“Synthesis of Photoswitchable Amino Acids”

Research Report

Institute of Organic Chemistry

University of Regensburg

Supervisor:

Period of research internship:

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List of Abbreviations and Symbols

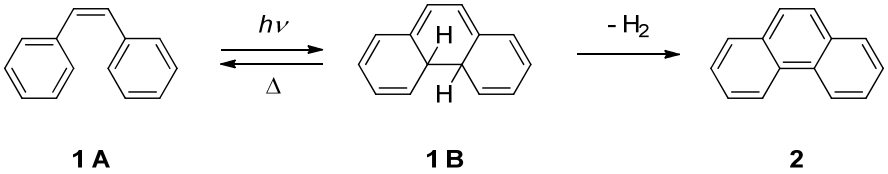
$AlCl_3$	aluminium chloride
Alloc	allyloxycarbonyl
Alloc-Cl	allylchloroformate
Δ	heat
DET	dithienylethene
DMF	dimethylformamide
EDTA	ethylenediaminetetraacetic acid
EE	ethyl acetate
equiv.	equivalent
Et_2O	diethyl ether
$FeCl_3$	iron chloride
Fmoc	fluorenylmethyloxycarbonyl
h	hour(s)
HCl	hydrochloric acid
$HClO_4$	perchloric acid
hv	photon
λ	wavelength
MeOH	methanol
min	minute(s)
mL	mililiter
NBS	*N*-bromosuccinimide
nm	nanometer
NMR	nuclear magnetic resonance
PE	petroleum ether
r.t.	room temperature
$S_{E, Ar}$	electrophilic aromatic substitution
$t_{1/2}$	half-life
THF	tetrahydrofuran
TLC	thin layer chromatography
µL	microliter

UV	ultraviolet
Vis	visible
$ZnCl_2$	zinc chloride

1. Introduction

1.1. Dithienylethenes as Photoinduced Molecular Switches

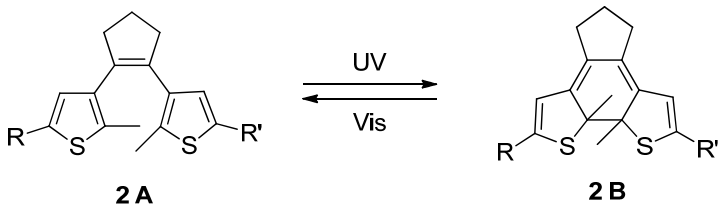
The discovery of the oxidative photocyclisation reaction of stilbenes and stilbenoids around the 1950s revealed a huge potential in this field of chemistry. It was discovered by Mallory during studies of the photochemical isomerisation of stilbenes.[1, 2] Stilbene **1 A** undergoes a cyclisation reaction upon irradiation to produce dihydrophenanthrene **1 B**. Under aerobic conditions and in the dark, the dihydrophenanthrene **1 B** returns to stilbene **1 A**. However, when air is present, an irreversible conversion to phenanthrene **2** occurs due to an oxidative elimination of hydrogen, as shown in Scheme 1.



Scheme 1. Photocyclisation and subsequent oxidative hydrogen-elimination reaction of stilbene to phenanthrene.[3]

Consequently this basic system of diarylethenes (s) is not reversibly switchable due to the oxidative elimination reaction. Further investigations showed that when the 2- and 6-positions of the phenyl groups of stilbene **1 A** were substituted with methyl groups, no elimination in the presence of oxygen took place any longer. Thus the methylated compound underwent a reversible photocyclisation reaction even though the thermal stability was not very good ($t_{1/2}$ = 1.5 min at 20 °C).[4] In 1967 Kellogg *et al.* found that by incorporating thiophene rings instead of phenyl rings the lifetimes of the closed isomers were prolonged (for 1,2-di(3-thienyl)ethane: 12-15 h in the dark in absence of oxygen).[5] Several diarylethenes with thiophene rings were tested.[3] Especially the maleic anhydride group as ethene moiety was of great interest since it shifts the absorption maxima of the dihydro-type isomer to longer wavelengths and prohibits the *cis* to *trans* photoisomerisation which might compete with the photocyclisation reaction. It is reported that photogenerated ring-closed form isomers of compounds with dicyano and maleic anhydride groups and fully methylated thiophene rings were stable in this closed constitution for more than 3 months in the dark, even at 80 °C and switched to the ring-open isomers by irradiation with visible light (λ > 450 nm).[3] Based on those observations a lot of compounds with different heterocyclic aryl ring systems with low aromatic

stabilisation energies (e.g. thiophenes, selenophenes, furans, thiazoles) for high thermal stability and methyl groups in the 2-positions of the heterocyclic rings for high fatigue resistance, i.e. the ability to stay in the ring-closed constitution for a long time, have been prepared. All these compounds share the same 1,3,5-hexatriene framework which, according to the Woodward-Hoffmann rule, undergoes a conrotatory 6-π cyclisation reaction induced by UV light (Scheme 2) and a disrotatory cyclisation reaction induced by heat.[6] Exposed to visible light (λ > 450 nm) the open-ring isomer **A** will be reobtained. For the dithienylmaleimides, investigated in this internship, both the high thermal stability of the open-ring- and the ring-closed isomer as well as a high fatigue resistance are given. These two criteria a very important in terms of applications as optoelectronic devices[3], regulators in biological processes[7] and molecular wires[8]. As well as s with the maleic anhydride group, the maleimide structure is also capable of suppressing the *cis* to *trans* photoisomerisation leaving the cyclisation reaction between the open-ring isomer and the ring-closed isomer to be the only reaction to occur upon irradiation with a certain wavelength.

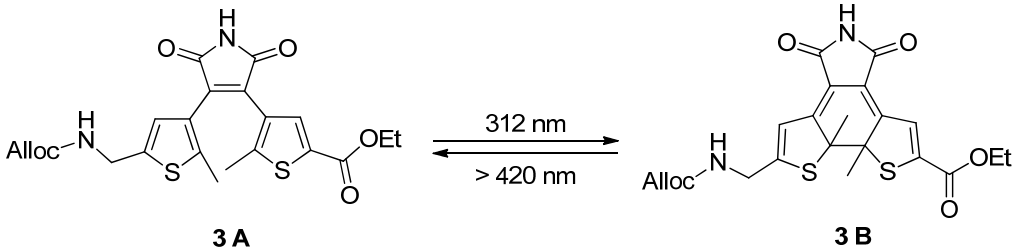


Scheme 2. Photochromic switching process between the open-ring isomer **A** and the ring-closed isomer **B** of a dithienylcyclopentene **2**.[3]

1.2. Dithienylmaleimides as Photoswitchable Amino Acids

In addition to the possible applications for DTEs stated above in section 1.1, another possible usage could be the incorporation of DTEs in form of photoswitchable amino acids **3** in peptide structures (e.g. oligopeptides, proteins, enzymes) to generate photoswitchable biologically active structures. Since the two different isomers **3 A** and **3 B** exhibit different molecular geometries this difference could also be superimposed to the macromolecular structure (e.g. the secondary or tertiary conformation of proteins) of bound substances. In order to incorporate the dithienylmaleimide into a peptide chain by solid-phase synthesis (e.g. using Wang resin with Fmoc strategy) it needs to have a

protected amino function in the position of substituent R (Scheme 2) and a carboxylic group in the position of R′ (Scheme 2). This is shown in Scheme 3.

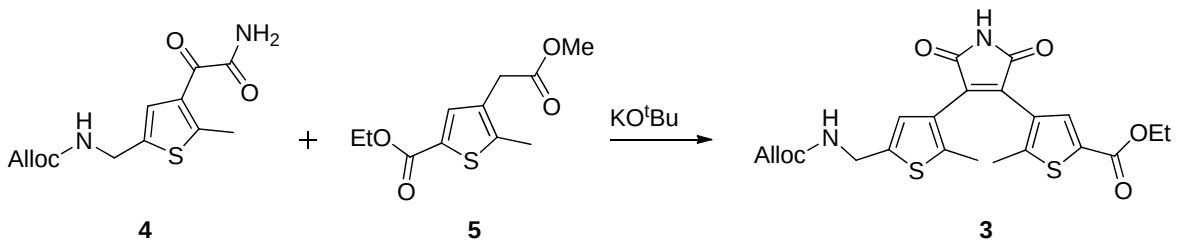


Scheme 3. Photochromic switching process between the open-ring isomer **A** and the ring-closed isomer **B** of the dithienylmaleimide photoswitchable amino acid **3**.

Another important feature for a photoswitchable amino acid is its solubility in water since almost all biologically active molecules are to be found in aqueous media. In comparison to the relatively unpolar cyclopentene compound in Scheme 2, the dithienylmaleimides exhibit a higher polarity due to their maleimide structure. Also the amino and carboxylic (in Scheme 3 shown as ethyl ester) functional group increase the polarity.[9]

1.3. Aim of this Internship

The aim of this internship was to synthesise the photoswitchable amino acid **3** by applying a Perkin condensation reaction of the N-terminal and the C-terminal precursor (Scheme 4) whereby the N-terminal precursor was to be synthesised from commercially available substrates. Since the synthetic approach has already been developed previously, the main task in this work was performing the reactions in larger scales. The focus was on optimisation of applied synthetic sequences, workup strategies compared to small scale workup and finally the investigation of the photochromic behaviour of the amino acid **3** measured by UV/Vis absorption spectroscopy.

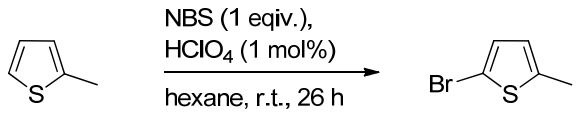


Scheme 4. Synthesis of the photoswitchable amino acid **3** via a Perkin condensation of ethyl 4-(2-methoxy-2-oxoethyl)-5-methylthiophene-2-carboxylate **5** and allyl ((4-(2-amino-2-oxoacetyl)-5-methylthiophen-2-yl)methyl)carbamate **4**.

2. Results and Discussion

2.1. Synthesis of the N-terminal Precursor

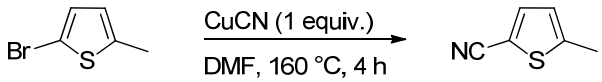
During this internship the N-terminal precursor allyl ((4-(2-amino-2-oxoacetyl)-5-methylthiophen-2-yl)methyl)carbamate **4** could not be synthesised completely. However, of the five step synthesis leading to **4**, the first three steps have been realised. The synthesis started from the commercially available 2-methylthiophene **5** (Scheme 5). According to Goldberg *et al.*[10], 2-bromo-5-methylthiophene **6** was synthesised in an electrophilic aromatic substitution. Using *N*-bromosuccinimide **5** was brominated in 5-position since the 5- and 2-positions are the most reactive positions in 5-membered heterocyclic aromatic ring systems. Due to the methyl group in 2-position of **5** bromination in 5-position was obtained selectively. This reaction was carried out in a scale of 183.4 mmol (17.76 mL) with a yield of 65 %. Compared to a smaller approach of 61 mmol (5.92 mL) tested by Sabine Möhle yielding 66 % of the substitution product (see Table 1), the larger scale worked equivalently well. Especially the work-up procedure was fully applicable to a large scale approach.



5 **6**

Scheme 5. Selective mono-bromination ($S_{E,Ar}$) in 5-position of **5** with NBS as bromine source.

The next step was a Rosenmund-von-Braun reaction, a copper catalyzed C-C coupling reaction converting arylhalides to arylnitriles generally using an excess of copper(I) cyanide in a polar protic solvent.[11] The reaction (Scheme 6) was carried out with an equal amount of the substrate 2-bromo-5-methylthiophene **6** and copper(I) cyanide (1 equivalent). Mechanistically it is a nucleophilic aromatic substitution reaction where copper inserts into the arylhalide bond by oxidative addition with a Cu(III) intermediate. In a following reductive elimination copper retrieves its electrons (Cu(III) -> Cu(I)) yielding 5-methyl-thiophene-2-carbonitrile **7** and copper bromide.



6 **7**

Scheme 6. Rosenmund-von-Braun reaction converting 2-bromo-5-methylthiophene **6** to 5-methyl-thiophene-2-carbonitrile **7**.

In comparison to a small scale approach, upscaling the reaction yielded almost 10 % more of the product (see Table 1).

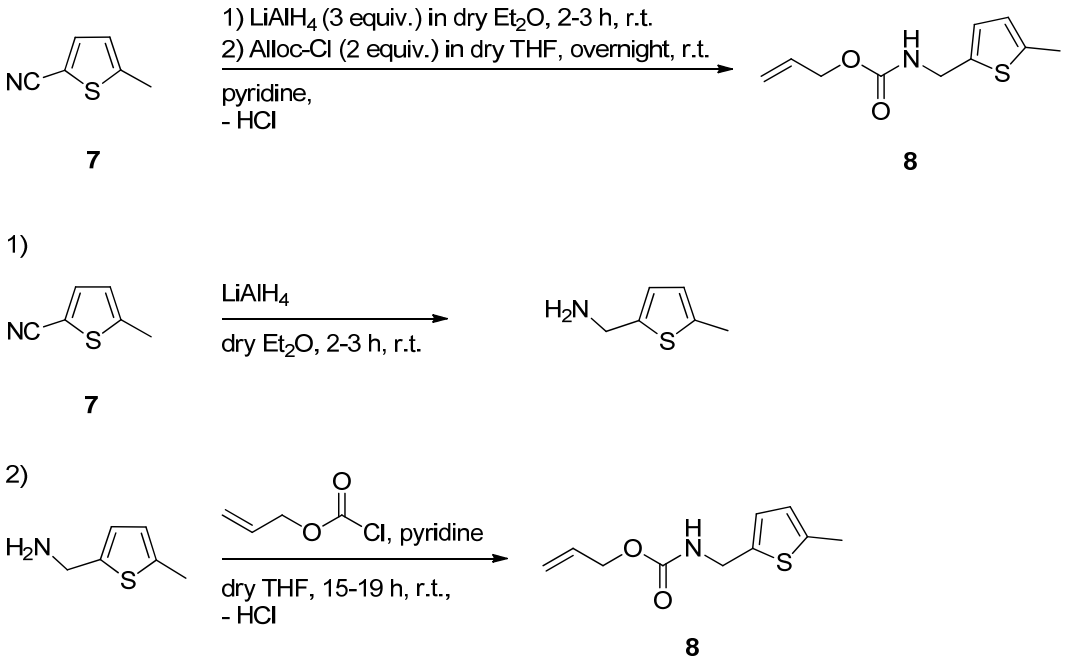
Table 1. Comparison of the first three reaction steps in small scale approaches carried out by Sabine Möhle (SM) and large scale approaches tested during this internship.

Entry	Scale/ mmol	Conversion*	Temperature	Yield
6 (TB1)	183.4	yes	r.t.	65 %
SM9	61.0	yes	r.t.	66 %
7 (TB3)	118.3	yes	160 °C	52 %
SM10	40.6	yes	160 °C	44 %
8 (TB2)	2.0	yes	r.t.	34 %
8 (TB6)	61.7	yes	r.t.	53 %
SM1	4.1	yes	r.t.	20 %
SM5	7.6	yes	r.t.	27 %

** TLC and ^{1}H-, ^{13}C NMR control*

In the first part of the third step (Scheme 7, 1)) the carbonitrile **7** was reduced to an amine using lithium aluminium hydride. This amine functionality was then protected by the Alloc protective group giving allyl((5-methylthiophen-2-yl)methyl)carbamate **8**. Due to the acidic conditions in the Friedel-Crafts acylation reaction in the next step and the basic conditions in the condensation reaction of the N-terminal and the C-terminal precursors, the Alloc group was preferred to the Fmoc group since the Fmoc group is not stable under basic conditions. The Alloc group was introduced through allylchloroformate as shown in scheme 7, 2. It can selectively be removed with tetrakis(triphenylphosphine)palladium(0) and a suitable nucleophile/scavenger.[12] The reaction for introducing the Alloc group was done according to Corey *et al.*[13]. As Table 1 shows, this two step reaction sequence worked better with a yield of more than 50 % in a large scale (61.7 mmol) than the two small scale approaches SM1 (as reported by

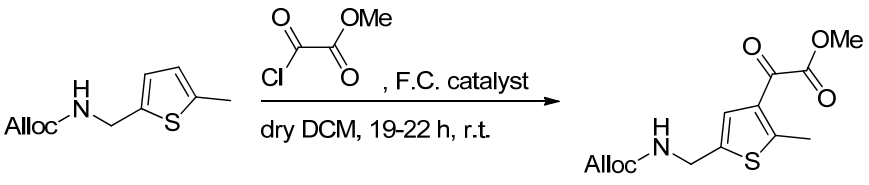
Albericio *et al.*[12]) and SM5 (as reported by Corey *et al.*[13]). The improved yield of 34 % in the small scale approach TB2 compared to SM5 might be a consequence of intense flame drying, almost strict nitrogen atmosphere, high vacuum evaporation of the free amine and the use of only dry solvents.



Scheme 7. Reduction of the nitrile **7** to an amine by the use of lithium aluminium hydride (1) and following protection of the amine function with the Alloc protective group in a nucleophilic acyl substitution reaction with pyridine as scavenger for the released HCl (2).

Up next was a Friedel-Crafts acylation reacting methyl oxalyl chloride with allyl((5-methylthiophen-2-yl)methyl) carbamate **8** to obtain methyl 2-(5-((((allyloxy)carbonyl)-amino)methyl)-2-methylthiophen-3-yl)-2-oxoacetate **9** (Scheme 8). Due to low yields of this reaction tested in previous approaches with aluminium chloride as the catalyst (see Table 2), it was tried to screen this reaction with two other metal catalysts in small scale approaches (substrate **8**: 0.24 mmol for TB4 and 0.20 mmol for TB5). Therefore $FeCl_3$ (0.96 mmol, 4 equiv.) was used in the first approach (TB4) and $ZnCl_2$ (0.80 mmol, 4 equiv.) was used in the second approach (TB5). Unfortunately neither iron chloride nor zinc chloride brought forth any conversion of the substrate. So the next step was to try the reaction with aluminium chloride as catalyst but in a large scale approach (23.7 mmol of **8**). According to TLC control conversion of **8** to **9** was successful. Unfortunately, after the final purification by automated flash column chromatography the ^{1}H NMR showed no product at all. A possible explanation for the loss of the product during work up could

be the use of a 1 M HCl solution in order to improve the work up procedure. It was applied during extraction for better phase separation. HCl possibly might have added to the double bond of the allyl moiety. Other reactions between HCl and **9** might also have happened.



8 **9**

Scheme 8. Friedel-Crafts acylation of allyl((5-methylthiophen-2-yl)methyl)carbamate **8** yielding methyl 2-(5-((((allyloxy)carbonyl)amino)methyl)-2-methylthiophen-3-yl)-2-oxoacetate **9**. F.C. catalyst: TB4: $FeCl_3$; TB5: ZnCl2;TB7: $AlCl_3$.

Table 2. Comparison of the Friedel-Crafts acylation reaction step with different catalysts.

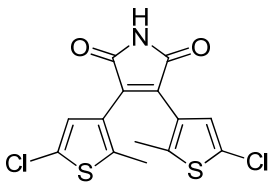
Entry	F.C. catalyst	Scale/ mmol	Conversion*	Yield
TB4	$FeCl_3$	0.24	no	-
TB5	$ZnCl_2$	0.20	no	-
TB7	$AlCl_3$	23.7	no	-
SM3	$AlCl_3$	0.83	yes	13 %
SM7	$AlCl_3$	0.95	yes	17 %

- *all at r.t. and overnight*

** TLC and ^{1}H-, ^{13}C NMR control*

2.2. Photochemical Properties

It was shown that the bis-chloro dithienylmaleimide **10** is able to switch from its ring-open form to its ring-closed form upon irradiation with UV light (366 nm).[14]



10

Scheme 10. Ring-open form of bis-chloro dithienylmaleimide **10**.

In order to confirm the ability of photoswitching the amino acid **3** a 50 µM solution of **3** in methanol was prepared and measured with UV/Vis absorption spectroscopy. The aim was to find out after what time all molecules of compound **3** switched from their open-ring form to the ring-closed form (photostationary form) and to see whether this switching process is repeatable for several times (cycle performance). Therefore, at first the solution was irradiated with UV light (312 nm) until all molecules switched from their open-ring form to their ring-closed form. This took 42 seconds of irradiation while the solution turned from colourless (0 s) to pink (42 s). Figure 1 shows the absorption maximum of the open-ring form of **3** at around 250 nm. Upon irradiation the maximum at 250 nm decreased while two new maxima appeared at 380 nm and 565 nmn (see black arrows in Figure 1). As can be seen in the absorption spectrum, the first signal (250 nm) and signal 2 (380 nm) and 3 (565 nm) change their intensities in opposite directions with progressive irradiation time. Signals 2 and 3 belong to the ring-closed form of compound **3** since this isomer has a larger conjugated π-system due to the ring closure and therefore absorbs at higher wavelengths.

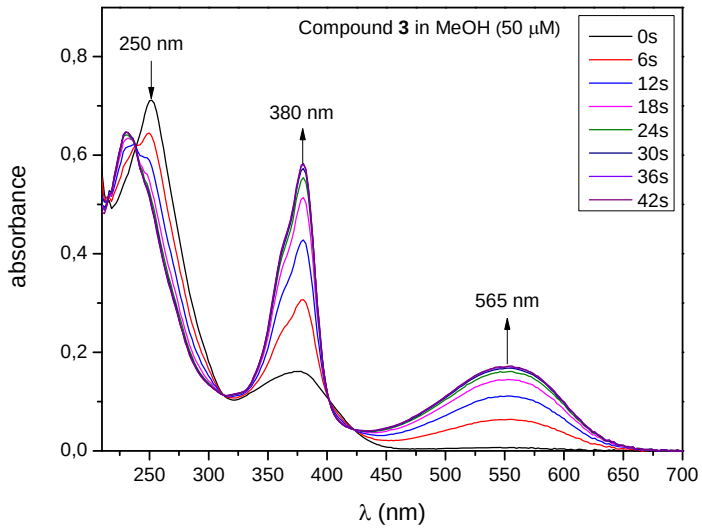


Figure 1. Absorption spectra of the photoswitchable amino acid **3** after irradiation with UV light (312 nm) for 42 seconds.

The performance of the repetitive cycling measurements (Figure 2) of the photoswitchable amino acid **3** showed very good fatigue resistance. After 7 cycles of irradiation with UV light (312 nm) for 42 s and subsequent irradiation with visible light (> 400 nm) only little signs of photodegradation were observed.

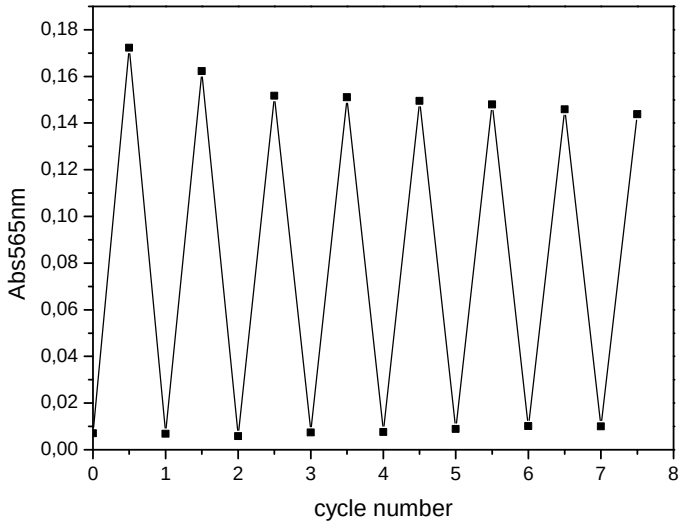


Figure 2. Repetitive switching cycles using λ = 312 nm for closing and λ ⍰ 400 nm for opening.

3. Conclusion

During the research internship the N-terminal precursor **3** should be synthesized from commercially available substrates. This aim was accomplished up to reaction step number three, the Friedel-Crafts acylation. There, three different catalysts $ZnCl_2$, $FeCl_3$ and $AlCl_3$ were tested. Although $AlCl_3$ already proved to be able to catalyse the reaction, in this internship the Friedel-Crafts acylation reaction step was not successful due to the failed workup procedure. However, in other successful experiments this reaction step had very low yields (10 - 20 %). So, reaction conditions are to be optimized or alternative reaction pathways are to be found. Since different types of catalysts have been tested, also the temperature and different stoichiometries are still to be screened. In general the large scale approaches worked just as good as equal small scale approaches or even better (see Table 1, **8** (scale: 61.7 mmol, yield: 53 %) compared to SM5 (scale: 7.6 mmol, yield: 27 %). The fatigue resistance of the free amino acid (i.e. no ester group but free carboxyl group and no protective group at the amine) is to be measured and the incorporation of the photoswitchable amino acid into a peptide is to be tested (e.g. by Fmoc peptide synthesis strategy using Wang resin). If the photoswitchable amino acid can successfully be incorporated into a peptide structure the influence of the different isomers on the secondary structure of the peptide can be determined either by circular dichroism, crystallograhic measurements, or by NMR spectroscopy.

4. Experimental Part

4.1. General Information

Following compounds were commercially available and used without further purification unless otherwise stated: 2-Methylthiophene (98 %, Sigma Aldrich), Allyl chloroformate (≥97 %, Fluka), Aluminium chloride (≥98 %, Merck), CuCN (99 %, Sigma Aldrich), Ethylenediaminetetraacetic acid (99 %, Alfa Aesar), Iron(III) chloride (for synthesis, Merck), Methyl oxalyl chloride (97 %, Alfa Aesar), *N*-Bromosuccinimide (99 %, Sigma Aldrich), Perchloric acid (70-72 %, Merck), Pyridine (>99 %, Acros Organics), Zinc(II) chloride (p.a. grade, Merck), $CDCl_3$ (99.8 %, Sigma Aldrich).

Standard solvents: Quality: >99 %, for analysis (Acros Organics), technical grade (redistilled) or dried according to common procedures.

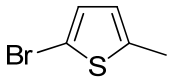
For flash column chromatography (fcc) the Biotagelsolera One automated flash purification system with UV-VIS detector and Sigma Aldrich MN silica gel 60 M, 0.040-0.063 mm, 230 – 400 mesh was used. For thin-layer chromatography (TLC) Merck silica gel plates (60F254, 0.2 mm) were used. Visualization was realised by UV light (254/366 nm).

All NMR spectra were measured using a Bruker Avance 400 (400 MHz for ^1H) or a Bruker Avance 300 (300 MHz for ^1H) NMR spectrometer in $CDCl_3$ at room temperature with $CDCl_3$ (δ_H = 7.26 ppm) as internal standard. Coupling constants (*J*) are given in Hertz (Hz) and chemical shifts are stated in δ-scale as parts per million (ppm). Resonance multiplicity: b = broad, s = singlet, d = doublet, t = triplet, q = quadruplet, , dd = doublet of doublets, dt = doublet of triplets and m = multiplet. In ^{13}C NMR spectra the abbreviation (+) = primary/tertiary, (-) = secondary, (q) = quarternary for carbon atoms result from DEPT-135 NMR experiments.

4.2. Synthesis of a Photoswitchable Amino Acid based on Dithienylmaleimide

2-Bromo-5-methylthiophene (TB1)

This compound was prepared according to a literature procedure.[10]



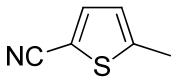
6 (TB1)
C_5H_5BrS
177.06 g/mol

This reaction was done in three parallel approaches with an overall mass of the substrate 2-methylthiophene of 17.76 mL (183.4 mmol).

A 100 ml flask was charged with a solution of 2-methylthiophene (5.92 mL, 61.1 mmol, 1.0 equiv.) in hexane (35 ml). *N*-bromosucinimide (10.88 g, 61.1 mmol, 1.0 equiv.) was added and the solution was vigorously stirred while perchloric acid (35 µL, 0.61 mmol, 0.01 equiv.) was added dropwise to the colourless solution. After full addition of the perchloric acid the resulting yellow suspension was cooled in an ice bath for a few minutes and subsequently stirred at room temperature for 26 h. After addition of potassium carbonate (140 mg, 1.00 mmol) a grey solid precipitated which was then filtered off with a glass frit under reduced pressure. The resulting solution was concentrated under reduced pressure and transferred to a 25 ml flask in order to apply Kugelrohr-distillation (105 – 120 °C, 8 mbar) for final purification. This last step gave compound **6** as a yellowish liquid.

Yield	21.05 g (118.9 mmol, 65 %).
^{1}H NMR (300 MHz, $CDCl_3$)	δ 6.83 (d, *J* = 3.6 Hz, 1H), 6.52 (dq, *J* = 3.6, 1.1 Hz, 1H), 2.43 (d, *J* = 1.0 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$)	δ 141.5 (q), 129.7 (+), 125.7 (+), 108.7 (q), 15.6 (+).

5-Methylthiophene-2-carbonitrile (TB3)



7 (TB3)
C_6H_5NS
123.18 g/mol

This reaction was done in eleven parallel approaches with an overall mass of the substrate 2-bromo-5-methylthiophene of 20.94 g (118.3 mmol).

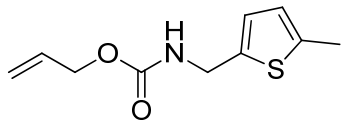
Ten glass vials were each charged with 2-bromo-5-methylthiophene (2.00 g, 11.3 mmol, 1.0 equiv.) and copper cyanide (1.00 g, 11.3 mmol, 1.0 equiv.). Additionally one vial was charged with 2-bromo-5-methylthiophene (0.94 g, 5.3 mmol, 0.46 equiv.) and copper cyanide (0.48 g, 5.3 mmol, 0.46 equiv.). Immediately after the reactants were dissolved in DMF (4 mL) the vials were closed with caps and stirred at 165 °C for 3.75 h using a heating block. After the reaction was finished the reaction mixtures were allowed to cool to room temperature and subsequently poured into an Erlenmeyer flask charged with a 1 M suspension of EDTA in distilled water (130 mL). This gave a turquoise suspension with brown-grey precipitate. The reaction vessels were washed with ethyl acetate (200 mL) into the Erlenmeyer flask. As a consequence a two phase system of a turquoise aqueous phase and a yellow organic phase was observed. Under repeated stirring with a spatula the brown-grey precipitate was then filtered off with a Buchner funnel and washed with ethyl acetate (300 mL). The solution was transferred to a separating funnel and the turquoise aqueous phase was extracted with ethyl acetate until the organic phase was colourless (5 x 100 mL). The combined orange organic phases were dried over $MgSO_4$, filtered with a glass frit and the solvent was evaporated under reduced pressure. The crude product was purified by automated flash column chromatography (PE:EE 3-10 %) yielding **7** as a yellow liquid.

Yield	7.61 g (61.7 mmol, 52 %)
^{1}H NMR (400 MHz, $CDCl_3$)	δ 7.43 (d, *J* = 3.7 Hz, 1H), 6.77 (dq, *J* = 3.6, 1.0 Hz, 1H), 2.53 (d, *J* = 1.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2 (q), 137.9 (+), 126.1 (+), 114.6 (q), 107.1 (q), 15.4 (+).

Allyl((5-methylthiophen-2-yl)methyl)carbamate (TB2)

This compound was prepared according to a literature procedure.[13]



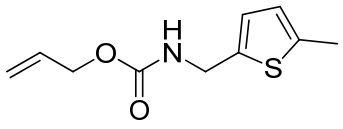
8 (TB2)
$C_{10}H_{13}NO_2S$
211.28 g/mol

A dry Schlenk tube was charged with 5-methylthiophene-2-carbonitrile (246 mg, 2.0 mmol, 1.0 equiv.) in 25 mL dry diethyl ether. Under heavy stirring and at 0 °C lithium aluminium hydride (227 mg, 6.0 mmol, 3.0 equiv.) was slowly added to the colourless solution to give a grey suspension. After 1.75 h at room temperature the suspension was cooled again in an ice bath and water (3 mL) was added dropwise to quench the remaining $LiAlH_4$. The suspension turned from grey to colourless with yellow precipitate at the bottom of the flask. Upon addition of saturated $NaHCO_3$ solution (aq., 4 mL) the precipitate turned white. The suspension was then filtered without vacuum and the aqueous phase was extracted with diethyl ether (2 x 8 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to give the crude product as yellow oil. It was then dissolved in dry THF (6 mL) and pyridine (324 µL, 4.0 mmol, 2.0 equiv.) was added to this solution. The reaction mixture was cooled to 0 °C in an ice bath and a solution of allylchloroformate (425 µL, 4.0 mmol, 2.0 equiv.) in dry THF (2.5 mL) was added dropwise. A colour change from yellow to pink was observed. With a bubble counter attached the reaction mixture was stirred for 15 h, at first in an ice bath at 0 °C and subsequently at room temperature. After addition of water (1 mL) the aqueous phase was extracted with ethyl acetate (2 x 8 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was evaporated and purification of the crude product by automated flash column chromatography (PE:EE 10-20 %) yielded compound **8** as yellow liquid.

Yield	142 mg (0.67 mmol, 34 %)
^{1}H NMR (400 MHz, $CDCl_3$)	δ 6.73 (d, *J* = 3.1 Hz, 1H), 6.59 – 6.55 (m, 1H), 5.92 (ddt, *J* = 16.2, 10.7, 5.5 Hz, 1H), 5.30 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 5.09 (bs, 1H), 4.58 (d, *J* = 5.1 Hz, 2H), 4.44 (d, *J* = 5.8 Hz, 2H), 2.44 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 155.9 (q), 139.8 (q), 138.8 (q), 132.8 (+), 125.7 (+), 124.8 (+), 117.7 (-), 66.7 (-), 40.1 (-), 15.3 (+).

Allyl((5-methylthiophen-2-yl)methyl)carbamate (TB6)

This compound was prepared according to a literature procedure.[13]



8 (TB6)
$C_{10}H_{13}NO_2S$
211.28 g/mol

A dry 500 mL Schlenk flask was charged with 5-methylthiophene-2-carbonitrile (7.61 g, 61.7 mmol, 1.0 equiv.) in dry diethyl ether (250 mL). Under heavy stirring and at 0 °C lithium aluminium hydride (7.00 g, 185.1 mmol, 3.0 equiv.) was slowly added to the colourless solution to give a grey suspension. After 4 h at room temperature the suspension was cooled again in an ice bath and carefully quenched with water (200 mL). The suspension turned from grey to colourless with yellow precipitate at the bottom of the flask. Upon addition of saturated $NaHCO_3$ solution (aq.) (200 mL) the precipitate turned white. The suspension was then filtered with a Buchner funnel under reduced pressure while the residue in the filter was washed several times with water and diethyl ether until the precipitate was colourless. The aqueous phase was extracted with diethyl ether (2 x 150 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure to give the crude product (4.48 g, 35.8 mmol) as yellow oil. It was then dissolved in dry THF (65 mL) and pyridine (5.8 mL, 71.6 mmol, 2.0 equiv.) was added to this solution. The reaction mixture was cooled to

0 °C in an ice bath and a solution of allylchloroformate (7.6 mL, 71.6 mmol, 2.0 equiv.) in dry THF (45 mL) was added with a dropping funnel. A colour change from pale yellow to orange was observed. With a bubble counter attached the reaction mixture was stirred for 19 h, at first in an ice bath at 0 °C and subsequently at room temperature. After addition of water (16 mL) the precipitate in the yellow-brown suspension completely dissolved. A dark yellow solution was observed. The aqueous phase was extracted with ethyl acetate (3 x 70 mL). The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was evaporated and purification of the crude product by automated flash column chromatography (PE:EE 10-20 %) yielded compound **8** as yellow liquid.

Yield	6.87 g (32.5 mmol, 53 %)
^{1}H NMR (400 MHz, $CDCl_3$)	δ 6.73 (d, *J* = 3.1 Hz, 1H), 6.59 – 6.55 (m, 1H), 5.92 (ddt, *J* = 16.3, 10.8, 5.6 Hz, 1H), 5.30 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.21 (dd, *J* = 10.4, 0.8 Hz, 1H), 5.08 (bs, 1H), 4.59 (d, *J* = 5.1 Hz, 2H), 4.44 (d, *J* = 5.8 Hz, 2H), 2.44 (d, *J* = 0.5 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$)	δ 156.0 (q), 140.0 (q), 138.9 (q), 132.9 (+), 125.8 (+), 124.9 (+), 117.8 (-), 65.8 (-), 40.2 (-), 15.5 (+).

4.3. Time Dependent Absorption Spectra

In order to examine the ability to change its structure upon irradiation and investigate the cycle performance, time dependent absorption spectra of compound **3** were recorded. Therefore a 50 µM solution (3 mL) of compound **3** in methanol was irradiated with UV light for 42 seconds in a 6 second interval and its absorption was immediately measured over a spectral range of 200 – 700 nm (see Figure 1 in chapter 2.2.). For the repetitive switching cycle measurement the solution was irradiated for 42 s with UV light at 312 nm to obtain the ring-closed isomer. To open the ring again the solution was irradiated with visible light above 400 nm (use of longpass filter) for 10 minutes.

5. References

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