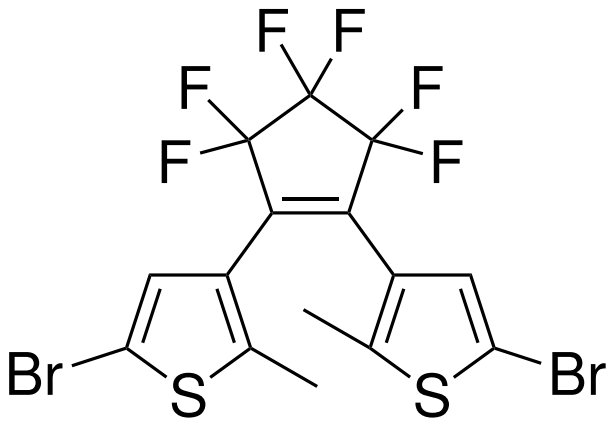
TU Clausthal

Institut für Organische Chemie, IOC

Organic chemistry practical course C

Four-step synthesis of 7,7'-(bis(5-methyl-2-bromothiophene))-perfluorocyclopentene



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Contents

1 Introduction

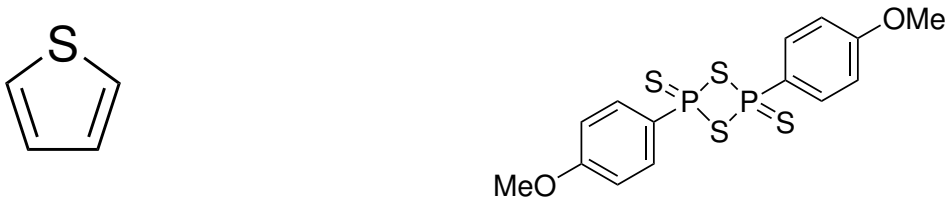
This report describes the four-step synthesis of 7,7'-(bis(5-methyl-2-bromothiophene))perfluorocyclopentene, whose structural formula is shown on the title page, starting from 2-methylthiophene.
First, the theoretical background of the reagents used during the synthesis and final product is discussed. Subsequently, the mechanism, procedure, and evaluation of the results of the four reactions carried out are presented.

2 Theoretical Background

2.1 Properties, reactions and methods of preparation of thiophenes

Planar, cyclically conjugated compounds that possess (4n+2) π electrons, where n = 1, 2, 3, ... , such as benzene, are particularly stable according to Hückel's rule and are referred to as aromatics. The π electrons are delocalized throughout the entire ring, resulting in a lower-energy and thus more stable state. If a cycle consists not only of carbon and hydrogen but also contains heteroatoms, such as nitrogen, oxygen, or sulfur, it is called a heterocycle. In the case of aromatic compounds, they are referred to as aromatic heterocycles or heteroaromatics. Aromatic heterocycles are an important class of compounds that account for an estimated two-thirds of all organic substances. This includes many compounds and especially pharmaceuticals that are important to humans.[1–3]
Thiophene is a five-membered sulfur-containing aromatic heterocycle, whose structural formula is shown in fig. 1a. At room temperature and atmospheric pressure it is a colorless liquid that is immiscible with water. It was discovered in 1883 by Victor Meyer in crude benzene. It occurs at a concentration of about 0.15% by weight in tar benzene, a component of crude oil, and can be extracted from it using concentrated sulfuric acid.[4]
Thiophene's physicochemical properties and reactivity are similar to that of benzene and it is therefore often used in pharmaceuticals as a bioisosteric substitute for a phenyl group. Nevertheless it is less reactive than its oxygen or nitrogen analogs, pyrrole and furan. This is because the sulfur atom's lone pair of electrons occupies a 3p orbital, which overlaps less effectively with the conjugated sp^2 orbitals of the ring carbon atoms than the 2p orbitals of oxygen or nitrogen. The structure of thiophenes can be expressed using mesomeric structural formulas, in which the sulfur's non-bonding electron pair also contributes to the mesomerism. The delocalization of this non-bonding pair of electrons increases the electron density in the ring, which makes the ring more nucleophilic, thereby facilitating electrophilic attacks on the ring, such as halogenation, nitration, sulfonation, mercuration or Friedel–Crafts reactions. Due to the distribution of electron density, it is almost exclusively the 2- or 5-position that reacts, and only the 3- or 4-position if these are already substituted. However, nucleophilic substitutions rarely occur on the thiophene itself. To make this possible, an activating group — such as a nitro, carbonyl, or sulfonyl group — is required, similar to the case with benzene.
Under normal conditions, thiophene does not undergo cycloaddition reactions. However, when oxidized by peracids, it forms thiophenesulfone, which participates in Diels-Alder reactions, including self-dimerization reactions. When thiophenesulfone reacts with alkynes in a Diels-Alder reaction, a substituted benzene derivative is formed along with the release of sulfur dioxide.
Although the thiophene ring cannot be opened by hydrolysis, it can be opened — along with

desulfurization — by catalytic hydrogenation using RANEY nickel leaving an acyclic saturated compound.[1–5]



(a) **(b)**

Figure 1: Structural formula of **(a)** thiophene and **(b)** LAWESSON's reagent.

Thiophene derivatives can be synthesized using hydrogen sulfide or other sulfur nucleophiles via the cyclodehydration of 1,4-dicarbonyl compounds. In practice, however, the two carbonyl groups are usually converted into unstable thiocarbonyls using an electrophilic reagent such as phosphorus(V) sulfide (P_2S_5), tetraphosphorus heptasulfide (P_4S_7) or LAWESSON's reagent, which then react to form thiophenes via cyclization, which is known as the PAAL-KNORR synthesis. The reaction scheme is shown in fig. 2a and the structure of the LAWESSON's reagent in fig. 1b. Another approach is the HINSBERG synthesis of 1,2-diketones or 3-thioglutaric acid esters using a strong non-nucleophilic base, as shown in fig. 2b. As depicted in fig. 2c, 2,5-dialkyl-thiophene derivatives can be prepared by adding hydrogen sulfide to 1,3-diines in an alkaline medium. Thiophene itself is produced industrially from *n*-butane and sulfur in the vapor phase at 500 to 600°C.[2–4,6]

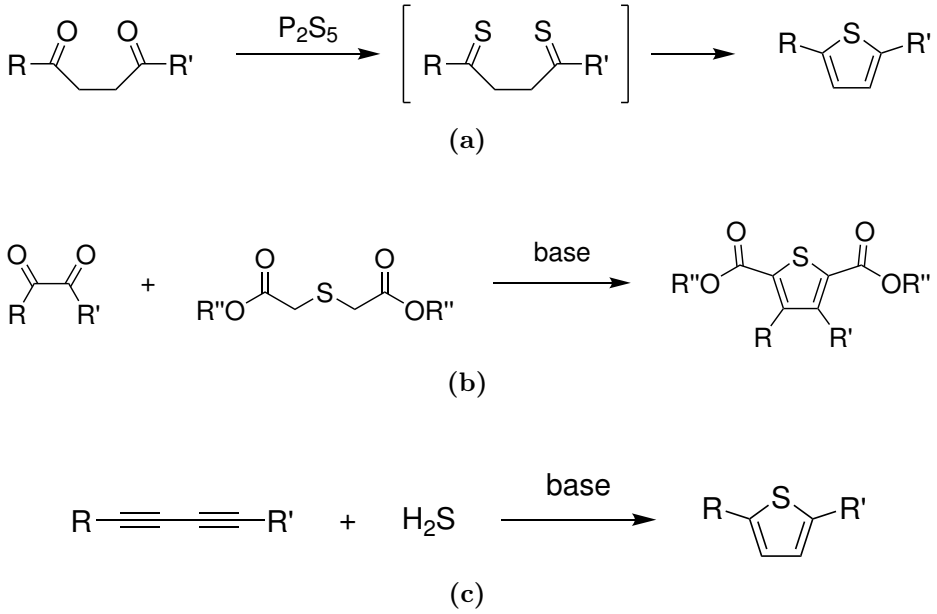


Figure 2: Preparation of thiophenes utilizing **(a)** the PAAL-KNORR synthesis, **(b)** the HINSBERG synthesis and **(c)** from 1,3-diines.

2.2 Electrocyclic reactions and bisthienylethenes as molecular photoswitches

The Diels-Alder reaction, mentioned earlier, is a named reaction of the cycloaddition type. This class of reactions belongs to the group of pericyclic reactions. A key feature of pericyclic reactions,

which distinguishes them from radical and polar reactions, is that they occur without involvement of radical, electrophilic, or nucleophilic reactants or intermediates. Bond cleavage and formation occur in a concerted manner, while the symmetry of the involved molecular orbitals controls the reaction via the orientation and geometry of the cyclic transition state.[7]

Another type of pericyclic reactions are electrocyclic reactions, in which an intramolecular ring closure (electrocyclization) or ring opening occurs. In this process, a new σ bond is formed at the ends of a conjugated polyene, or the reverse process takes place.

The stereochemical outcome of the electrocyclization depends on whether it takes place under thermal or photochemical conditions and on the number of π electrons involved. If the ring closure occurs in a disrotatory manner, with the terminal p orbitals rotating in opposite directions to ensure constructive overlap, *cis* configuration is retained. In contrast, if ring closure proceeds in a conrotatory manner, with both ends rotating in the same direction, this preserves the *trans* configuration. This orbital rotation directly determines the resulting stereochemistry of the product and explains why electrocyclic reactions exhibit high stereospecificity, as illustrated in fig. 3.[2,7]

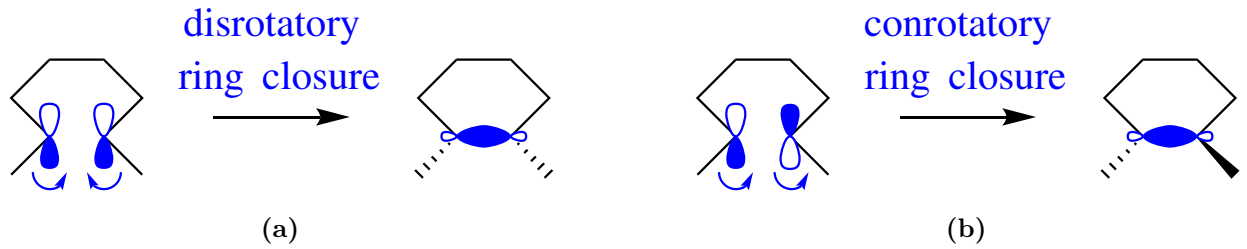


Figure 3: **(a)** Disrotatory and **(b)** conrotatory patterns of orbital rotation determine the stereochemistry of electrocyclisation reactions.

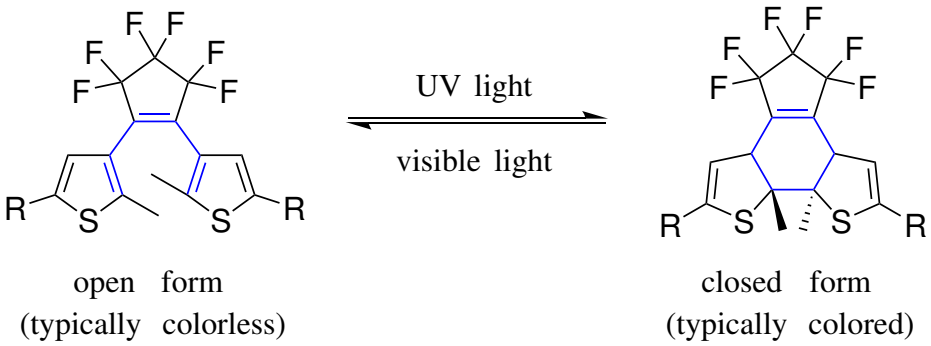


Figure 4: Photoinduced reversible electrocyclisation reaction of bisthiophenethenes.

One class of compounds for which this reaction is of fundamental importance is bisthiophenethenes (BTEs), which, due to their properties, can be used as molecular photoswitches. Their structure is based on the framework of stilbene. In BTEs, the ethene unit of stilbene has been replaced by a perfluorinated cyclopentyl ring, and instead of phenyl units, thiophene substituents are present. When exposed to UV light, these compounds undergo a conrotatory electrocyclization reaction and are thus converted into a closed form, most often characterized by an intense color. When irradiated with visible light, the reverse, ring opening reaction can occur, resulting in the open form, which is typically colorless. Consequently, a photoinduced, but also reversible color change is observed, as shown in fig. 4.[8–10]

2.3 Properties, reactions and methods of preparation of organolithium compounds

Organometallic compounds are characterized by more or less polar direct bonds between metal and carbon. In the case of lithium, these are specifically referred to as organolithium compounds. They can be prepared from lithium metal with organic halides or via metallation of a C-H acidic compound with n-butyllithium or other commercially-available organolithium compounds as presented in fig. 5.[11]

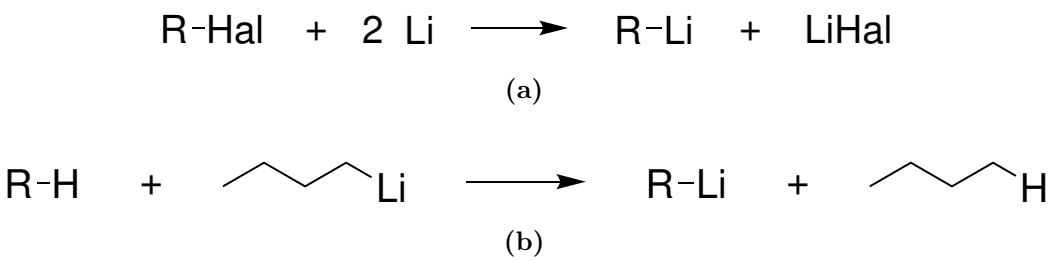


Figure 5: Preparation of organolithium compounds **(a)** from lithium metal with organic halides or **(b)** via metallation with n-butyllithium.

A distinctive feature of organolithium compounds is their tendency to form oligomeric units $[\mathrm{R-Li}]_n$ via association in the form of molecular clusters, both in solution and in the solid state. Individual molecules are only rarely observed. The degree of association is largely determined by the properties of the solvent. This was confirmed by osmometric molecular weight measurements, as well as by Li NMR and ESR spectroscopy. The detection of corresponding fragments by mass spectrometry shows that the association is also maintained in the gas phase. The nature of the associates formed has a significant effect on the kinetics of the reactions carried out using them.[11,12]

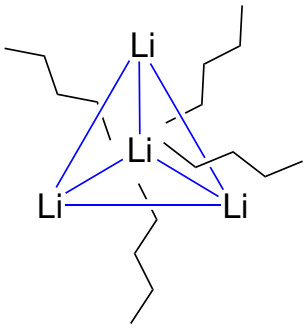


Figure 6: Tetrahedral structure of $[n\mathrm{-BuLi}]_4$-tetramer formed in diethyl ether and tetrahydrofuran.

In solutions, organic lithium compounds form complex dynamic equilibrium systems. Both intramolecular bond fluctuations and intermolecular exchange are assumed to occur. This means that there is a balance between ionic and covalent lithium-carbon bonds, and that the organic substituents can be interchanged. This occurs due to the lack of valence electrons in the lithium atoms. To compensate for this electron deficiency, multicenter bonds are formed within the oligomeric units.[11] Due to their high reactivity and sensitivity to air, organolithium compounds must be handled in an inert gas atmosphere. They are usually stored in inert hydrocarbons such as hexane, since they even often react with ethers. Organolithium compounds are important for the synthesis of complex

molecules. Their behavior and reactions are similar to those of GRIGNARD reagents, but they are even more reactive. However, they are also less stable.[11,13]
One of the most important reactions mediated by organolithium compounds is the lithiation reaction. In this process, a lithium atom is introduced into the molecule, which makes it more convenient to introduce various functional groups or other substituents later on. Other notable reactions include the deprotonation of organophosphium ions, which is of great importance for the WITTIG reaction, addition to multiple bonds, which is used, for example, to initiate the polymerization of synthetic rubber, and, lastly, reactions with main-group elements and transition metal halides for the synthesis of other organometallic compounds and complexes.[11]

3 Synthesis

3.1 Step I

The first step in the synthesis of the target compound is the bromination of 2-methylthiophene at the 3- and 5-positions with *N*-bromosuccinimide (NBS) in two consecutive electrophilic aromatic substitution reactions as shown in fig. 7.

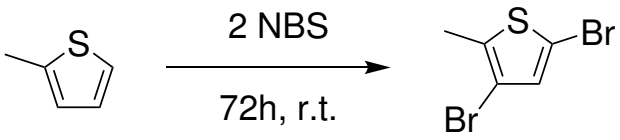


Figure 7: Dibromination of 2-methylthiophene with NBS.

Proposed mechanism

Electrophilic aromatic substitutions (S_EAr) are a classic method for functionalizing aromatic compounds. First, the electrophile must be released from the reagent (or mixture) used. In this reaction, it is a bromonium ion that is released from NBS. Because nitrogen has a higher electronegativity than bromine — a factor further enhanced by the two adjacent carbonyl groups — the nitrogen-bromine bond is polarized. As a result, the bromine atom carries a partial positive charge and can be easily cleaved. Thereafter, the reaction proceeds essentially via a two-step addition-elimination mechanism depicted in fig. 8. A preliminary third step — the formation of a π-complex in which the π electrons of the aromatic compound interact weakly with the electrophile — is generally of secondary importance for understanding the reaction.
In the first step of the reaction, the electrophile and the aromatic compound, which in this case is 2-methylthiophene, form a non-aromatic mesomerically stabilized cation as an intermediate, commonly referred to as a σ- or WHELAND complex. It is the result of the superposition of the mesomeric structural formulas. σ-complexes are high-energy intermediates because they lack the fully conjugated aromatic electrons found in the product and educt. Consequently, the formation of these complexes is the rate-determining step in nearly every S_EAr. In the following, second step, the aromatic ring is regenerated by the elimination of a cation from the carbon atom that was attacked by the electrophile, which leads to the formation of 2-bromo-5-methylthiophene in this reaction. The eliminated cation is usually a proton. Only very rarely is it a cation other than a proton, such as *tert*-butyl, sulfonyl or silyl cations.[3,7,14]

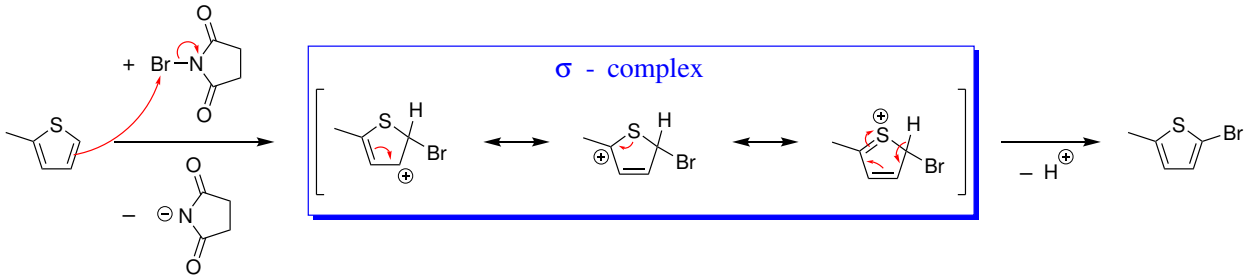


Figure 8: The first S_EAr reaction yields 2-bromo-5-methylthiophene.

The resulting 2-bromo-5-methylthiophene undergoes a second bromination by NBS in a further S_EAr reaction, shown in fig. 9, according to the described reaction mechanism. In this process, the regioselectivity is determined by the combined effects of substituent groups — such as mesomeric and inductive effects — and the heteroatom. This leads to the formation of 3,5-dibromo-2-methylthiophene as the product of this first step of the synthesis.[3]

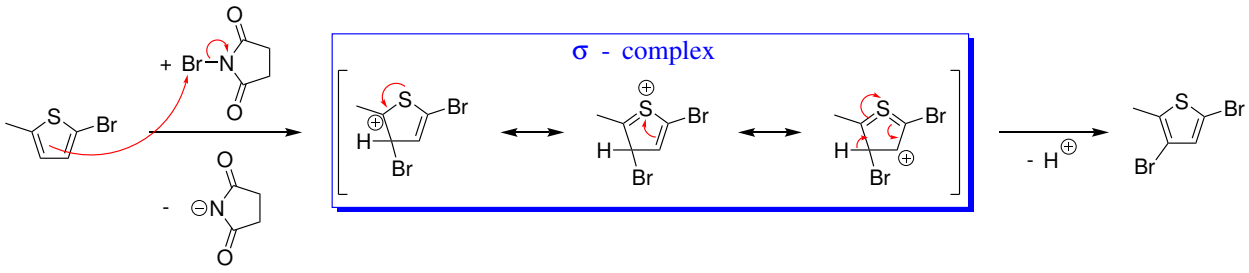


Figure 9: The second S_EAr reaction yields 3,5-dibromo-2-methylthiophene.

Procedure

In a round-bottom flask, 5.008 g of 2-methylthiophene $\left(M_{C_5H_6S} = 98.169\ \mathrm{g\,mol^{-1}}\right)$ is mixed with 50 mL of glacial acetic acid. A total of 20.159 g of NBS $\left(M_{C_4H_4O_2NBr} = 177.985\ \mathrm{g\,mol^{-1}}\right)$ is added in portions of approximately 5 g every 10 min, and the mixture is stirred for 72 h at room temperature. After the reaction is complete, the mixture, which has turned a reddish-orange color, is neutralized with sodium carbonate, extracted with diethyl ether, and dried over magnesium sulfate. After filtering out the desiccant, the diethyl ether is rotary evaporated off.

The crude product is purified by column chromatography using petroleum ether over silica gel. The fractions collected in test tubes containing the desired product are identified using thin-layer chromatography with petroleum ether as the mobile phase and UV light for detection and are then transferred to a round-bottom flask with dichloromethane. The solvents are rotary evaporated off, yielding 12.070 g of the product 3,5-dibromo-2-methylthiophene $\left(M_{C_5H_4SBr_2} = 255.961\ \mathrm{g\,mol^{-1}}\right)$ as a yellowish liquid.

A ^{1}H spectrum of the product dissolved in deuterated chloroform, is measured using a 400 MHz NMR spectrometer and tetramethylsilane as a reference.

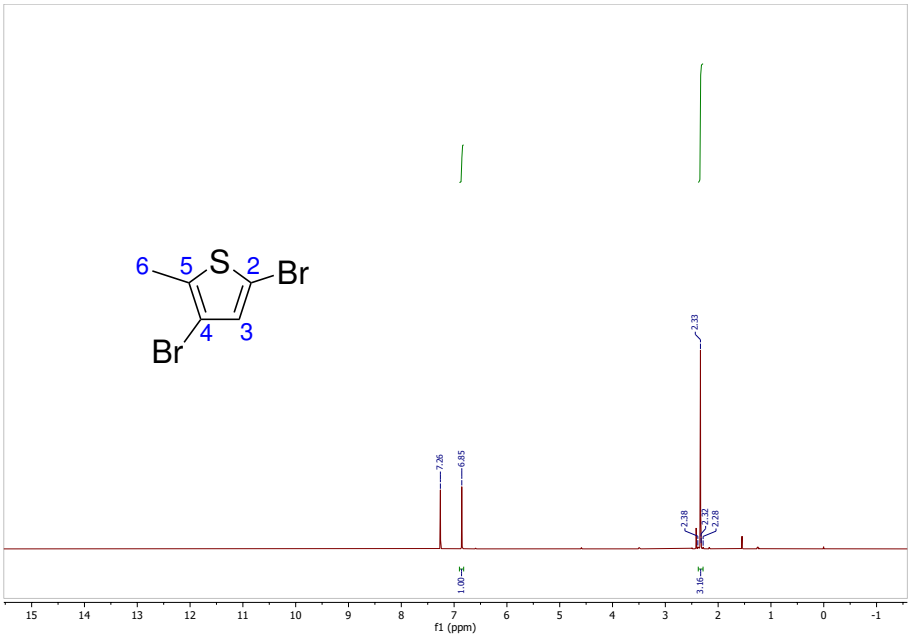
Results and Analysis

Yield Calculation

$$\begin{aligned} \text{Actual yield} &= 12.070 \text{ g} \\ \text{Theoretical yield} &= 13.058 \text{ g} \\ \text{Percentage yield} &= \frac{\text{Actual yield}}{\text{Theoretical yield}} \cdot 100\% \\ &= \frac{12.070 \text{ g}}{13.058 \text{ g}} \cdot 100\% = \underline{\underline{92.4\%}} \end{aligned}$$

A comparable procedure described in the literature[15] achieved a yield of 99%, which, while slightly higher, is comparable to the yield achieved in this stage of the synthesis.

^{1}H NMR spectrum



^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (s, 1H, 3-H), 2.33 (s, 3H, 6-H) ppm.

Figure 10: ^{1}H NMR spectrum of the product from the first step of the synthesis.

The ^{1}H NMR spectrum of the product obtained, shown in fig. 10, indicates that the target compound was successfully synthesized and is consistent with literature data.[10]
The spectrum exhibits two singlets corresponding to the expected proton environments of the target compound. The signal at $\delta = 6.85$ ppm can be assigned to the remaining thiophene proton in the aromatic region, while the singlet at $\delta = 2.33$ ppm corresponds to the methyl substituent attached to the thiophene ring. The integral ratio of 1:3 matches the expected proton count.
The absence of additional splitting is consistent with the substitution pattern of the molecule, since no vicinal proton coupling is possible within the substituted thiophene system. Minor impurity signals are present. However, their intensities are low compared to the product signals, indicating sufficient purity for further synthetic use.

3.2 Step II

The second step in the synthesis of the target compound involves introducing a trimethylsilyl protecting group in place of the bromine atom at the α position of the thiophene ring via an electrophilic substitution reaction, after lithiation of this position with *n*-butyllithium as shown in fig. 11. This results in 3-bromo-2-methyl-5-trimethylsilylthiophene being obtained as the product of this synthesis step.

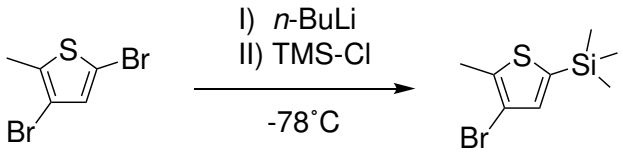


Figure 11: Introduction of a TMS protecting group at the α position of the thiophene ring following lithium–halogen exchange.

Proposed mechanism

The first reaction in this synthetic step is a metal–halogen exchange reaction in which the bromine atom at the α position of the thiophene ring is replaced by a lithium atom derived from the organometallic reagent *n*-butyllithium. This reaction could also be carried out with GRIGNARD compounds, metallic lithium or *tert*-butyllithium. However, on a small scale, *n*-butyllithium proves to be very convenient.

The exact mechanism of lithium–halogen exchange reactions is not yet fully understood and still discussed in the literature. It is generally assumed that rapidly equilibrating ate-type intermediates are involved.

The thiophene and *n*-butyllithium initially form a lithium salt. Its anionic moiety contains a divalent, negatively charged bromine atom. This species is referred to as the ate-type ion. The lithium salt is accordingly called an ate-type complex. This ate-type complex subsequently decomposes to yield the lithiated thiophene species and *n*-butyl bromide.[14]

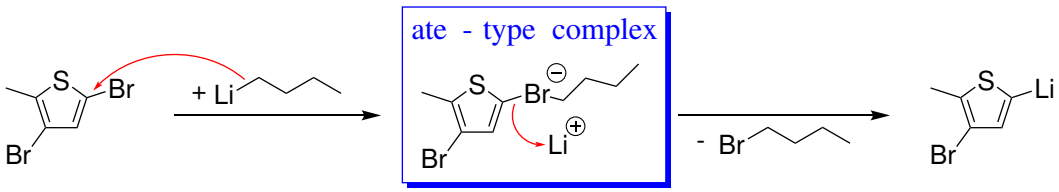


Figure 12: Lithiation reaction of 2,4-bromo-5-methylthiophene with an ate-type complex as an intermediate.

The reaction of the metallated aromatics obtained in this way with electrophiles yields products that would not be accessible, or would not be accessible selectively, via classical S_EAr reactions. Since bromine is generally easier to introduce into aromatic compounds than chlorine or iodine, the corresponding transformations are most important when dealing with aryl bromides.[14]

The second reaction is an S_N2-Si reaction. Certain organosilicon compounds, such as chlorotrimethylsilane, are capable of reacting in the same way as their carbon analogues. With a suitable leaving

group at the silicon atom of the trimethylsilyl group, it can be selectively substituted by an electrophile. In this case, it is the nucleophilic carbon atom bound to the lithium atom. The reaction proceeds bimolecularly as depicted in fig. 13. In a concerted step, the lithiated thiophene species acts as a nucleophile and attacks the electrophilic silicon atom of chlorotrimethylsilane, while chloride acts as the leaving group. This leads to the formation of 3-bromo-2-methyl-5-trimethylsilylthiophene as the product of this reaction.[13]

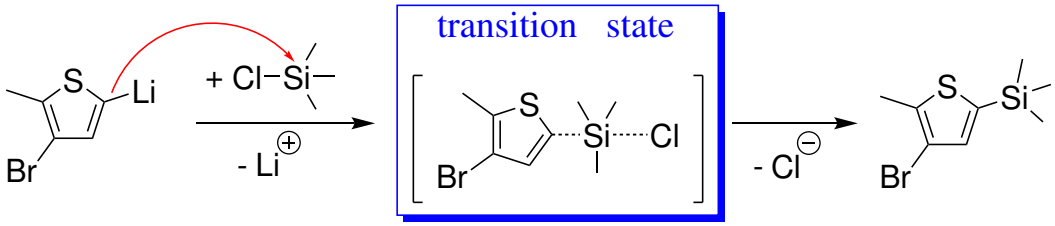


Figure 13: S_N2-Si of lithiated thiophene with chlorotrimethylsilane.

Procedure

6.006 g of 2,4-bromo-5-methylthiophene $\left(M_{C_5H_4SBr_2} = 255.961\ g\,mol^{-1}\right)$ are placed in a SCHLENK flask and cooled to —78 °C using acetone and liquid nitrogen under nitrogen atmosphere. 50 mL of absolute tetrahydrofuran are added as the solvent. While stirring, 9.1 mL of a 24% solution of *n*-butyllithium in cyclohexane $\left(M_{C_4H_9Li} = 64.057\ g\,mol^{-1},\ \rho = 0.75\ g\,cm^{-3}\ \text{at}\ 20°C\right)$[16] is added. The reaction mixture first turns an intense blue-green color, then red-orange. After 15 min of stirring, 3.2 mL of chlorotrimethylsilane $\left(M_{C_3H_9SiCl} = 108.643\ g\,mol^{-1},\ \rho = 0.859\ g\,cm^{-3}\ \text{at}\ 20°C\right)$[17] is added dropwise, causing the reaction mixture to turn yellow. Stirring is continued overnight.
After the reaction is complete, the reaction mixture is washed with saturated sodium chloride solution, extracted with diethyl ether, and dried over magnesium sulfate. The desiccant is filtered off and the solvents are rotary evaporated, leaving an orange-brown liquid.
The crude product is purified by column chromatography using petroleum ether over silica gel. The fractions collected in test tubes containing the desired product are identified using thin-layer chromatography with petroleum ether as the mobile phase and UV light for detection and are then transferred to a round-bottom flask with dichloromethane. The solvents are rotary evaporated off, yielding 5.406 g of the product 3-bromo-2-methyl-5-trimethylsilylthiophene $\left(M_{C_8H_{13}SBrSi} = 249.247\ g\,mol^{-1}\right)$ as a yellowish liquid.
A ^1H spectrum of the product dissolved in deuterated chloroform, is measured using a 400 MHz NMR spectrometer and tetramethylsilane as a reference.

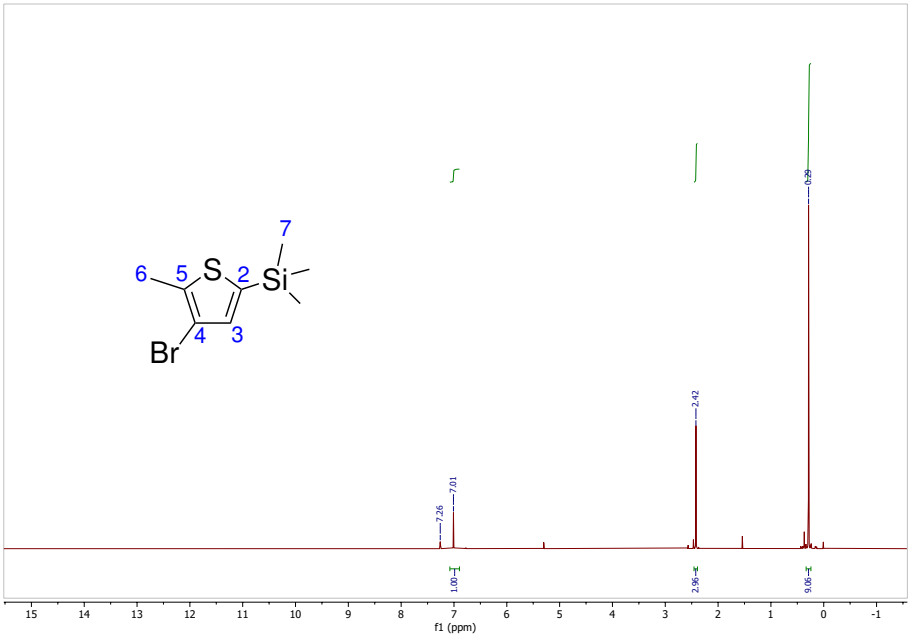
Results and Analysis

Yield Calculation

$$\begin{aligned} \text{Actual yield} &= 5.406 \text{ g} \\ \text{Theoretical yield} &= 5.849 \text{ g} \\ \text{Percentage yield} &= \frac{\text{Actual yield}}{\text{Theoretical yield}} \cdot 100\% \\ &= \frac{5.406 \text{ g}}{5.849 \text{ g}} \cdot 100\% = \underline{\underline{92.4\%}} \end{aligned}$$

A comparable procedure described in the literature[18] achieved a yield of 97%, which, while slightly higher, is comparable to the yield achieved in this stage of the synthesis.

^{1}H NMR spectrum



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (s, 1H, 3-H), 2.42 (s, 3H, 6-H), 0.29 (s, 9H, 7-H) ppm.

Figure 14: ^{1}H NMR spectrum of the product from the second step of the synthesis.

The ^{1}H NMR spectrum of the product obtained, shown in fig. 14, indicates that the target compound was successfully synthesized and is consistent with literature data.[10]
Compared to the spectrum of the previous intermediate, an additional singlet appears at $\delta = 0.29$ ppm, which is characteristic of the trimethylsilyl protecting group. Due to the strong shielding effect of silicon, the corresponding methyl protons resonate in the high-field region. The thiophene proton remains visible as a singlet at $\delta = 7.01$ ppm, whereas the methyl substituent gives rise to a singlet at $\delta = 2.42$ ppm.
The integral ratios are consistent with the expected proton distribution of the target molecule. The absence of signal splitting agrees with the substitution pattern of the thiophene ring. Only small

impurity signals are observed, suggesting that the product possesses sufficient purity for use in the subsequent synthesis step.

3.3 Step III

The third step involves nucleophilic substitution of perfluorocyclopentene with lithiated 3-bromo-2-methyl-5-trimethylsilylthiophene.

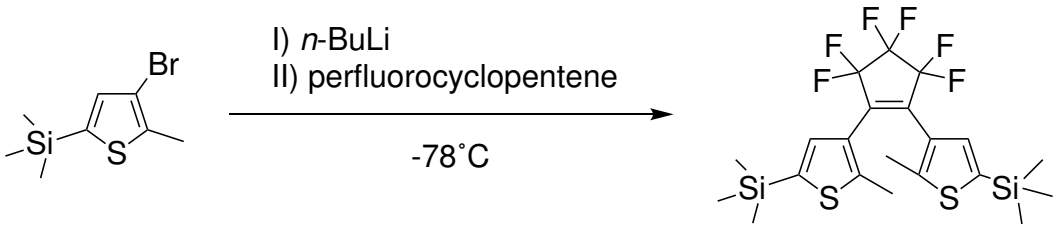


Figure 15: Lithium–halogen exchange and nucleophilic substitution of perfluorocyclopentene.

Proposed mechanism

The first reaction in this synthetic step is a metal–halogen exchange reaction in which the bromine atom at the β position of the thiophene ring is replaced by a lithium atom derived from the organometallic reagent n-butyllithium, as shown in fig. 16. Hereby, the intermediate formation of the ate-type complex and its subsequent decomposition with the release of n-butyl bromide occur, similar to the mechanism described in the previous step.

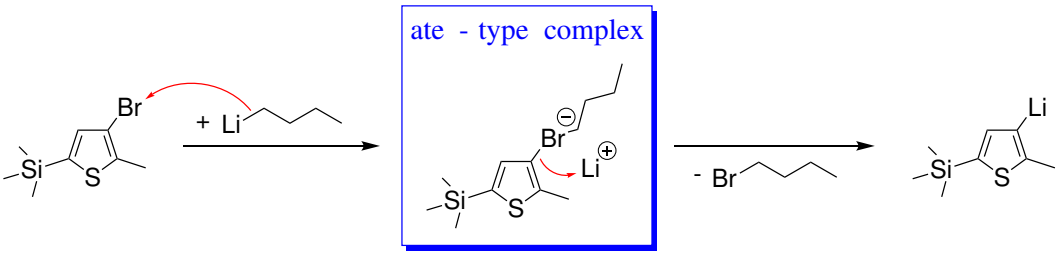


Figure 16: Lithiation reaction of 3-bromo-2-methyl-5-trimethylsilylthiophene with an ate-type complex as an intermediate.

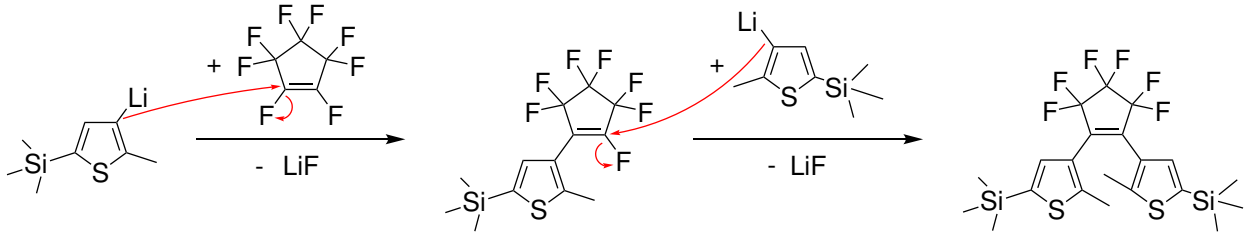


Figure 17: Nucleophilic substitution of perfluorocyclopentene.

In the second reaction of this step two equivalents of the lithiated thiophene species previously formed by lithium-halogen exchange react with perfluorocyclopentene in a nucleophilic substitution reaction, with elimination of lithium fluoride, to form a symmetrically disubstituted perfluorocyclopentene derivative. In this reaction, the lithiated carbon atom of the thiophene acts as a nucleophile. The

carbon atoms of the perfluorinated double bond of the perfluorocyclopentene act as electrophilic centers due to the strong electron-withdrawing inductive effect of the fluorine atoms and can therefore be attacked by nucleophiles such as the lithiated thiophene species yielding 7,7'-(bis(5-methylthiophene-2-trimethylsilyl))perfluorocyclopentene.[19]

Procedure

5.180 g of 3-bromo-2-methyl-5-trimethylsilylthiophene $\left(\mathrm{M}_{\mathrm{C_8H_{13}SBrSi}} = 249.247\ \mathrm{g\,mol^{-1}}\right)$ are placed in a SCHLENK flask and cooled to —78 °C using acetone and liquid nitrogen under nitrogen atmosphere. 20 mL of absolute tetrahydrofuran are added as the solvent. While stirring, 8.05 mL of a 24% solution of *n*-butyllithium in cyclohexane $\left(\mathrm{M}_{\mathrm{C_4H_9Li}} = 64.057\ \mathrm{g\,mol^{-1}},\ \rho = 0.75\ \mathrm{g\,cm^{-3}}\text{ at }20°\mathrm{C}\right)$[16] is added. The reaction mixture turns an orange color. After 15 min of stirring, 1.3 mL of perfluorocyclopentene $\left(\mathrm{M}_{\mathrm{C_5F_8}} = 212.042\ \mathrm{g\,mol^{-1}},\ \rho = 1.58\ \mathrm{g\,cm^{-3}}\text{ at }20°\mathrm{C}\right)$[20] is added quickly, causing the reaction mixture to turn black. Stirring is continued overnight.
After the reaction is complete, the reaction mixture is washed with saturated sodium chloride solution, extracted with diethyl ether, and dried over magnesium sulfate. The desiccant is filtered off and the solvents are rotary evaporated, leaving an orange-brown liquid.
The crude product is purified by column chromatography using petroleum ether over silica gel. The fractions collected in test tubes containing the desired product are identified using thin-layer chromatography with petroleum ether as the mobile phase and UV light for detection and are then transferred to a round-bottom flask with dichloromethane. The solvents are rotary evaporated off, yielding 3.965 g of the product 7,7'-(bis(5-methylthiophene-2-trimethylsilyl))perfluorocyclopentene $\left(\mathrm{M}_{\mathrm{C_{21}H_{26}F_6S_2Si_2}} = 512.731\ \mathrm{g\,mol^{-1}}\right)$ as an orange solid.
A ^{1}H spectrum of the product dissolved in deuterated chloroform, is measured using a 400 MHz NMR spectrometer and tetramethylsilane as a reference.

Results and Analysis

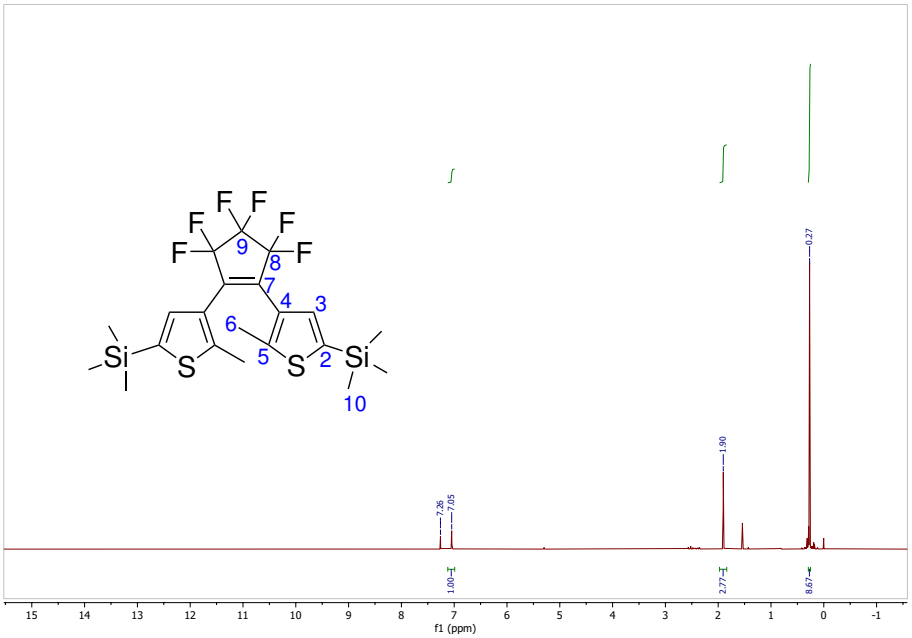
Yield Calculation

$$\begin{aligned}\text{Actual yield} &= 3.965\ \mathrm{g}\\ \text{Theoretical yield} &= 4.967\ \mathrm{g}\\ \text{Percentage yield} &= \frac{\text{Actual yield}}{\text{Theoretical yield}} \cdot 100\%\\ &= \frac{3.965\ \mathrm{g}}{4.967\ \mathrm{g}} \cdot 100\% = \underline{\underline{79.8\%}}\end{aligned}$$

A comparable procedure described in the literature[18] achieved a yield of 50%. While other sources cite yields of up to 92%, the yield obtained here appears to be acceptable and comparable.

^{1}H NMR spectrum

The ^{1}H NMR spectrum of the product obtained, shown in fig. 18, indicates that the target compound was successfully synthesized and is consistent with literature data.[10]
Since the reaction primarily introduces the perfluorocyclopentene bridge without significantly altering the proton-containing substituents, the spectral appearance remains similar to that of the precursor



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (s, 1H, 3-H), 1.90 (s, 3H, 6-H), 0.27 (s, 9H, 10-H) ppm.

Figure 18: ^{1}H NMR spectrum of the product from the third step of the synthesis.

compound. The aromatic thiophene proton appears as a singlet at $\delta = 7.05$ ppm, while the methyl substituent resonates at $\delta = 1.90$ ppm. The trimethylsilyl groups give rise to the characteristic high-field singlet at $\delta = 0.27$ ppm.
The observed integral ratios correspond well to the expected proton numbers of the symmetric target structure. Furthermore, the absence of proton-proton splitting is in agreement with the substitution pattern of the thiophene rings. Minor impurity signals are visible but do not significantly interfere with identification of the desired product.

3.4 Step IV

The fourth and final step in the synthesis involves deprotection by removing the trimethylsilyl groups from the thiophene rings and substituting them with a bromine atom, as shown in fig. 19.

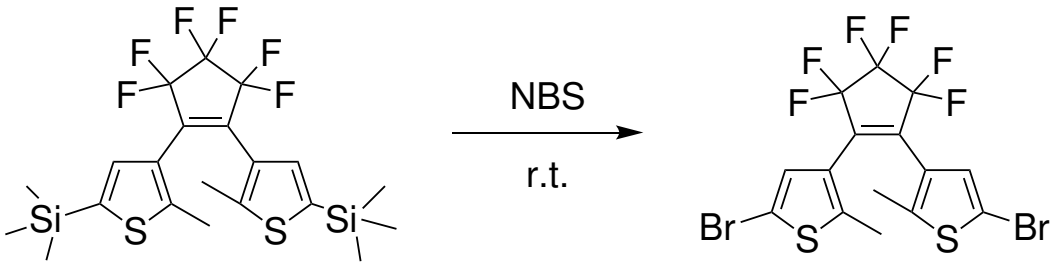


Figure 19: Deprotection by substitution of the trimethylsilyl groups with bromine atoms.

Proposed mechanism

The underlying mechanism is electrophilic desilylation and bears a strong resemblance to the S_EAr mechanism from the first step of the synthesis. However, the usual rules regarding the *ortho*-, *meta*-, or, where possible, *para*-directing effects of the substituents and the hetero atom do not apply. Instead, substitution by the electrophile occurs at the *ipso* position, the same atom of the thiophene ring that bears the silyl group. This selectivity is due to the fact that the most stable cation is formed in this case, which is stabilized by the silicon atom.[2]
This reaction occurs twice, first on one thiophene ring of the molecule and then on the other, as shown in fig. 20. This yields 7,7'-(bis(5-methyl-2-bromothiophene))perfluorocyclopentene as the product of the final step of the synthesis.

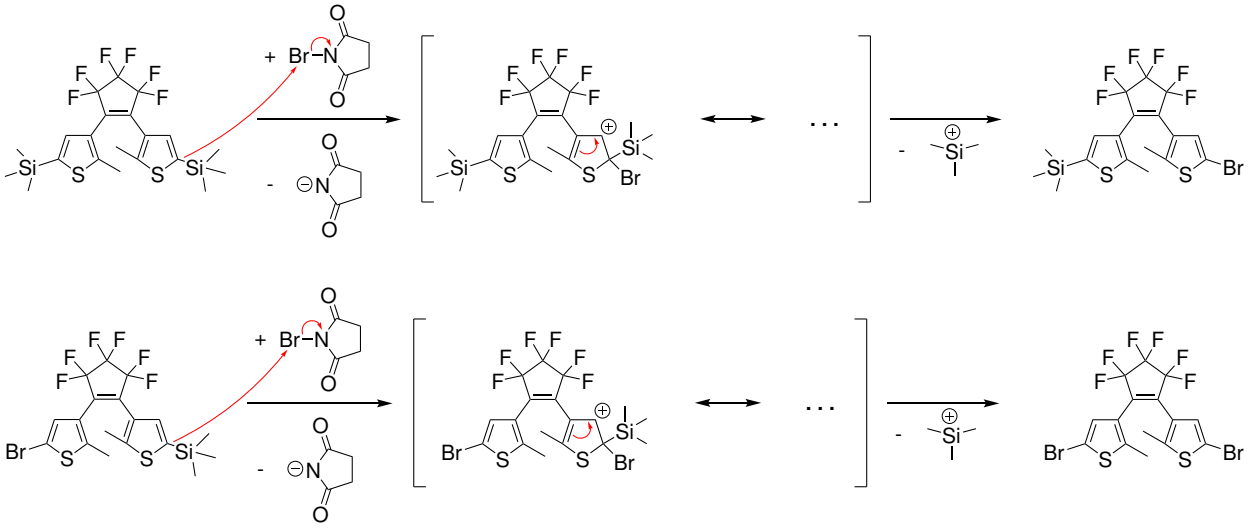


Figure 20: Electrophilic desilylation yields the final product of the synthesis.

Procedure

3.965 g of the product from the previous step 7,7'-(bis(5-methylthiophene-2-trimethylsilyl))perfluorocyclopentene $\left(M_{C_{21}H_{26}F_6S_2Si_2} = 512.731\ \mathrm{g\,mol^{-1}}\right)$ are dissolved in 40 mL of tetrahydrofuran in a round-bottom flask, and 3.351 g of NBS $\left(M_{C_4H_4O_2NBr} = 177.985\ \mathrm{g\,mol^{-1}}\right)$ are added in portions over a period of 15 minutes. The reaction mixture turns yellow-orange. Stirring is continued overnight. After the reaction is complete, the reaction mixture is washed with saturated sodium chloride solution, extracted with diethyl ether, and dried over magnesium sulfate. The desiccant is filtered off and the solvents are rotary evaporated, leaving a white-pink solid.
The crude product is purified by column chromatography using petroleum ether over silica gel. The fractions collected in test tubes containing the desired product are identified using thin-layer chromatography with petroleum ether as the mobile phase and UV light for detection and are then transferred to a round-bottom flask with dichloromethane. The solvents are rotary evaporated off, yielding 2.744 g of the product 7,7'-(bis(5-methyl-2-bromothiophene))perfluorocyclopentene $\left(M_{C_{15}H_{17}F_6S_2Br_2} = 526.159\ \mathrm{g\,mol^{-1}}\right)$ as a white solid.

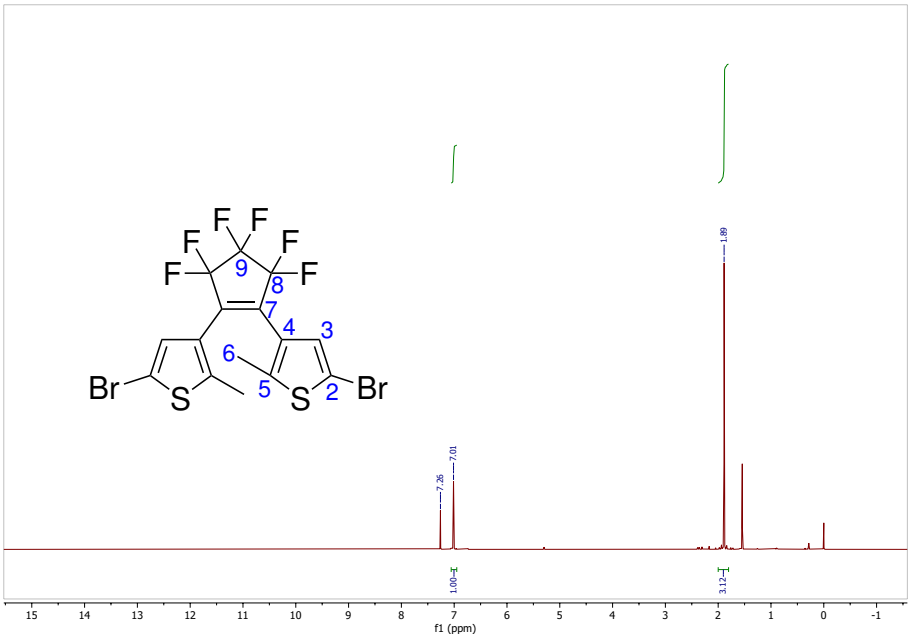
Results and Analysis

Yield Calculation

$$\begin{aligned}\text{Actual yield} &= 2.744\ \text{g}\\ \text{Theoretical yield} &= 4.069\ \text{g}\\ \text{Percentage yield} &= \frac{\text{Actual yield}}{\text{Theoretical yield}} \cdot 100\%\\ &= \frac{2.744\ \text{g}}{4.069\ \text{g}} \cdot 100\% = \underline{\underline{67.4\%}}\end{aligned}$$

A comparable procedure described in the literature[18] achieved a yield of 99%. The yield of this synthesis step is therefore significantly lower. This can likely be attributed to losses during column chromatography, since fractions containing product may have been discarded due to co-eluting impurities. These impurities are also detected by ^{1}H NMR spectroscopy. Further column chromatography purification of these fractions using a different mobile phase may resolve the issue.

^{1}H NMR spectrum



^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (s, 1H, 3-H), 1.89 (s, 3H, 6-H) ppm.

Figure 21: ^{1}H NMR spectrum of the product from the fourth step of the synthesis.

The ^{1}H NMR spectrum of the final product obtained, shown in fig. 21, indicates that the target compound was successfully synthesized and is consistent with literature data.[10]
Compared to the spectrum of the previous intermediate, the characteristic trimethylsilyl signal in the high-field region is no longer present, indicating successful desilylation and bromination of the thiophene rings. The aromatic thiophene proton appears as a singlet at $\delta = 7.01$ ppm, while the methyl substituent gives rise to a singlet at $\delta = 1.89$ ppm.
The integral ratio of the signals matches the expected proton distribution of the target compound.

The absence of signal splitting is consistent with the highly substituted thiophene system.
In addition to the product signals, several low-intensity impurity signals are observed, indicating that the isolated product still contains minor byproducts or residual impurities. Nevertheless, the desired compound could be identified unambiguously.

4 Conclusion

In summary, it can be said that the synthesis of the target compound using the methods and procedures described in this protocol was successful, and the observations — and, for the most part, the yields — were consistent with those reported in the literature. The bromine atoms on the thiophene rings of the product can be substituted in subsequent reactions, thereby making a wide variety of photoswitchable molecules accessible that are suited for further research.

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