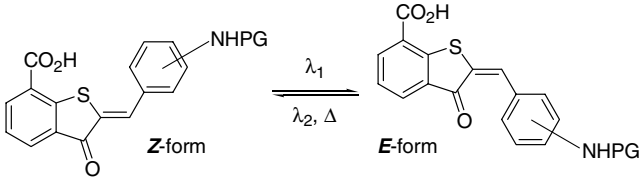
Abstract—The synthesis of novel *N*-Boc- and *N*-Fmoc protected hemithioindigo-based ω-amino acids is described. An approach to modulate the thermal stability of a hemithioindigo subunit is presented. Placing the amino-group in the stilbene part from the *para*- to *meta*-position leads to an increase of the half-life of the thermally labile *E*-form from 19 h to 47 h.

The analysis and modulation of the conformation and function of biomolecules (e.g., ion transport,[1] protein folding,[2] cell signaling[3] and cell adhesion[4,5]) with photochromic switches is an area of increasing interest.[6] Among the photoisomerizable subunits for the photomodulation of secondary structure elements in peptides and proteins photosensitive ω-amino acids are highly promising candidates. Hemithioindigos possess favourable properties for use in biological systems.[1,3,7–10] Isomerization ($Z \rightarrow E$; $E \rightarrow Z$) of hemithioindigos (HTI) occurs on a picosecond timescale, and contrary to most other photoswitches only in the visible range.[7] Both photoisomers are planar and unstrained.[1] UV/visible absorption data and thermal stability depend on the nature and the position of substituents, as well as medium effects (e.g., concentration, solvent, pH value).[11]

Hemithioindigos are also attractive photoregulators for the fast initiation of processes of peptides and protein folding and their investigation.[3,12] In addition, hemithioindigos are interesting as active ingredients for medicinal applications, for example, as human sphingosine kinase inhibitors,[13] antitumor drugs,[14,15] antimalarial HDP inhibitors[16] and photoswitchable lipoxygenase inhibitors.[17] To effectively use the hemithioindigo scaffold in the design of photoswitchable ω-amino acids, the rigidity of both photochromic isomers and the substantial end-to-end distance change during isomerization should not be compromised by a flexible tether. Consequently, we focused on the development of novel ω-amino acids with the amino group attached directly to the stilbene part of the hemithioindigo (Scheme 1).

Amino acids have been prepared bearing the amino group in *para*- and in *meta*-position, respectively, to evaluate the impact of this change in substitution pattern on the thermal *E*-to-*Z*-isomerization. A beneficial *meta*-substitution effect has been studied in several works on thermal cis-to-trans isomerization of azobenzenes,[18,19] leading to a pronounced increase in thermal stability.[9,20] Synthetic routes to Fmoc- and Boc-protected derivatives for SPPS[21] are shown in Scheme 2. We, herein, report on acidic conditions for the condensation of appropriate Fmoc-protected aldehyde precursors with the thioindoxyl **1**,[22] followed by hydrolysis of the carboxylic acid chloride furnishing the Fmoc-protected ω-amino acids **2a**,**b**. For the synthesis of the Boc-protected building blocks the methods previously reported by us were applied.[7,8]

The aldehydes[23] **4a** and **4b** were prepared from the parent amino-substituted benzyl alcohols by Fmoc-protection[24] and subsequent oxidation with manganese oxide[23] in DCM using standard procedures (Scheme 3).



Scheme 1. Structures of hemithioindigo isomers (Z/E).

Keywords: Hemithioindigo; Amino acids; Cis/trans-isomerization; Photoswitch.
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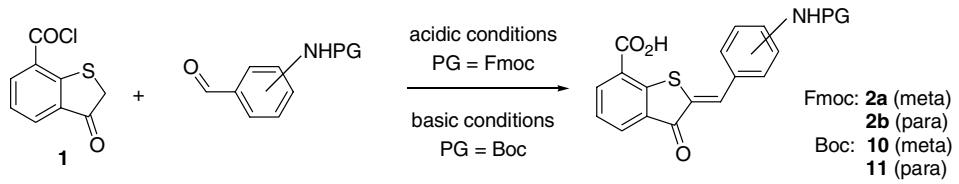
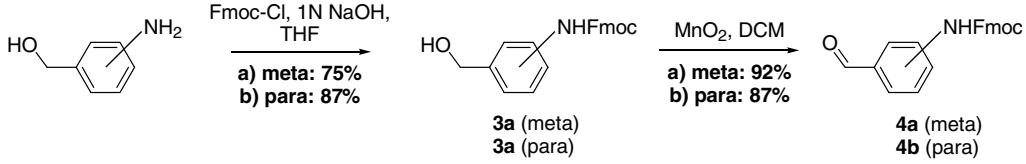
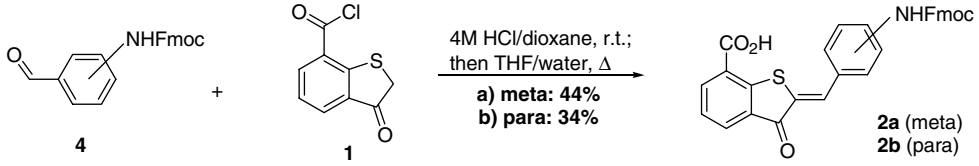


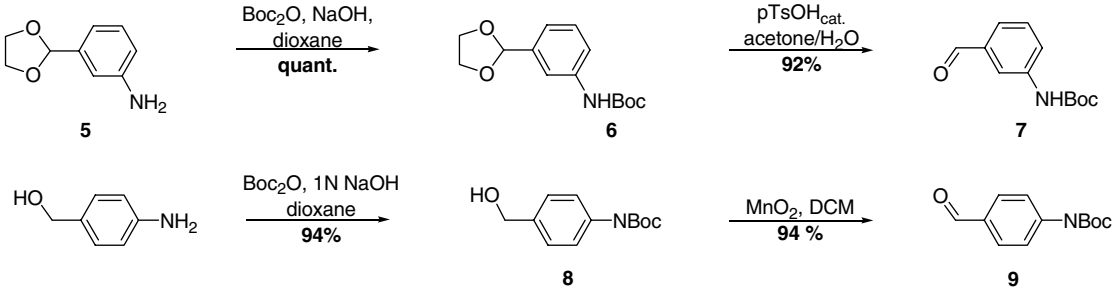
Scheme 2. Hemithioindigo ω-amino acids: *meta*- and *para*-substitution pattern.



Scheme 3. Synthesis of aldehydes **4a**,**b**.



Scheme 4. Synthesis of the *N*-Fmoc-protected hemithioindigo based ω-amino acids **2a**,**b**.

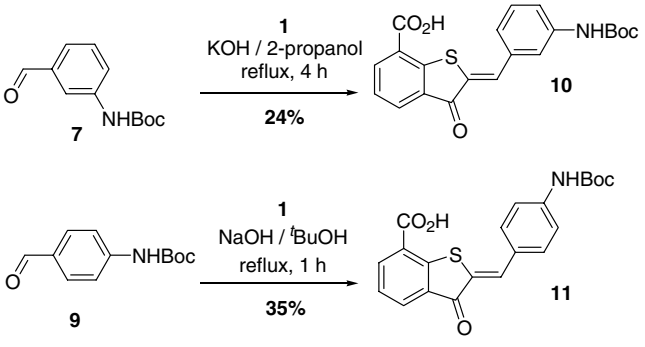


Scheme 5. Synthesis of aldehydes **7** and **9**.

The aldehydes were condensed with thioindoxyl **1** using 4 M HCl in dioxane, followed by treatment with THF/water (3:1) under reflux to hydrolyze the acid chloride. The purities of the crude products were estimated by ^{1}H NMR spectroscopy as 60–70% (**2a**) and 50–60% (**2b**), respectively. Compound **2a** was purified by recrystallization from ethyl acetate/THF (5:1, twice) to furnish 6.6 g (44%) of a yellow-brown solid, whereas 2.2 g (34%) of **2b** were obtained after flash chromatography on silica (DCM/MeOH) (Scheme 4). Purification is hampered by thioindigo side-products of low solubility stemming from the thioindoxyl acid chloride.

The Fmoc-protected ω-amino acids **2a**,**b** showed insufficient solubility in methanol-d_4 for UV/visible as well as ^{1}H NMR studies to determinate the ratio of isomers in the pss. However, for these measurements the Boc-protected building blocks **10** and **11** are well suited.

The aldehydes **7** and **9** for the synthesis of the compounds **10** and **11** were prepared according to Scheme 5 in two steps. Boc-protection of the commercially available dioxolane **5** and subsequent removal of the acetal protecting group furnished aldehyde **7**. Aldehyde **9** was obtained from 4-aminobenzylalcohol by Boc-protection and subsequent oxidation.[25,26]



Scheme 6. Synthesis of the Boc-protected ω-amino acids **10** and **11**.

Table 1. Photochromic properties of the Boc-protected hemithioindigo ω-amino acids **10** and **11**.

Substance	λ_{max} [*Z*] (nm)	ε_Z (dm^3 M^{-1} cm^{-1})	Isosb. points (nm)	λ_{max} [pss][a] (nm)	*Z*:*E* [pss][a]	$t_{1/2}$[b] (h)
10[c]	433	1.3×10^4	360.4, 451.8	447	19:81	47.2
11[d]	446	2.6×10^4	390.8, 468.6	469	22:78	19.3

[a] 415 nm.
[b] Determination of $t_{1/2}$ at (303 ± 2) K.
[c] 6.0×10^{-5} M (MeOH).
[d] 3.9×10^{-5} M (MeOH).

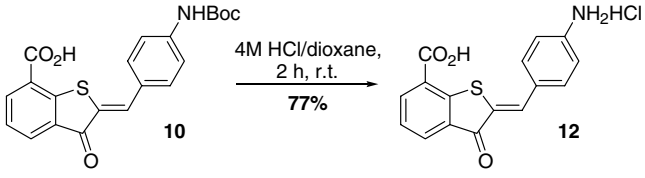
Condensation of these aldehydes with thioindoxyl **1** and subsequent hydrolysis was achieved under basic conditions in a one-pot procedure. In the condensation of aldehyde **7** aqueous KOH (2 wt %)/2-propanol (3:1) was applied. Purification by flash chromatography (Florisil; ethyl acetate/acetic acid) followed by recrystallization (methanol) furnished the *meta*-substituted ω-amino acid **10** in 24% yield with high purity in non-optimized yield. Reaction of aldehyde **9** in aqueous NaOH (1 wt %)/*tert*-butanol (6:1) gave the *para*-substituted analogue **11** in 35% yield after flash chromatography (Florisil). The synthesis and purification of all compounds were not optimized (Scheme 6).

The photochromic properties of the Boc-protected ω-amino acids **10** and **11** are summarized in Table 1. The absorption maximum of *Z*-**11** is shifted to 446 nm in comparison to *Z*-**10** (433 nm). This distinct difference in the absorption maximum and the doubling of the extinction coefficient of **11** relative to **10** is addressed to the push–pull substitution pattern in compound **11**. The *E*-to-*Z* ratios at 415 nm were determined in MeOH-d_4 by ^{1}H NMR spectroscopy in the photostationary state (pss) as 81:19 for the *meta*-substituted compound **11**, and as 78:22 for the *para*-substituted hemithioindigo **10**. Irradiation at 514 nm gave nearly the pure thermally stable *Z*-isomers for both compounds.

Determination of the half-lives of **10** and **11** were carried out in degassed methanol (HPLC-grade) by recording the absorbance change during thermal *E*-to-*Z* isomerization. Assuming that the thermal *E*-to-*Z* isomerization of hemithioindigos in solution follows a first order kinetic, the rate constant *k* can be determined according to Eq. 1.[19,27]

$$kt = \ln \frac{A_z - A_{pss}}{A_z - A_t} \quad (1)$$

The half-lives of **10** and **11** were 47.2 h and 19.3 h, respectively. Both graphical determinations showed a good coefficient of determination. To investigate the more pronounced push–pull effect of the unprotected *para*-substituted ω-amino acid derived from **11**, deprotection was carried out with 4 M HCl in dioxane to furnish the hydrochloride **12** (Scheme 7). As expected, the UV/visible absorption spectrum of **12** in the pss could only be recorded by femtosecond spectroscopy, due to the very fast thermal *E*-to-*Z*-isomerization.[28]



Scheme 7. Deprotection of **10** furnishing hydrochloride **12**.

In summary, the syntheses of Fmoc- and Boc-protected building blocks of two novel hemithioindigo-based ω-amino acids are reported. By changing the substitution pattern from *para*- to *meta*-substitution in the stilbene part the half-life could be increased by a factor 2.4. The half-lives of **10** and **11**, and the ratios of isomers in the photostationary states at 415 nm (*E*:*Z* ratio ~80:20) and 514 nm (*Z*:*E* ratio >95:5) make these novel ω-amino acids attractive candidates as photochromic switches for biological investigations.

Acknowledgements

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Supplementary data

The synthesis and complete characterisation (^{1}H NMR, ^{13}C NMR, mp, R_f, MS, HR-MS, IR, copies of ^{1}H and ^{13}C); UV/visible absorption spectra and graphical determination of the half-life time of **10** and **11** (according to Scheme 1) are provided as Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.110.

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27. A_z is the absorption of the Z isomer (before subjected to light), A_{pss} is the absorption in the photostationary state and A_t is the absorption at a certain time t during relaxation.
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