Synthesis of conjugated oligomers : the preparation and characterization of oligothiophenes and oligophenyls

Degenhart, G.H.

Synthesis of Conjugated Oligomers

The Preparation and Characterization of Oligothiophenes and Oligophenyls

Proefschrift

Ter verkrijging van de graad van Doctor aan de Universiteit Leiden, op gezag van de Rector Magnificus Prof. Dr. Mr. P. F. van der Heijden, volgens besluit van het College van Promoties, te verdedigen op 4 december 2008 klokke 10:00 uur.

door:

Geerten Herman Degenhart

Geboren te Rotterdam in 1977

Promotor:	Prof. Dr. H. J. M. de Groot Prof. Dr. H. S. Overkleeft
Committee Members:	Prof. Dr. J. Brouwer Prof. Dr. G.A. v.d. Marel Dr. Ing. M. Overhand Dr. M. A. Hempenius Dr. R. L. P. de Jong

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List of Abbreviations

SAM	Self-assembled Monolayer
LR	Lawesson's Reagent
DCC	Dicyclohexylcarbodiimide
DCU	Dicyclohexylurea
Au(111)	Gold (crystal face 111)
NHS	n-Hydroxy Succinimide
THF	Tetrahydrofuran
DCM	Dichloromethylene
DMF	Dimethylformamide
NBS	n-Bromo Succinimide
N-Buli	n-Butyl Lithium
DME	Dimethoxyethane
OEP	Octaethylporphyrine
TEA	Triethylamine
LDA	Lithium Diisopropylamide
PTS	p-Toluene Sulfonic acid
BMIM	1-Butyl-3-methylimidazolium
DIBAL	Diisobutylaluminium (hydride)
NTA	Nitrilotriacetic Acid
OLED	Organic Light-Emitting Diode
TMSCl	Trimethyl Silyl Chloride
DDQ	Dichloro Dicyano Quinone
NMR	Nuclear Magnetic Resonance
FTIR	Fourier-Transform Infrared Spectroscopy

1 General Introduction

1.1 Synthesis of Functional Oligomers

Oligomers are short polymers, consisting of a low number of repeat units. Especially conjugated oligomers (oligomers with an extended π-system) are important for the construction of novel materials, such as organic conductors and semiconductors.

1.1.1 Molecular Electronics

Commercial electronics mostly consists of metal conductors and silicon semiconductors. However, with the development of doped polypyrrole[1], doped polypyridine[2] and doped polyacetylene[3], organic semiconductors were introduced, consisting of organic conjugated polymers. This represented a breakthrough in chemistry, which earned the Nobel Prize in 2000. Organic conducting and semiconducting materials are considered important because cheap manufacturing, easy processing and mechanical flexibility make these materials attractive alternatives for use in many applications. Another reason why organic materials are an interesting concept in electronics, is the possibility of self-assembly on a surface and in a third dimension. Last but not least, hybrid materials and devices exist such as metal organic frameworks, chemical sensors and DNA-chips, which require interaction between an organic, biochemical part and an inorganic component. Although at present, (partly) organic electronic devices are hardly commercially competitive due to short lifetimes and poor performance, there is ongoing research in this field that leads to rapid technological growth and improvement.

1.1.2 Scope of this thesis

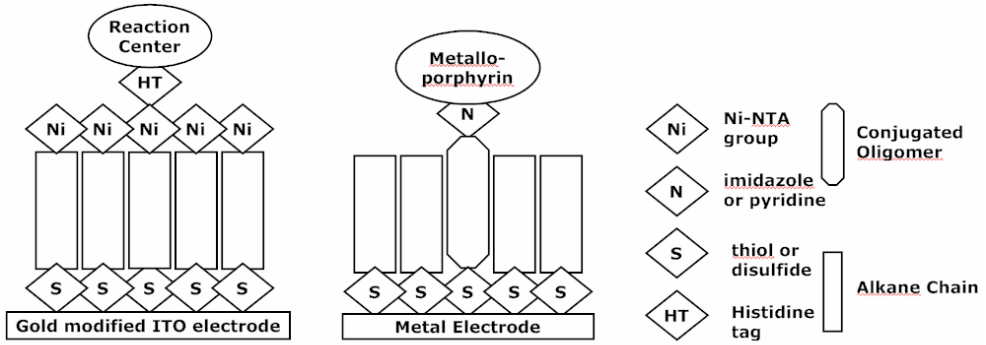
The work described in this thesis is primarily focused on the synthesis of conjugated oligomers and the introduction of functional groups in these compounds.
Chapter 2 deals with substituted oligophenyls, using coupling reactions to create functionalized oligomers and exploring cyclization.
In chapter 3, syntheses of oligothiophenes using the Paal-Knorr and Stetter reactions are described. The focus is on the formation of oligomers with sparse substituents on the sidechain for increased solubility. The use of hexyl substituents is avoided because their presence is considered detrimental if the oligomers are to be used in self-assembled monolayers (SAMs) [4,5,6,7].
In chapter 4, the incorporation of several functional groups in various stages of the process is described. The synthesis of the important asymmetric synthons **4-19** and **4-14** is described in this chapter.
In chapter 5, the production of traditional self-assembling molecules is described, with histamine or imidazole moieties exposed from the surface. Conjugated materials play an important role in molecular electronics and in the work described in this thesis. Oligomers can be used as building blocks for block-copolymers and for materials with a well-defined molecular architecture.

1.1.3 Surface Nanochemistry and artificial photosynthesis

Nanotechnology is a burgeoning scientific field on the boundaries between physics, chemistry and biology that focuses on the precise construction of macromolecules and supramolecular compouds. Current practice in constructing electronic device architectures mainly consist of joining semiconductor and metal parts. For a biological phase to coexist with inorganic materials, however, surface modifications are necessary. Usually, materials that are very dissimilar have unfavorable interactions with each other. Proteins are easily destroyed by surfaces due to the breakdown of the protein structure by hydrophobic-hydrophobic interactions. SAMs on metals, conducting oxides[8,9] or semiconductors[10, 11] with a suitable terminal group can be used as an interface layer to avoid such unfavorable interactions.

Photosynthetic reaction centers, the biological solar cells, have been bonded to gold using an alkanethiol interface (scheme 1-1). The SAM consists of linear molecules that have an affinity for the surface on one end, and affinity for the biological phase on the other side. For instance, a –SH group binds to gold and a nickel-NTA site can bind to a histamine tag attached to a reaction center.

Scheme 1-1: reaction center connected to gold surface using a SAM[12, 13] (left) and a proposed artificial photosystem (right)

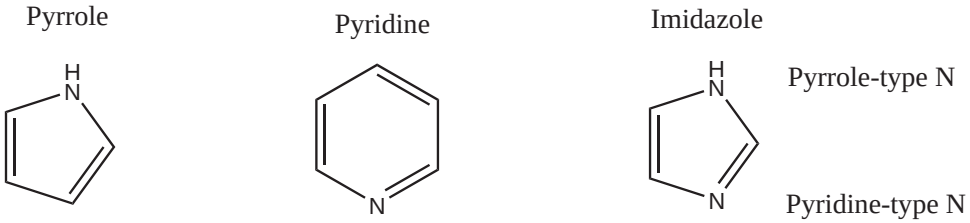


In scheme 1-1 on the right side, an asymmetric conjugated oligomer with two different terminal substituents is sketched. This is a proposed artificial light harvesting system. Like the left-side system, a biological phase and a metal electrode are in contact, with an intermediate phase in between. The important parts in this assembly are the porphyrin and the imidazole or pyridine moieties, the conjugated oligomer, and the electrode with the anchoring thiol or disulfide group that tethers the molecule to the electrode.

The porphyrin and imidazole (or pyridine)

Metalloporphyrins are capable of capturing photons and transmitting them. A macromolecular assembly of metalloporphyrins acts as a light harvesting antenna[14]. Porphyrins and phthalocyanins are bound preferentially by pyridine-type nitrogen. This is an aromatic nitrogen atom, such as present in pyridine and imidazole and many other heteroaromatic compounds. See scheme 1-2.

Scheme 1-2: Pyridine-type nitrogen explained.



Pyrrole-type: lone pair on nitrogen is part of the delocalized system and thus unavailable for coordination. Pyridine-type: lone pair on nitrogen is localized and available for coordination.

The conjugated oligomer

Conjugated oligomers are better electron conductors than aliphatic molecules. Incoming photons or excitons are subject to charge separation due to the possibility of electron transfer to the surface. The positive charge or electron hole that is left behind has to be compensated in both systems, for example by an electrolyte or in a solid-state device.

The reason why a conjugated oligomer is necessary at all instead of binding directly to the metal is also to prevent dissipation of excited states close to the metal. It is assumed that electrons do travel through the conjugated oligomers while excitons (delocalized and mobile excited states) do not travel through the oligomer.

In principle, electron transfer to conducting surfaces from biological structures has been achieved (see scheme 1-1 left side), and since aliphatic monolayers are poor conductors, this is one example where conjugated oligomers may become useful. In addition, the excitons generated by the chromophore are subject to dissipation if they are close to a metal surface.

The anchoring group and electrode

Hence metal electrodes in direct contact with proteins and porphyrins that have excited states must be avoided. Thiols and disulfides bind very well to gold and other metals. If conducting oxide electrodes such as ITO (indium-tin oxide) are used, phosphates or carboxylic acids would be proper binding groups.

The effect of SAMs and their terminal groups has been well-documented; and a logical next step is the replacement of the stable (but electrically resistive) saturated alkyl spacer by a conjugated oligomer, with the same terminal groups that are in use for traditional SAMs. There is some experience with conjugated SAMs[15], but applying functional groups remains difficult. In particular the synthesis of asymmetric, terminally functionalized conjugated oligomers remains a challenge.

In some cases, the surface part of an artificial photosystem will require an asymmetric oligomer containing both a thiol group and a pyridine-type nitrogen, on opposite sides.

1.1.4 Design of a functionalized oligomer

In order to be used as an interface, conjugated oligomers need to be linear, of uniform size and functionalised in such a manner that they can carry two different end-groups. Other constraints to the design of conducting oligomers are stability, solubility and processability. In order to be useful in surface chemistry, the more crystalline the compound, the better, although some degree of solubility is required. In addition, purification of crystalline compounds is straightforward. The larger the linear molecule becomes, the more it will tend to crystallize, unless bulky alkyl side-chains are present that hamper crystallization. For example, conducting polythiophene is rather intractable while poly(3-hexyl)thiophene can be dissolved in regular organic solvents. Other substituents might also be desirable, in order to alter properties such as the bandgap of the material or to make it water soluble.

The thiol part can be introduced directly, or indirectly. The $-SCH_3$ moiety is a stable group that can be deprotected at a later stage to the less stable –SH group[16]. It has been proven that aromatic thiols are indeed suitable for binding gold[17]. The energetic matching of the conjugated organic molecule with the metal surface[18] is not considered in this study.

1.1.5 Conjugated materials

Conjugated molecules are fully or partially unsaturated molecules, such as benzene or ethylene, where π-electrons are present. Fully conjugated polymers can be considered a molecular wire[19] because of electron delocalization. Oligomers are short polymers with 2-100 repeat units. Unlike polymers, they

can be made as pure compounds, while polymer samples are mixtures of polymer chains of different length. In scheme 1-3 a fully conjugated structure is shown on the left and a highly unsaturated, but not fully conjugated structure on the right.

Scheme 1-3: conjugation

Linear fully conjugated structure *Broken conjugated structure*

Whereas sp^3 carbon-carbon bonds do not facilitate electron transport, sp^2 carbon-carbon bonds do allow electron transport, even though electron mobility is often not nearly as large as seen in metals or classical semiconductors. Conjugated organic molecules are thus potentially conducting, while saturated carbon-carbon bonds are inherently resistive.

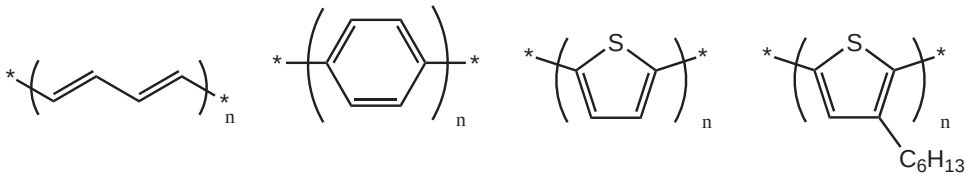
Electron delocalization over the entire molecule is required for effective long-range molecular electron transport, and preferably in an extended structure. The best conductivities are obtained with all-*E* polyalkenes, 1,4 phenyl based polymers and 2,5 thiophene based polymers. The conductivity of the right side molecule in scheme 1-3 will be drastically diminished compared to the left side molecule, due to the interrupted sp^2 structure. In a conducting polymer, such interruptions are called sp^3 defects. In addition, in synthetic polymers there are many regiodefects such as isolated *Z*-bonds in polyalkene, 3,5-couplings in polythiophenes or 1,3-couplings in polyphenyls.

Organic materials are poor semiconductors, unless they are doped, *i.e.* minimally oxidized or reduced, to generate free charge carriers (electrons or “electron holes”, positive charges) in the valence or conduction band. For example, polyacetylene is doped with I_3^- to make it *p*-type semiconducting by oxidation. Most organic semiconductors are *p*-type. They have a slight deficiency of electrons, which means positive majority charge carriers in the valence band. It is of interest some organic compounds such as phthalocyanin are intrinsic *p*-type semiconductors not requiring doping.
n-type organic semiconductors, with a slight excess of electrons, have negative majority charge carriers in the conduction band. They tend to be unstable and are much more uncommon than the *p*-type.

Para-coupled polyphenyl and 2,5-coupled thiophene polymers are well-known classes of organic semiconductors, and they are starting to be commercially applied in OLEDs, organic solar cells and printed circuitry. Oligomeric analogs

of these polymers are also capable of conducting electrons. Possible candidates for conducting oligomers include oligoacetylenes, oligophenyls and oligothiophenes.

Scheme 1-4: conjugated poly- and oligomer building blocks

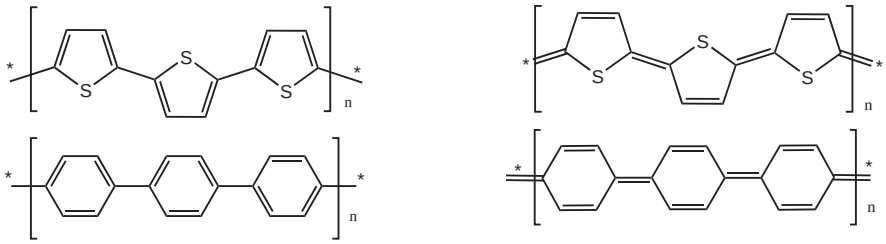


a. Polyalkene (polyacetylene) | b. Poly(para) phenyl | c. Polythiophene | d. Poly(3-hexyl) thiophene

Polymeric and oligomeric structures in this scheme are conjugated and potentially conducting.

All polymers in scheme 1-4 are semiconducting in the pristine (undoped) state, with poly(3-hexyl)thiophene being the standard organic semiconductor used in organic transistors. The other three are intractable solids. In scheme 1-5, the polymers and their mesomeric structures are plotted.

Scheme 1-5: Conjugation of SP2 polymers



a. Poly(para)phenylene (top) polythiophene (bottom) | b. Conjugation models

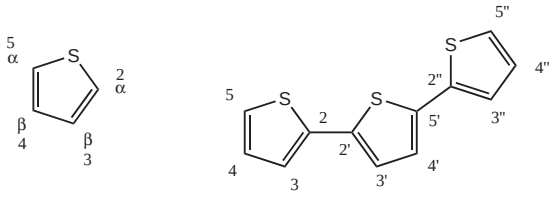
1.2 Thiophene and Polythiophene: Suitable building blocks for conjugated oligomers

The synthesis of thiophene oligomers as has been performed in the past will be briefly reviewed in the next section. First of all, the thiophene molecule and its reactivity will be discussed, as well as preparation methods for thiophene and

thiophene derivatives. The coupling of substituted and unsubstituted thiophenes into oligomers will be described next, followed by the formation of thiophene oligomers through cyclization reactions. The incorporation of a number of functional groups into the thiophene oligomer will be described in the next section, with a brief description of some recent oligomer-based applications.

Thiophene and pyrrole are frequently used as building blocks for conjugated polymers and oligomers. Furan[20], selenophene[21] and tellurophene[22] can be polymerized as well, though they have been investigated much less than thiophene based materials. Polythiophenes[23] are the most stable of these polymers, and their conductivity depends on the method of production.

Scheme 1-6: thiophene (left) and terthienyl (right) carbon atom numbers and nomenclature



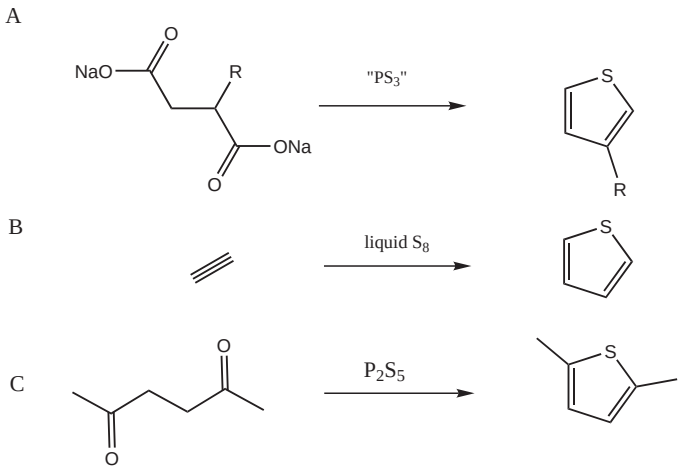
Polythiophene can be prepared *in situ*, in the form of a coating on an electrode by electrodeposition of thiophene[24] and polymerization driven by reactions at the electrode. Poly(3-alkyl)thiophenes are more soluble and can be spin-coated, which makes them more versatile than bare polythiophene. Poly(3-hexyl)thiophene is the most commonly used polythiophene, its properties are slightly superior to the equivalents with butyl to octyl chains, and polythiophenes with longer chains are less conducting[25] than P3HT.

A nice anecdote is in order here. Thiophene was discovered by accident by Victor Meyer in 1883[26] as an impurity in benzene. Isatin was used as a color agent to detect benzene in those days, and the isatin test failed on a benzene sample that had been prepared from benzoic acid instead of commercially available benzene. This led to the discovery of thiophene, which had been present as a minor contaminant in benzene and had been the compound detected by the isatin test.

In the years that followed its discovery, thiophene was prepared in a number of ways. Ring closure reactions from saturated compounds and phosphorus

sulfide were successful for making thiophene. In particular, 3-alkylthiophene was made from succinates[27] and 2,5-substituted thiophene was prepared from 1,4-diketones[28]. Pyrroles could be prepared in a similar manner by substituting phosphorus sulfide by ammonia or ammonia salts[29]. Thiophene has been made from pyrite or molten sulfur and unsaturated compounds as well[30]. These reactions can also be used to make thiophene oligomers, as will be described in this thesis.

Scheme 1-7: early ring closure reactions for the formation of thiophenes



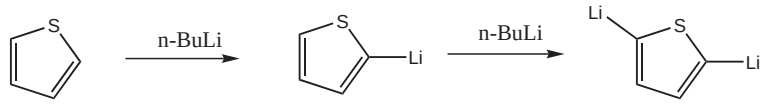
1.2.1 Thiophene Reactivity

While thiophene is a common substance present in petroleum, oligothiophenes also occur naturally, but only in very small amounts. For instance, Zechmeister and co-workers[31] obtained terthienyl from marigold flower petals, in a yield of about 15 mg terthienyl per kg fresh material. To produce oligothiophenes on a gram scale, synthetic pathways have been developed, and recently developed transition metal catalyzed reactions appear most practical.

The thiophene molecule and its derivatives are far more reactive than phenyl equivalents. The α-carbons are the most reactive positions on the thiophene molecule, and most transformations take place exclusively on the α-carbon. Ring opening reactions are more difficult than for furan and require special conditions. Thiophene is more electron rich than benzene, and electrophilic substitutions represent an important class of reactions. In particular nitration[32],

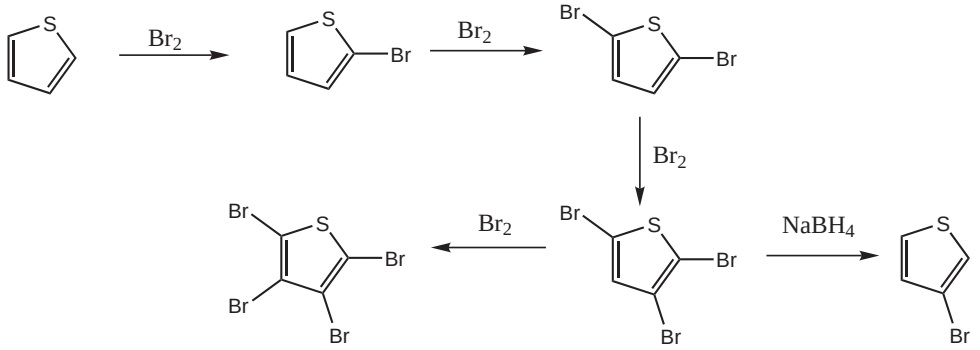
sulfonation[33], Vilsmeier formylation[34] and Friedel-Crafts acylation[35] can take place on thiophene, its analogues, and oligomers. Tin (IV) chloride has to be used instead of the more common aluminum (III) chloride that is used in many textbook examples of Friedel-Crafts reactions. The most synthetically relevant reactions for this thesis involve thienyllithium and thienylhalide intermediates, because these intermediates can be converted to the starting compounds for the coupling reactions described in this thesis.

Scheme 1-8: Thiophene deprotonation



Thiophene has relatively acidic protons, when compared with benzene. Butyllithium is capable of deprotonating thiophene, and with some effort[36] it is possible to deprotonate thiophene twice. The α-protons are the most acidic ones.

Scheme 1-9: Thiophene bromination



Bromination of thiophene can proceed up to tetrabromothiophene. Again, the α-positions are first to react. Even though mixtures of isomers will appear, the bromination reaction is mostly selective at temperatures around 0°C. Reductive debromination is also selective. If two equivalents of reductant are used, the bromine atoms at the 2 and 5-position will be preferably removed. In fact, this method is the most practical way to obtain 3-functionalized thiophenes on a laboratory scale[37].

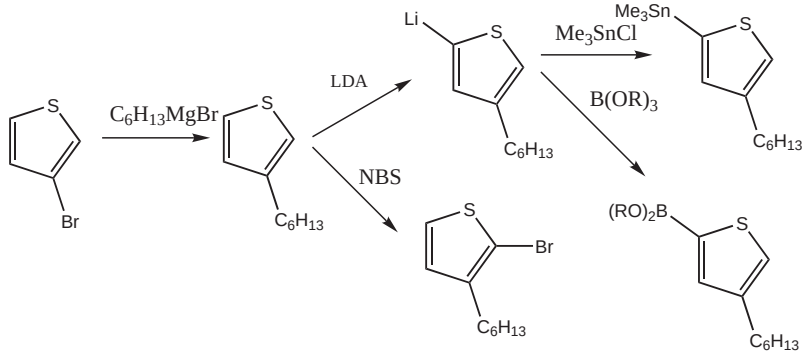
Both the thienyllithium compounds and the brominated thiophenes are reactive intermediates that can be used productively in order to make customized

thiophene oligomers. The thienyllithium intermediates can be used to obtain several functionalized thiophenes since the thienyllithium is a powerful nucleophile.

Oligothiophenes to be discussed in this thesis are α-coupled oligothiophene chains. It is also possible to create β-coupled oligothiophenes and fused oligothiophenes[38, 39]. β-coupled oligothiophenes are conjugated with reduced electron mobility along the chain. It is common practice to include an alkyl chain on the 3-position of thiophene for increased solubility and processability of the longer chain oligomers and polymers.

In this work, 3-alkylthiophenes were used as precursors for substituted oligothiophenes. They can be made by procedures derived from the late 19th century methods of Volhard and Paal, and the Volhard procedure works best for the production of 3-methylthiophenes. The yield decreases considerably for larger side-chains, and the Paal method requires expensive precursors. The most common procedure for the preparation of 3-alkylthiophene starts from 3-bromothiophene and alkylmagnesium halide[40]. The 3-bromothiophene is synthesized from thiophene, from tribromothiophene using a reductive dehalogenation (scheme 1-9) or from monobromothiophene using the halogen dance[41]. 3-alkylthiophenes can be functionalized selectively [42] (see scheme 1-8) because of the different chemical environment of the α-carbons when an alkyl substituent is present.

Scheme 1-10: Selective functionalization of thiophene

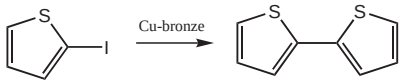


1.2.2 Thiophene Couplings

In this section, several methods for the formation of thiophene oligomers will be described, starting from thiophene monomers. The reactions here are mostly metal catalyzed coupling reactions that lead to oligomers of discrete size.

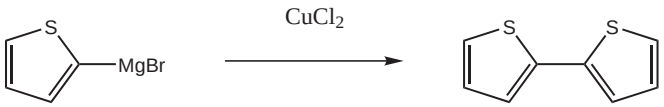
Thiophene dimers and higher oligomers can be compared to the analogous oligophenyls. The coupling of arenes was pioneered by Ullmann and co-workers[43]. The Ullmann procedure involves heating aryl halides with copper-bronze. This reaction leads to the coupling of phenyls and works for thienyl halides as well. However, the Ullmann reaction works best for electron poor phenylhalides, and low yields were obtained for thiophene dimers, although oligomers up to the heptamer were isolated in small amounts.

Scheme 1-11: Ullmann reaction



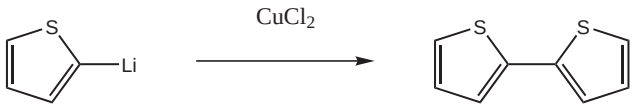
Steinkopf and coworkers[44] achieved a better result in their synthesis of dithienyl using the Grignard reagent of thiophene with Cu^{2+}, however, this oxidative coupling reaction produced a mixture of oligothiophenes.

Scheme 1-12: Steinkopfs dithienyl synthesis



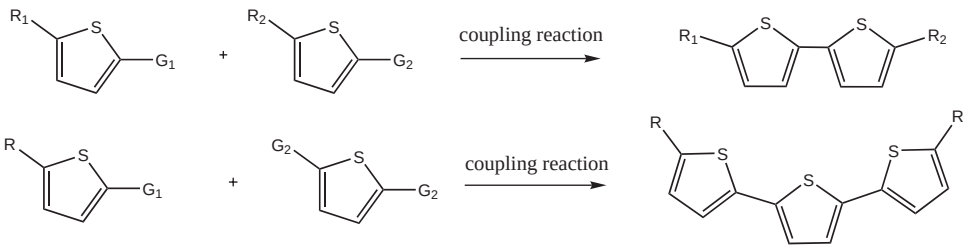
A similar procedure using thienyllithium was developed by Gronowitz and co-workers[45]. This procedure was very successful (yielding 85%), if more than one copper chloride equivalent was used.

Scheme 1-13: Gronowitz' dithienyl synthesis



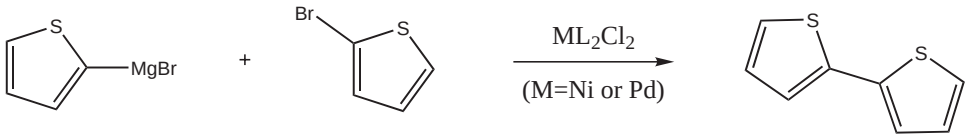
Kumada and co-workers[46] developed a procedure for the production of both thiophene oligomers and polymers, in a period in which there was much attention for conducting polymers. The development of the Kumada reaction was a significant step forward for the oligothiophene field, since it enabled the straightforward preparation of terthiophenes (synthesis of terthienyl from 1,4-diketones had already been performed). The Kumada reaction requires two different reagents. Coupling reactions of the Kumada type are usually metal catalyzed. For all the coupling reactions, dithienyl formation occurs, and the transformations shown in scheme 1-14 are usually possible as well.

Scheme 1-14: Coupling reactions in general: either a possibly asymmetric dimer (top) or a symmetric trimer (bottom) is formed.



The Kumada reaction will be described more in detail in chapter 2. Briefly, Grignard reagents of thiophene and other aromatic compounds react with aryl halides, catalyzed by nickel[47] or sometimes palladium (scheme 1-15). Since the reaction makes use of Grignard reagents, this limits the choice and nature of substituents. Thienylbromide can be prepared conveniently and in case of alkylthiophenes, regioselectively, using NBS[48].

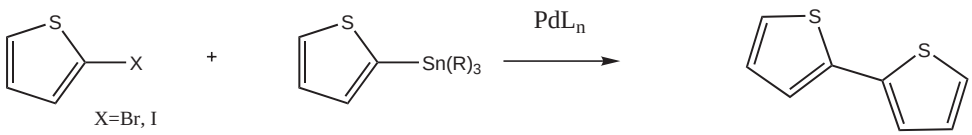
Scheme 1-15: Kumada coupling



Another catalyzed reaction that is very useful for the production of oligothiophene fragments is the Stille reaction (scheme 1-16) applied to

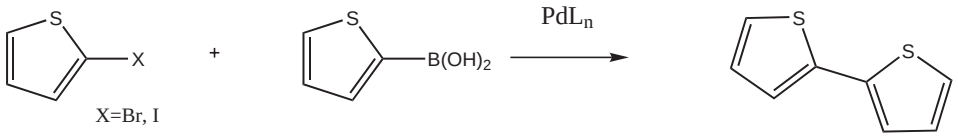
thiophenes. Thienylstannanes can be made from thienyllithium (scheme 1-8) and trialkyltin compounds.

Scheme 1-16: Stille Coupling



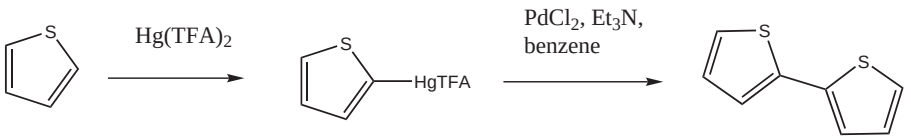
Thienylboronic acid and thienylhalide can be coupled with the Suzuki coupling reaction, which takes place in aqueous solution together with an organic solvent and is catalyzed by palladium, in the ligated Pd(0) form or as a palladium salt (scheme 1-17). Thienylboronic acids are prepared from thienyllithium or thienylmagnesiumbromide and a trialkylboronic ester, followed by hydrolysis.

Scheme 1-17: Suzuki Coupling



Mercury salts react with thiophene and its derivatives at the 2-position. These organomercury compounds will engage in a palladium-catalyzed homocoupling (scheme 1-18).

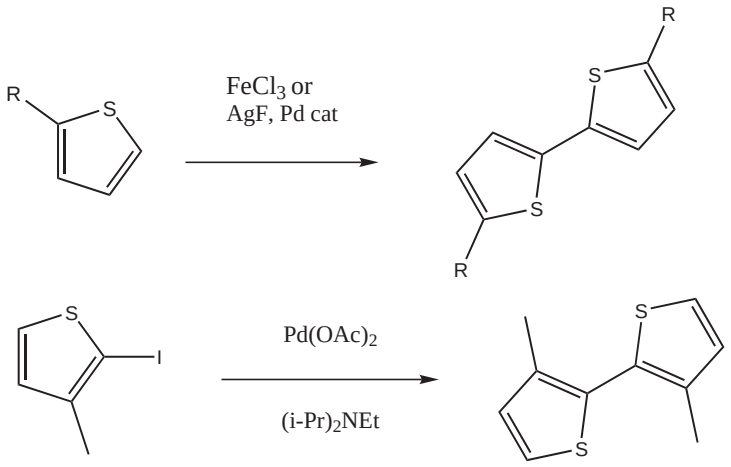
Scheme 1-18: Mercury driven thiophene coupling[49]



All coupling procedures that were discussed require a reactive moiety on the thiophene ring. It would be economical to have a procedure for direct C-H coupling. The thiophene polymerization agent[50] $FeCl_3$ can be used for a simple coupling reaction, if both reagents are monosubstituted thiophenes. Silver fluoride can also be used, with more tolerance for R-groups[51]. For example, 2,

2'-bithienyldibromide can be synthesized in one step from silver fluoride and 2-bromothiophene.

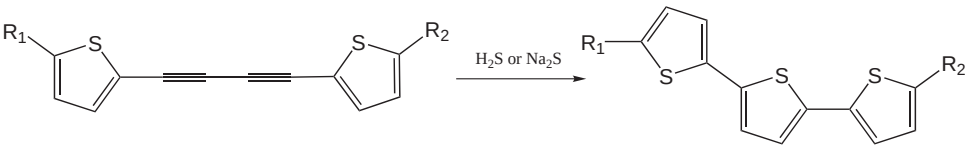
Scheme 1-19: C-H homocoupling of thiophenes[52, 53, 54]



1.2.3 Cyclization reactions leading to the formation of substituted thiophene

Besides coupling reactions, cyclization of non-aromatic precursors to thiophene oligomers are possible. These reactions are in fact no different from the preparations of substituted and unsubstituted thiophene monomer described earlier. Like the reactions shown in scheme 1-7, the precursors are 1,4-diketones and acetylenes.

Scheme 1-20: formation of thiophene oligomers from diyne precursors

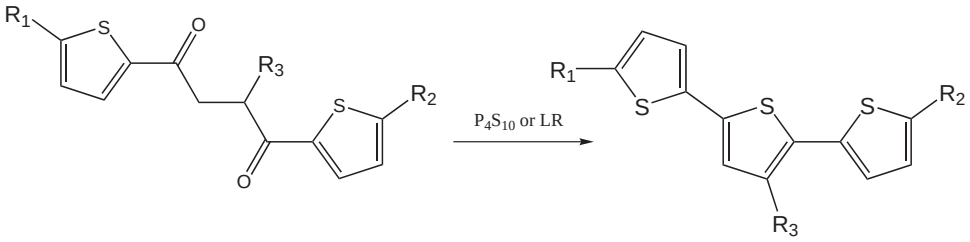


It is possible to synthesize precursors of thiophene oligomers that will form a fully aromaticized oligothiophene when treated with the appropriate sulfur compound. The diyne in Scheme 1-20 can be cyclicized by hydrogen sulfide or by $Na_2S \cdot 9\ H_2O$ in THF as solvent[55]. Evidently, no substituents can be present

on the acetylenic carbons, and therefore substituents cannot be introduced on the thiophene ring that is formed in this reaction.

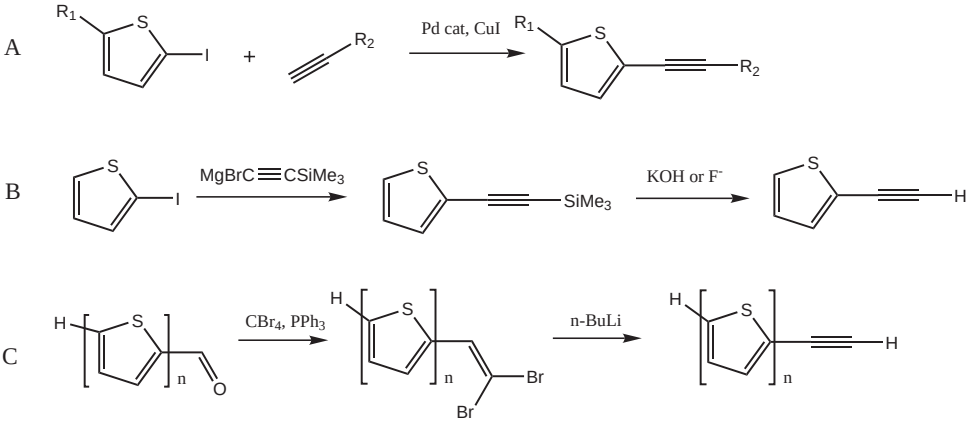
1,4-diketones can also be cyclized when heated with hydrogen sulfide and hydrogen chloride[56] or phosphorus-sulfur compounds such as phosphorus pentasulfide or Lawesson's reagent. This reaction allows the incorporation of side-chains on the heterocycle that is formed in the reaction. Both the 1,4-diketones as well as the 1,3-diynes require some synthetic effort to obtain.

Scheme 1-21: formation of thiophene oligomers from 1,4-diketone precursors



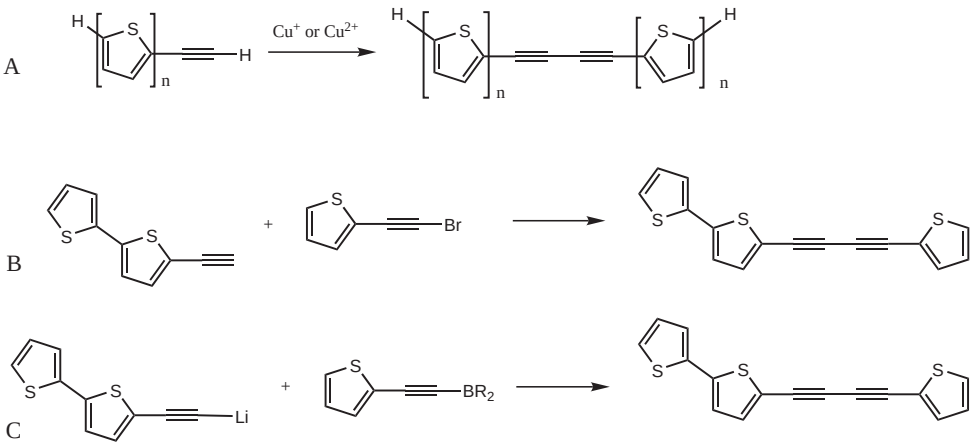
Thienylacetylenes and thienylbutadiynes are an important class of compounds, not only as precursors for oligothiophenes, but they are also valuable oligomeric structures in nanoarchitecture. In scheme 1-20 a thienylbutadiyne structure is shown. Thienylacetylenes are conveniently formed using the Sonogashira-Hagihara coupling[57,58] (scheme 1-22A). Other procedures that also give good results start with the Grignard reagent of the acetylene compound and iodothiophene. The Wittig reaction of thienylcarboxaldehyde with carbon tetrabromide, followed by treatment with strong base, will lead to the formation of the thienylacetylene[59,60]. Vinylthiophene[61] can be brominated and treated with strong base for the same result[62].

Scheme: 1-22: Formation of thienylacetylenes



If R_2 in scheme 1.22 is hydrogen, two thienylacetylene derivatives can homo-couple into a butadiyne derivative. A heterocoupling is possible as well (scheme 1-22A). A disadvantage of acetylenes as precursors for thiophene rings is the lack of the possibility to incorporate sidechains in the product. The yield of this reaction apparently improves with longer oligomers (n).

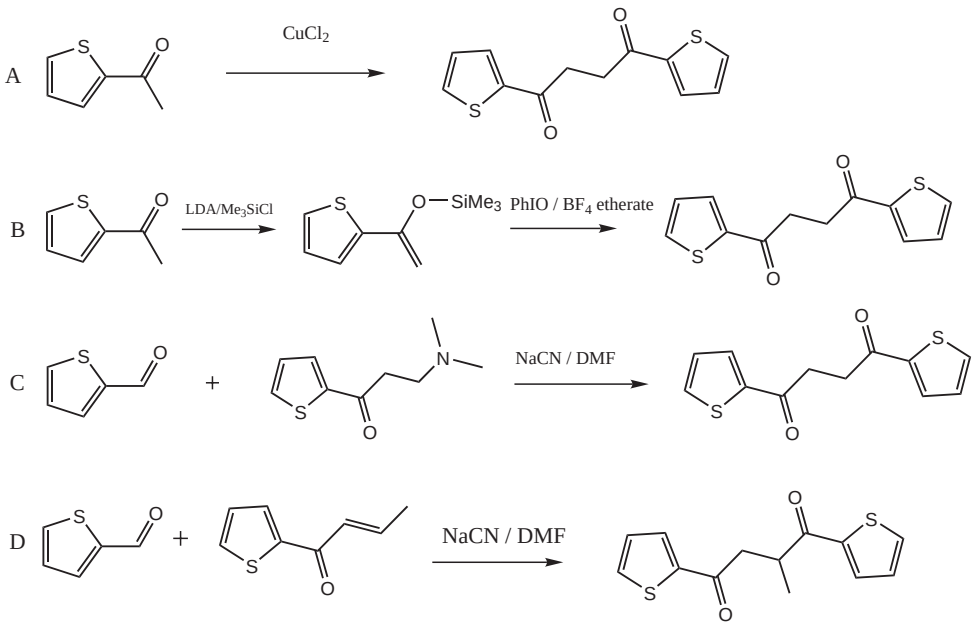
Scheme 1-23: Formation of butadiynes



1,4-diketones are more versatile than butadiynes as precursors for oligomers because the sp^3 alkane chain can hold substituents that will end up in the 3 and 4 positions on the thiophene rings in ring formation reactions.

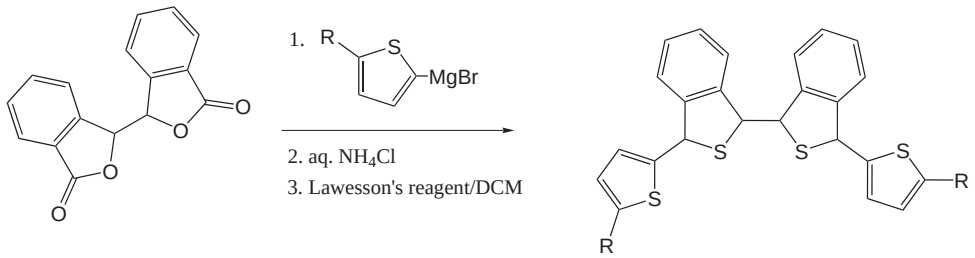
For the Friedel-Crafts acylation reaction that works well on thiophene a low yield was reported if thiophene was replaced by the dimer dithienyl. Succinyl chloride was coupled to two equivalent of thiophene with good result[63]. 1,4-diketones were produced using $CuCl_2$ oxidation of enolates (1-24A)[64]. Homocoupling of the acetylthiophene derivative led to a symmetric 1,4-diketone[65] (1-24B) and heterocoupling of an aldehyde with a Mannich base led to an asymmetric 1,4-diketone[66] (1-24C). A similar reaction takes place between aldehyde and a Michael acceptor in the so-called Stetter reaction[67] (scheme 1-24D, and chapters 3 and 4)

Scheme 1-24: Formation of 1,4-diketones

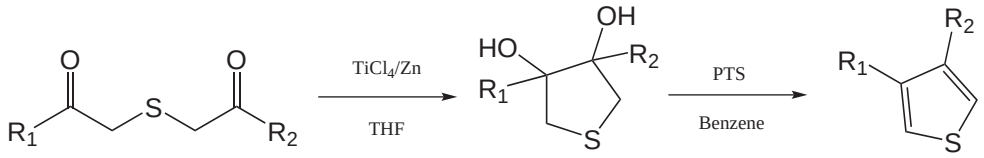


Instead of 1,4-diketones, γ-butyrolactones can be used as precursors. A Grignard reagent leads to ring opening of the lactone. Treatment with phosphorus-sulfur compounds will result in thiophene formation.

Scheme 1-25: formation of thiophene oligomers from γ-butyrolactones[68]



Scheme 1-26: formation of thiophene oligomers from 3-thiapentanes-1,5-diones[69]

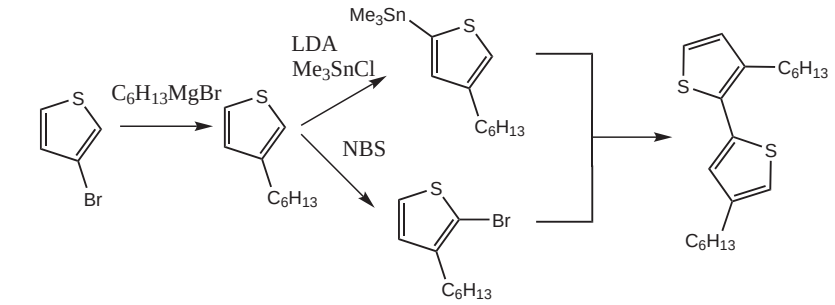


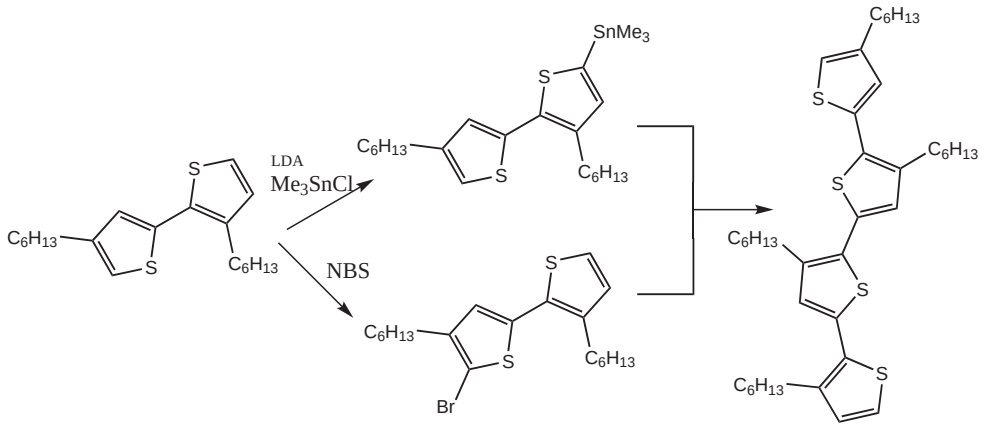
1,5-diones are usually cyclisized to 6-membered heterocycles in a similar way as described for 1,4-diketones and 5-membered heterocycles, if a heteroatom donor is present. However, it is possible to make 5-membered thiophene rings from 3-thiapentanes-1,5-diones. In scheme 1-26, titanium is reduced by zinc and this leads to the reduction of the 1,5-diketone to a vicinal diol, forming a 5-ring. This vicinal diol is dehydrated using p-toluene sulfonic acid catalyst in benzene.

1.2.4 The formation of thiophene oligomers

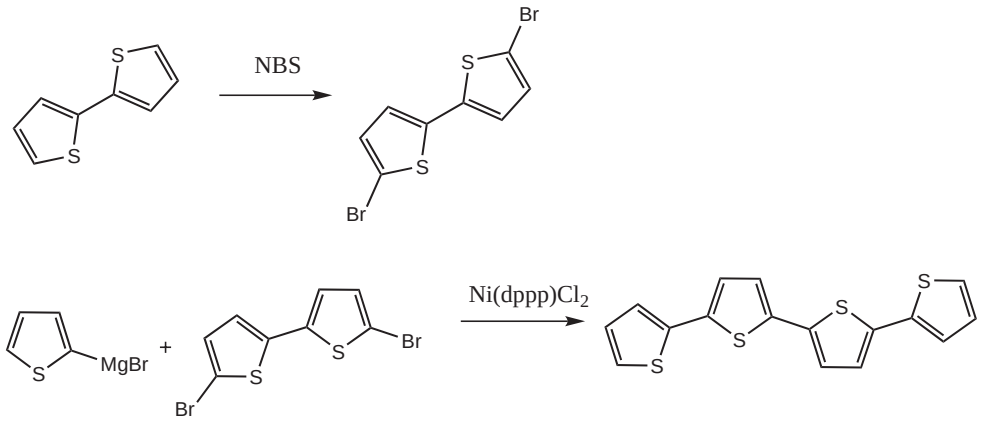
The coupling- and cyclization reactions described above can be used to prepare higher and more complex oligomers. The reactivity of thiophene as described earlier is conserved for thiophene oligomers such as terthienyl. The α-carbons of thiophene react in a similar manner as the α-carbons of dithienyl. It is therefore possible to couple not only thiophene to thiophene, but for example dithienyl to dithienyl to obtain quaterthienyl. Theoretically, these steps can be repeated over and over again.

Scheme 1-27: formation of longer oligomers[42]



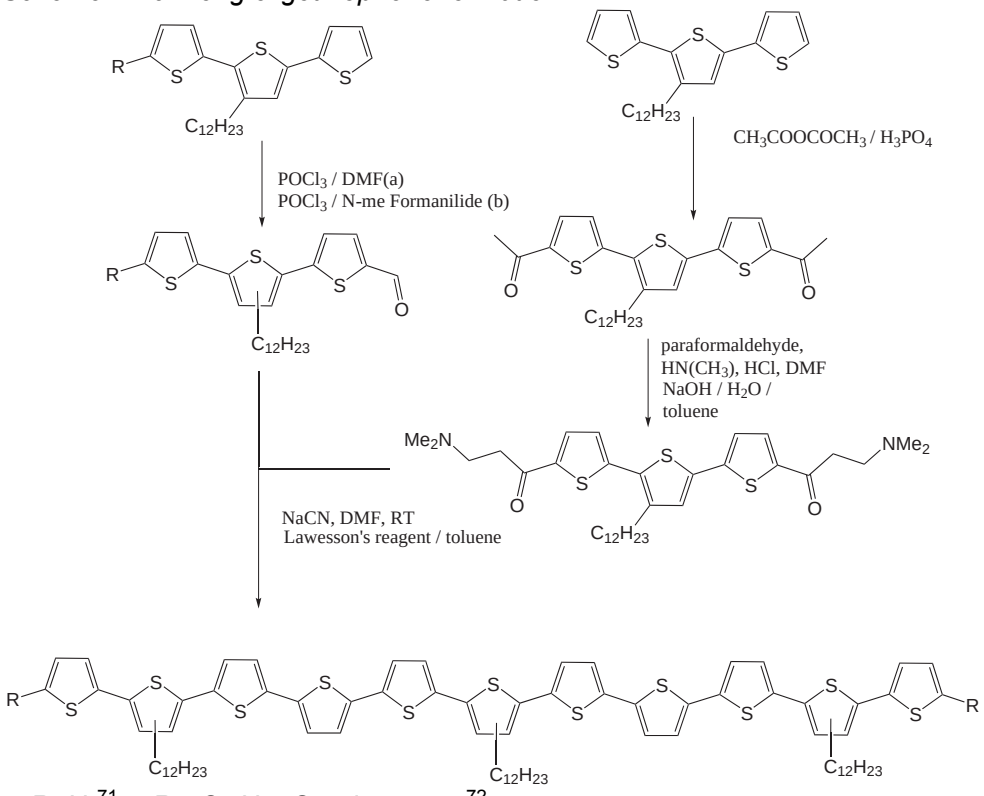


Scheme 1-28: Kumada coupling leading to symmetrically functionalized quaterthiophene[70]



In schemes 1-27 and 1-28, coupling reactions are used for the formation of a longer oligomer. In scheme 1-29, a Stetter related procedure is employed for the synthesis of long oligothiophenes.

Scheme 1-29: Long oligothiophene formation



a. R=H [71];b. R=-$C_{10}H_{20}$-O-polystyrene[72]

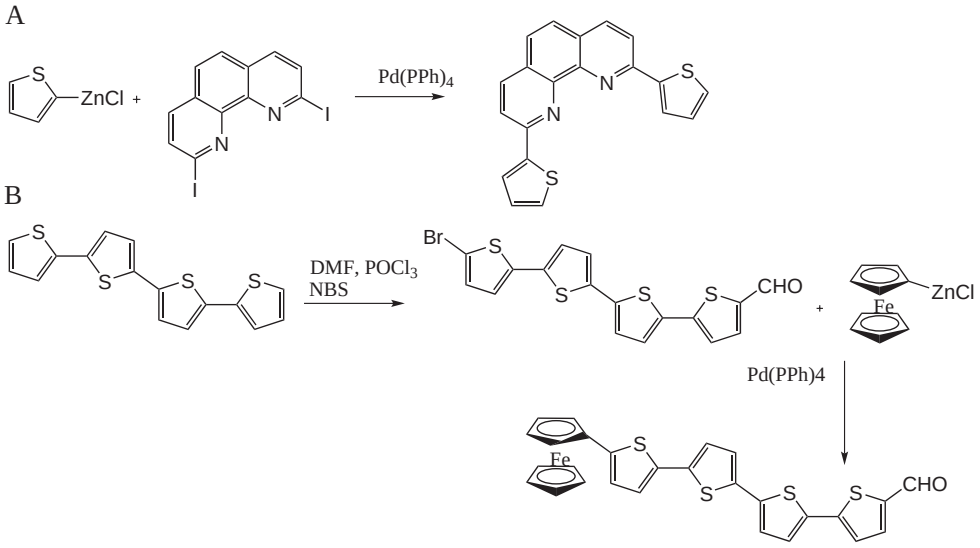
1.2.5 Functionalization of Thiophene Oligomers

The coupling reactions and cyclization reactions that were described result in the formation of thiophene oligomers with no other terminal substituents than the ones present on the precursors. It is also possible to couple other conjugated moieties to an oligothiophene, often using the same synthetic strategies.

The Negishi coupling can be used in some occasions where the Kumada coupling will not work, with organozinc compounds instead of organomagnesium compounds, catalyzed by palladium. Organozinc reagents

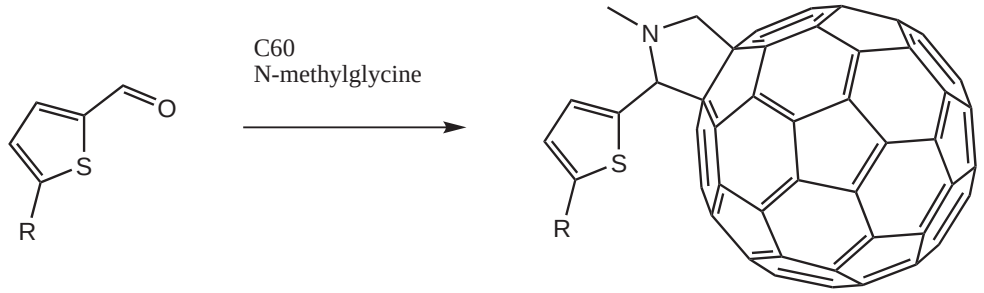
are less nucleophilic than the arylmagnesium compounds and allow the presence of groups that would be attacked by a Grignard reagent, such as an aldehyde. (see Scheme 1-30B).

Scheme 1-30: Negishi coupling of active ligands[73,74]



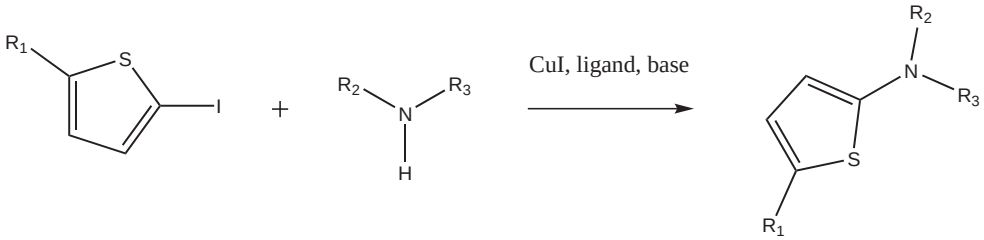
C60-fullerene is a structure that finds use in light-harvesting structures and polymeric (BHJ) solar cells because it is a good electron acceptor. In a characteristic D-π-A structure[75], the fullerene (A) is connected to the oligothiophene (π) covalently via one sp^3 carbon. See scheme 1-31 for the formation of the aldehyde.

Scheme 1-31: coupling of C60-fullerene to oligothiophene[52, 76]



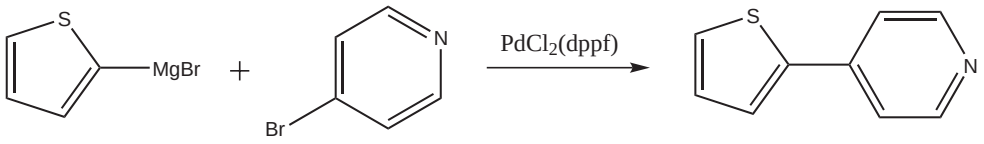
The Ullmann reaction as described earlier was the first aryl-aryl coupling procedure reported. Modifications of this procedure have been developed throughout the years using solvents and catalysts and copper(I) salts instead of copper bronze. It is thus possible to perform aryl-aryl couplings with better yield than for the original Ullmann reaction. In addition to C-C couplings, in the last decade, a variation on the Ullmann reaction that can be used for C-N couplings has been discovered. It allows for binding of the important imidazole moiety to thiophene derivatives. Proline can be used as a ligand in this reaction, and other ligands have been applied as well[77, 78].

Scheme 1-32: Ullmann coupling



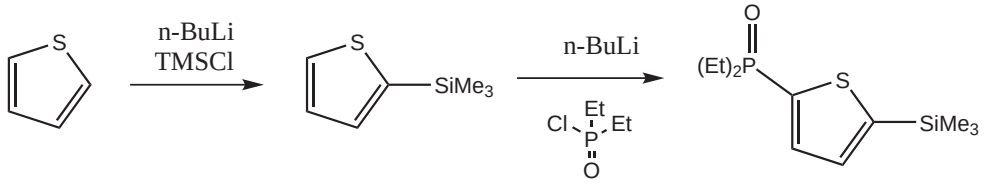
Pyridine can be coupled to thiophene using the Kumada reaction, starting from available pyridine halogenides[79].

Scheme 1-33: Coupling of pyridine to thiophene using the Kumada reaction



Thiophene phosphonates are surprisingly difficult to prepare from thienyllithium and phosphorus compounds. It is possible to perform a nickel catalyzed Arbusoff reaction [80] or to use thienyllithium on dialkylhalophosphonates.

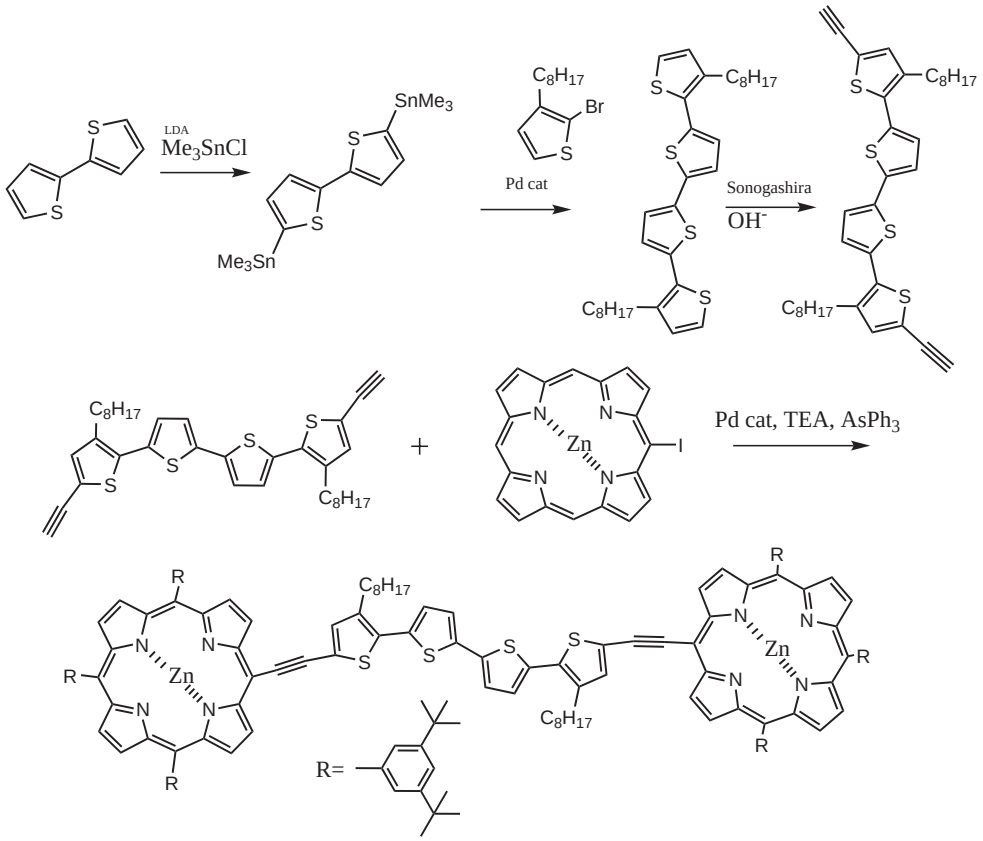
Scheme 1-34: Phosphonate introduction on thiophene



1.2.6 Nanostructure oligothiophenes

In the recent past, a number of interesting molecular constructs have been prepared, containing conjugated oligomers. In scheme 1-34, the synthesis of a porphyrin dyad[81] is shown. In this dyad, an oligothiophene-ethynyl bridge promotes strong electronic interactions between both termini. Many structures function as dyad, and an oligothiophene of some kind is commonly a part of these dyads[82].

Scheme 1-35: Synthetic route leading to a thiophene oligomer based dyad



1.3 Conclusion

The purpose of this concise review was to show that in both current and older literature a considerable number of procedures to a.) synthesize thiophene oligomers and b.) to incorporate active groups in an oligomer are available. Selecting and applying the most promising of those techniques make up the major part of the research described in this thesis.

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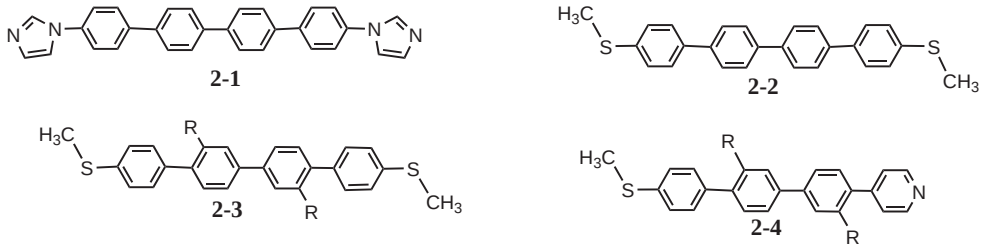
2 Synthesis of (semi)conducting oligothiophenyls

2.1 Introduction

This chapter describes the synthesis of oligophenyls that can be used as an interface layer between electrodes and chromophores. These molecules must conduct electrons from one side to the other, and be stably bound to both phases. If these requirements are met, then the molecule serves as a 'bridge' between electron donor and electron acceptor.

The end-groups on these oligomers should bind preferably to the desired surface, to allow the molecules to orient uniformly. Metal surfaces have affinity for thiols, while porphyrins and phthalocyanins are bound preferentially by pyridine-type nitrogens. The target compounds for this chapter are thus oligophenyl compounds with asymmetric end-groups, one of which is a protected sulphur, the other an imidazole or pyridine group. The active site of both groups is the sp^2 'pyridine-type nitrogen'. The $–SCH_3$ moiety is a stable group that can be deprotected at a later stage to the less stable –SH group[1]. Thiol-gold binding and disulfide-gold binding are good ways to construct an alkanethiol SAM[2]. In the case of arylic (thus conjugated) molecules, the $–SCH_3$ group is commonly introduced. An oligomer with this group is by itself a poor adsorbent, but a –SH or related functional group directly bound to an aryl ring (thiophene, phenyl) is not stable. Deprotection of $–SCH_3$ to –SH can be achieved with tBuSNa[3].

Figure 2-1:



Target structures: conjugated molecules capped with 1. terminal aromatic nitrogen; 2. protected sulphur; 3. protected sulphur and substituted with alkyl side-chains; 4. all of the above.

Oligophenyls compare favourably with oligothiophenes where it comes to stability, but their reactivity is consequently lower. Notably selective deprotonation or halogenation of the 2 and 5 position of thiophenes is commonly used, which makes oligothiophenes usually the oligomer of choice. Unsubstituted oligophenyls tend to be more crystalline (and thus less soluble) than oligothiophenes.

2.2 Results and Discussion

Symmetric conjugated and conducting oligomers, with the same end-group on both ends, have been made successfully in the past. To make such an oligomer is much less complicated than synthesizing an asymmetric one. Symmetric molecules are still useful, however, as a model system: compound **2**-**1** in figure 2-1 should bind to porphyrins forming a sandwich-like supramolecular complex, while compound **2**-**2** is a short molecular wire that can connect two metal nanoelectrodes.

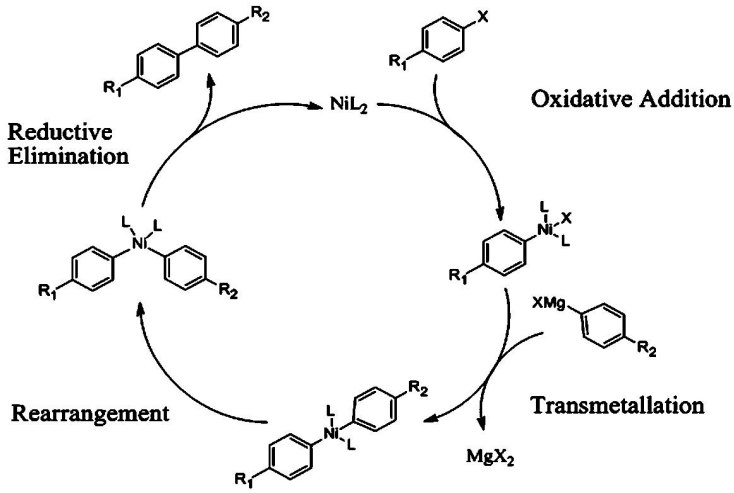
The most common synthesis techniques for symmetric oligomers are coupling reactions of functionalized phenyls into the desired oligomer, from Grignard reagents and catalyzed by Ni(dppp) or Pd(dppf) in the Kumada reaction, or by Suzuki reactions catalyzed by different Pd compounds. These two different types of reactions are very suitable for coupling reactions in general, if functionalized biphenyls are the intended product. They have been applied successfully for both the sulphur group and the pyridine nitrogen.

Both the Kumada and the Suzuki coupling reactions allow for side-chains to be present on the monomers (see Figure 2-1, compounds **2-3** and **2-4**) if these side-chains are on the monomers. The synthesis of substituted oligomers in

the absence of regioisomers is difficult, thus a different route towards oligomers was also explored. If the phenyl rings are constructed from non-aromatic precursors, it may be possible to custom build the desired oligomer with substituents.

The Kumada coupling[3] is a Ni (or rarely Pd) catalyzed C-C bond formation reaction using Grignard reagents and aryl halides. A Grignard reagent and an arylhalide react with each other and a C-C bond is formed between them. The Kumada reaction reliably produces good results for aryl-aryl couplings.

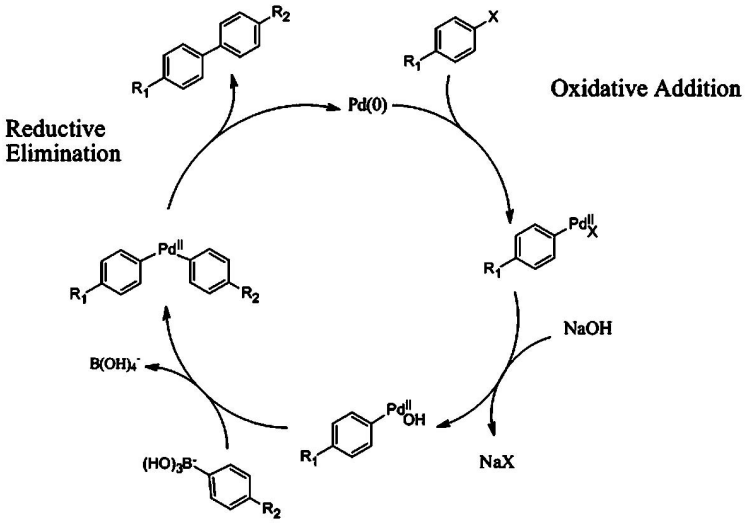
Scheme 2-2: Catalytic cycle of the general Kumada reaction: Nickel(II) catalyzes the reaction between the Grignard reagent and the relatively unreactive arylhalide.



Suzuki reactions can also be used to couple aryl compounds with similar results as Kumada reactions, although the mechanism is somewhat different. One reactant is an arylboronic acid, the other an aryl bromide. Suzuki reactions can be considered more versatile than Kumada reactions because most functional groups can be present. In contrast, the Grignard reagents used in the Kumada reaction do not allow any functional group to be present that is susceptible to nucleophilic attack or that is even slightly acidic.

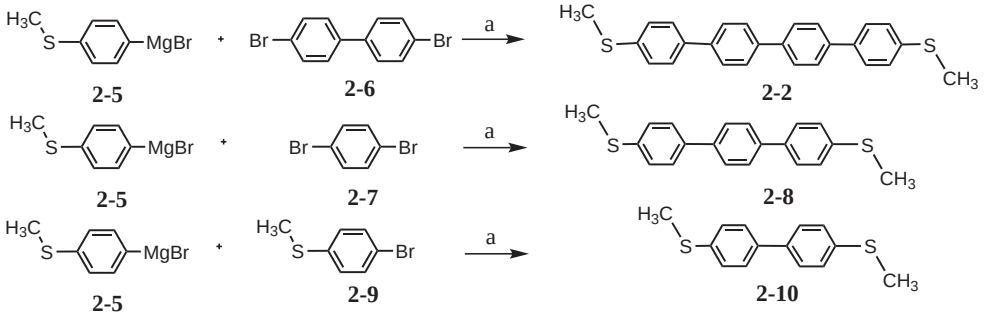
A disadvantage of both procedures is that in order to obtain an asymmetric oligomer and not a mixture of several possible products, the reaction has to take place between two larger fragments that make up the target oligomer.

Scheme 2-3: Catalytic cycle of the general Suzuki reaction: Palladium(0) catalyzes the reaction between the boronic acid and the relatively unreactive arylhalide.



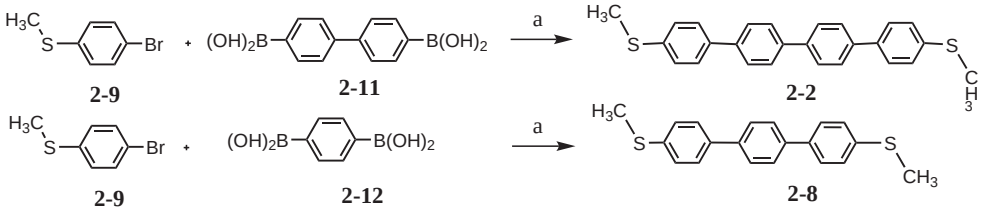
Both the Suzuki and the Kumada coupling reactions were applied in order to synthesize bifunctional oligomers containing a $-SCH_3$ moiety[4,5] and an imidazole or pyridine moiety as R group. See scheme 2-2 (Kumada) and 2-3 (Suzuki).

Scheme 2.4: terminal methylmercapto substituted oligomers made using the Kumada reaction



a: THF, Ni(dpppf)Cl₂.

Scheme 2.5: terminal methylmercapto substituted oligomers made using the Suzuki reaction.

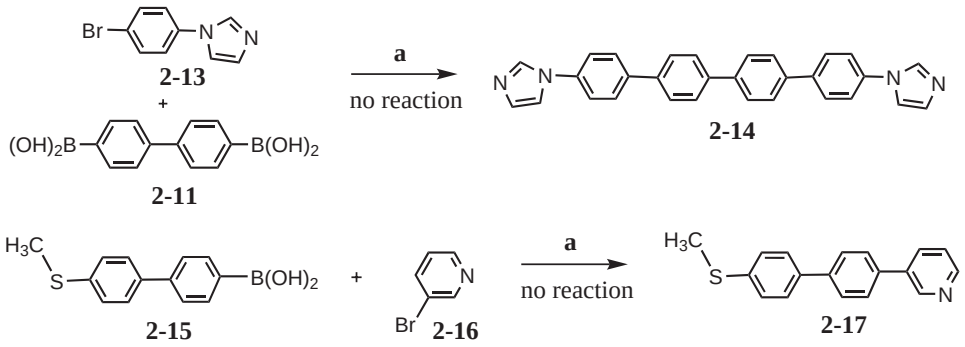


a: $Pd(PPh)_4$, $NaCO_3$, DME/water (reflux), 16h.

The precursors for both the Suzuki and the Kumada reactions are commercially available or can be made easily from commercial starting materials. The products **2-2** and **2-8** are very sparsely soluble in regular solvents, especially **2-8**. It takes solvents such as DMSO or o-dichlorobenzene at high temperatures to dissolve a good fraction of this material, while the analogous 4,4'-bismethylmercaptobiphenyl (compound **2-11**) dissolves in dichloromethane and other solvents.

Coupling of imidazole phenyls to longer chains in any appreciable yield failed: small amounts of symmetric oligomers were formed, but they were inseparable from the intractable major products of this reaction (scheme 2-6). Coupling of pyridine to a mixed precursor was attempted but no product could be isolated. This result is in line with previous reports[6], where Albers and co-workers describe difficulties isolating symmetric thiophene oligomers with pyridine end-groups. Had this reaction been successful, then the next step would have been to include two species of reactant to the mixture, instead of two equivalent of the same reactant, so that a mixture would appear with a significant fraction of asymmetric product.

Scheme 2-6: Suzuki couplings of pyridine-type nitrogen oligomers



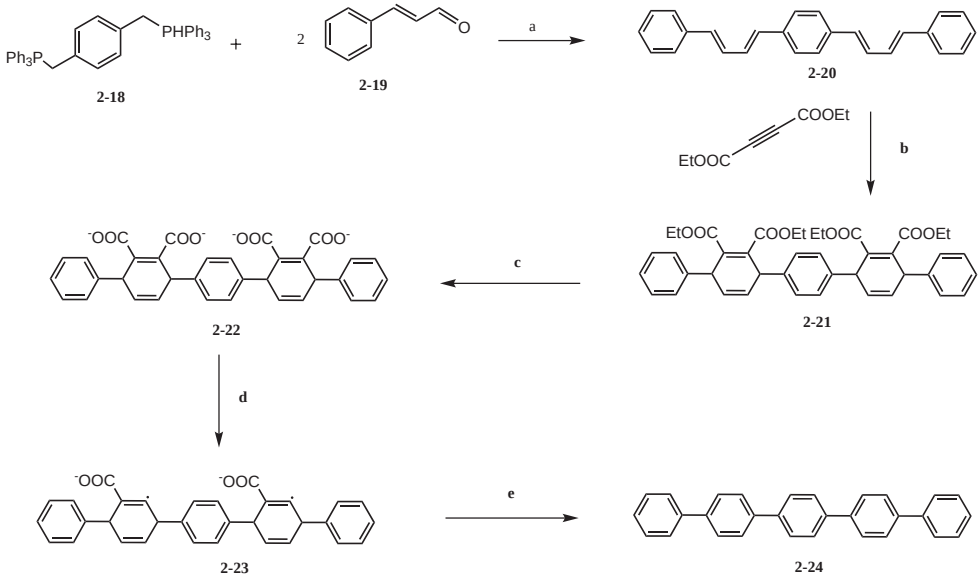
a: $Pd(PPh)_4$, $NaCO_3$, DME/water (reflux), 16h.

These results imply that there is some difficulty with the pyridine nitrogen in oligomers, most likely due to poor solubility. Even if the synthesis of **2-17** had succeeded, still the reactions described above are most suited for symmetric products if longer chains are desired. Considering that solubility was already an issue when the methylmercapto-group was present, another option was explored.

Another type of reaction has been performed in the attempt of creating substituted oligomers. This reaction allows substituents to be introduced on the rings, which is difficult to achieve using the Kumada and Suzuki reactions. It is known from polymer science that alkyl substituents make a polymer less crystalline and thus more processible. If a polymer is sufficiently 'alkane-like' it becomes oily and soluble rather than crystalline and intractible. The same is true for oligomers.

While the carbon-carbon cross-coupling reactions as described above are very well-documented and commonly used, much less is known about how to form phenyls from nonaromatic compounds. In the synthesis of para-quinquephenyl, a cyclohexadiene has been formed through Diels-Alder addition on a butadiene by an alkyne followed by decarboxylation and dehydrogenation (scheme 2-7). Decarboxylation of one carboxyl group leads to aromatization of the cyclohexadiene in this situation, which may explain why the reaction takes place. This approach was taken and adapted to be used for the synthesis of a functionalized oligomer.

Scheme 2-7: formation of p-quinquephenyl by McDonald et al.[7]

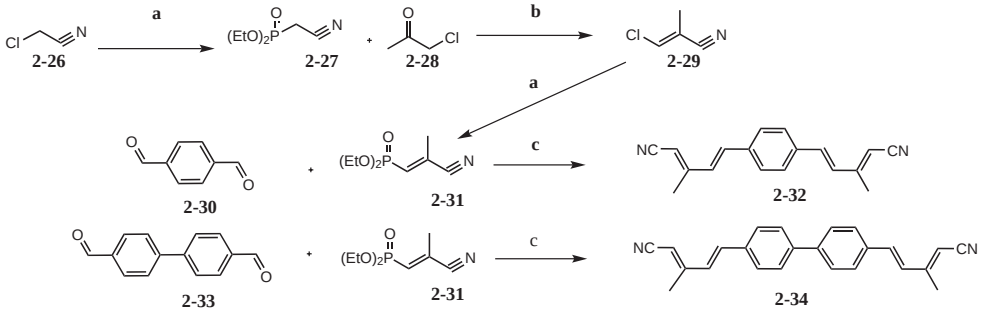


Reagents and condions: a. LiOEt, EtOH, RT; b. acetylenedicarboxylic diethylester, reflux in dichlorobenzene; c. KOH, reflux in ethanol; d. stirring with $K_3Fe(CN)_6$ overnight; e. same as d.

McDonald applied this technique to a range of substituted oligomers, with mixed results. In this light, it was attempted to obtain a methyl-substituted oligomer with a nitrile functional group in the *para* position. A Wittig reaction is used to obtain a diene, followed by Diels-Alder reaction. Using a compound that has been used in Wittig reactions successfully before (compound **2**-**31**), the dienes **2**-**32** and **2**-**34** could be formed in moderate to good yields. (scheme 2-8)

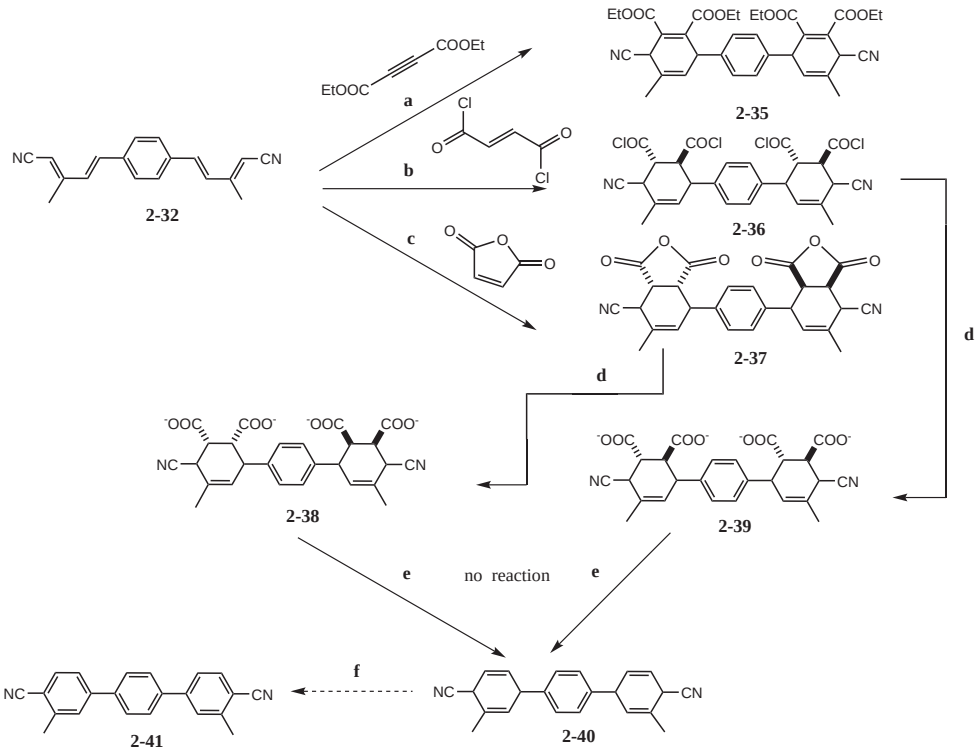
Compound **2**-**31** can be made easily on a large scale and from cheap precursors, starting from chloroacetonitrile and chloroacetone, and it may be assumed that related unsaturated phosphonates with different functional groups will also participate in a Wittig reaction successfully. Because of the methyl group of compound **2-31**, the product is a branched diene with a methyl-group always in an *ortho* position relative to the cyanide.

Scheme 2-8: Reagents and conditions: a. Triethylphosphite, 150^{o}C; b. NaH, THF; c. n-BuLi, THF



The Diels-Alder reaction is sensitive to electronic effects and may or may not proceed, depending on the substituent. As it turned out, the –CN group (scheme 2-8) instead of a phenyl group (scheme 2-7) in the terminal position is sufficiently deactivating a Diels-Alder reaction that it will not proceed when the dienophile is an alkyne (see reaction a; compound **2**-**35**). An electron withdrawing group such as –CN provides strong hindrance for Diels-Alder reactions. This is in line with the findings of McDonald and coworkers who succeeded at this reaction when there was a phenyl substituent. However, they reported a failure to obtain 4, 4’’’’-dinitro quinquephenyl using the same conditions. Nitrophenyl is a strong electron withdrawing group, as is nitrile. To circumvent this problem, the use of a different dienophile was attempted, with an additional step in mind to arrive at the same product.

Scheme 2-9:



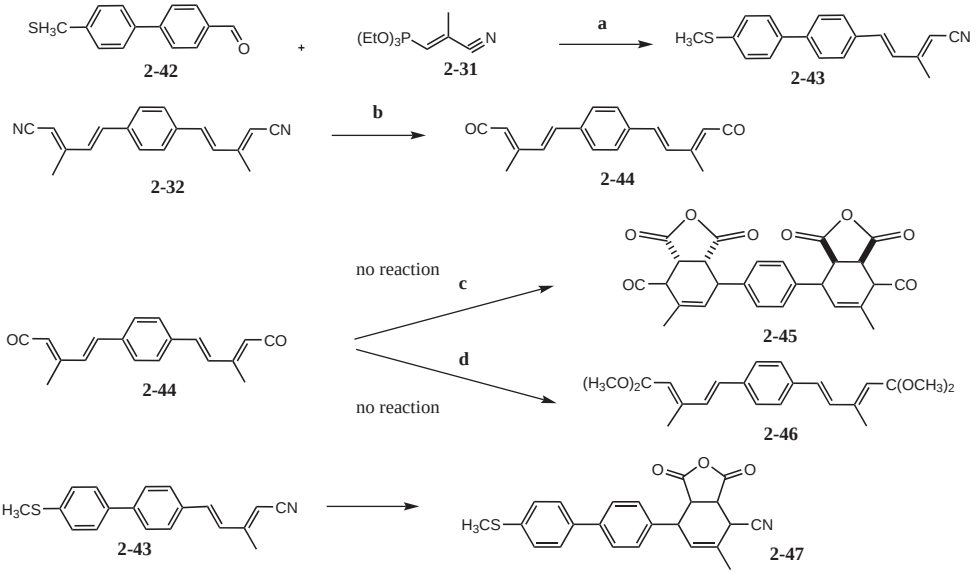
a. *acetylenedicarboxylic ethylester, reflux in dichlorobenzene. No reaction; b. fumaryl chloride at 150°C. c. maleic anhydride at 150°C; d. NaOH, reflux in water; e. $Pb(OAc)_4$/heat or $K_3Fe(CN)_6$/heat.; f. DDQ (assumption)*

Using the powerful dienophiles maleic anhydride or fumaryl chloride leads to a successful reaction even if the diene is deactivated by a –CN group (reaction **b and c**), and these dienophiles have been used as 'alkyne equivalents' because it is sometimes possible to decarboxylate the adduct, leading to the formation of a double bond, *i.e.* the product that would have been obtained from an alkyne dienophile, compare compounds **2-35** and **2-36/2-37**. Unfortunately, decarboxylation did not proceed, probably because decarboxylation does not yield an energetically favorable aromatization, in contrast with the McDonald case. Instead, in scheme 2-7, reaction ***e*** would give a cyclohexadiene ring, not a benzene ring. Using $Pb(OAc)_4$ does not result in a decarboxylated product.

As an alternative approach, it was attempted to convert the nitrile **2-32** to an aldehyde **44** before the Diels-Alder addition of an alkyne, using DIBAL (scheme 2-10, reaction **b**). Reduction of **2-32** proceeded as expected, but the follow-up

Diels-Alder reaction was not successful, most likely because the high temperatures involved allow the formation of six-membered rings with the aldehyde oxygen, although no well-defined products were positively identified. Protection of the aldehyde through acetalization was also not successful, which means that this triconjugated aldehyde is a very unstable compound.

Scheme 2-10: other reactions in the phenyl formation sequence



a. n-BuLi, THF; b. DIBAL, THF, -40^{o}C. c. maleic anhydride, 150^{o}C; d. triethylorthoformiate, methanol, PTS

The route towards compound **2-41** will lead to symmetric products functionalized by cyanide. Alternatively, if an asymmetric (monofunctionalized) product is desired, the starting compound **2-30** can be replaced by a different aldehyde (such as **2-42**). The Diels-Alder behaviour of compound **2-43** is similar to compound **2-32**. Decarboxylation did not take place in this case either.

2.3 Conclusion

Two very different routes have been applied in order to create functionalized oligomers. Coupling reactions (Kumada and Suzuki reactions) led to limited success, while the phenyl formation reaction route stranded.

While it is possible to synthesize molecules with an aromatic, conducting body (compounds **2-4** and **2-5**), and even functionalize them with protected sulfur, it

is problematic to functionalize any oligomer with pyridine-type nitrogen. Should this have been a feasible synthesis, still the expected solubility of the target compounds would have been very poor. Asymmetry is an option using these coupling reactions, but can be achieved only if either a mixture of compounds is the intended result, or if reactants with more than 2 rings are coupled in a modification of the biaryl coupling reactions.

Using the phenyl formation reaction that starts with a Diels-Alder addition to a diene, there is no feasible way to complete the aromatization from a substituted cyclohexene ring. It appears that the result of the Diels-Alder reaction has to be a cyclohexadiene for aromatization to proceed. It is obvious that the cyanide group plays an undesirable role on a diene during the Diels-Alder reaction. If another functional group would allow an alkyne to react as a dienophile then this sequence could in fact be quite successful. (see Chapter 6) Alternatively, electrochemical procedures, for instance Kolbe decarboxylation, might be helpful in decarboxylation of the problematic adduct **2-36 or 2-37**.

2.4 Experimental section

General methods and materials: p-dibromobenzene, 4,4'-dibromobiphenyl, p-bromothioanisole, 1,4-terephtaldehyde and 4,4'-biphenyldicarboxaldehyde and 1,4-phenyldiboronic acid were purchased from Sigma-Aldrich. THF, if needed dry, was dried by distillation over $LiAlH_4$. Fumaryl chloride and triethylphosphite was obtained from Acros Organics. Every reaction that took place using either Grignard reagents, n-BuLi and DIBAL was performed under a stream of argon.

p-methylmercapto magnesiumbromide (**2-5**): 40.6 g p-bromo thioanisole (0.2 mol) was dissolved in 1000 ml THF and this solution was slowly added to a THF suspension of activated magnesium in such a manner that the Grignard reagent is formed under slow reflux. The yield of this step is not calculated separately but is included in subsequent reactions.

4,4' biphenyldiboronic acid (**2-12**): 130 ml of n-BuLi in hexane (1.6M) was added to 200 ml THF. 23.3g (0.10 mol) 4,4' p-dibromobiphenyl was dissolved in 500 ml hot THF. The solution of p-bromobiphenyl was added slowly to the n-BuLi solution under a stream of argon and constant stirring. The reaction vessel was cooled and kept at a temperature below -50 ^{o} C. The suspension of dilithiobiphenyl was allowed to warm to 0 ^{o} C after the addition was completed. A solution of 50 ml trimethylborate (>4 eq) in 300 ml THF was cooled to -78 ^{o} C and the dilithiobiphenyl suspension was added in portions to this large excess

of trimethylborate solution. The temperature was kept at -20 ^{o} C during the addition and allowed to rise to room temperature afterwards. The reaction mixture was stirred forcefully during and after the addition. After 2 hours, the reaction mixture was quenched in a large amount of saturated aqueous and ice-cold hydrogen chloride and extracted with THF, then by ether. The extracts were washed with water, dried over $MgSO_4$ and evaporated to dryness. 16.6 g of 4,4' biphenyldiboronic acid was obtained (69% yield). Note: A similar procedure has been applied to produce 1,4-phenyldiboronic acid in a large quantity after the commercially obtained amount had run out. NMR: 8.03 S (4H), 7.88 D (4H), 7.48 D (4H)

4,4'', bismethylmercaptoterphenyl (**2-8**): A solution is prepared containing 2.35 g 1,4 dibromobenzene (compound **2-3**; 0.01 mol) in 50 ml THF and heated to reflux. $Ni(dppf_2)Cl_2$ was added in catalytic amount (0.001 mol was used) and the Grignard solution (5) is added to the solution, at such a pace as to maintain a gentle reflux. After two hours, the reaction was ended by quenching in aqueous ammonium chloride. Insoluble compounds were isolated and refluxed in water then in THF for a further 2 hours to obtain compound **2-5**. 3.0 g product was obtained, or 93%.

4,4''', bismethylmercaptoquaterphenyl (**2-2**): A solution is prepared containing 3.12 g 4,4' dibromobiphenyl (compound **2**; 0.01 mol) in 50 ml THF and heated to reflux. $Ni(dppf_2)Cl_2$ was added in catalytic amount (0.001 mol was used) and the Grignard solution is added to the solution, at such a pace as to maintain a gentle reflux. Insoluble compounds were isolated and refluxed in water then in THF for a further 2 hours to obtain 2.9 g compound **2-4** (73%). NMR: 7.53 D (J=0.03 ppm, 4H), 7.40 (J=0.03 ppm, 4H), 2.47 S (6 H)

4,4-phenyldiboronic acid (**2-11**): A solution of 15.5 g (0.05 mol) 4,4'-biphenyldibromide in 250 ml THF is cooled to -40°C. 65 ml n-BuLi (1.6 M in hexane) is added dropwise to the solution under argon. After the addition, the reaction vessel is allowed to warm up to room temperature. The solution is cooled to -40°C and 15 g (0.03 eq.) and trimethylborate is added at once under stirring. The reaction mixture was allowed to warm up to room temperature after the addition was completed, stirred for 3 more hours and subsequently quenched with aqueous ammonium chloride, extracted with THF and ether, dried over $MgSO_4$ and evaporated to dryness. Recrystallization from ethanol yielded 8.7 g of compound **2-11** (71% yield). NMR: 7.76 S (4H), 6.81 S (4H)

4.4'-biphenylthioanisole (**2-10**): 100 ml of a 0.2M p-methylmercapto magnesiumbromide solution in THF (**2-5**) is stirred in a cooled three-necked flask with reflux condenser. 0.001 mol $Ni(dpppf)Cl_2$ was added to the solution. 4.06 g p-bromothioanisole (0.02 mol) was dissolved in 50 ml THF and added to the solution dropwise. After the addition, cooling was removed and the solution was refluxed for 30 minutes before being allowed to assume room temperature, stirred for 3 more hours and subsequently quenched with aqueous ammonium chloride, extracted with THF and ether, dried over $MgSO_4$ and evaporated to dryness. Recrystallization from ethanol yielded 2.2 g compound **2-11** (90% yield). NMR: 7.49 M (4H), 7.30 M (4H), 2.48 S (6H)

4-methylmercapto, 4'-biphenylboronic acid **(2-15**): A solution of 3.12 g (0.01 mol) biphenyldibromide in 50 ml THF is cooled to -40°C. 6.5 ml n-BuLi (1.6 M in hexane) is added dropwise to the solution under argon. After the addition, the mixture is allowed to warm up to 0°C. It is again cooled to -40°C and 0.73 g (0.01 mol) methylthiocyanate is added. After the addition, the mixture is allowed to warm up to -20°C. 6.5 ml n-BuLi (1.6 M in hexane) is added dropwise to the solution under argon. After the addition, the mixture is allowed to warm up to -20°C. It is again cooled to -40°C and 1.3 g (0.013 mol) trimethylborate is added. This reaction is difficult since bromobutane present in the mixture will be subject to nucleophilic addition at temperatures close to 0°C. After the addition, the mixture is allowed to warm up to room temperature. The reaction is quenched with aqueous ammonium chloride and extracted with THF, then ether. Combined organic fractions were dried over $MgSO_4$ and evaporated to dryness. The grey compound that was obtained was redissolved in ether, filtrated, evaporated to dryness and then the residue was recrystallized from ethanol. Yield 1.41 g or 58% of compound **2-15**. NMR: 10.05 S (1H), 7.94 D (2H), 7.71 D (2H), 7.57 D (2H), 7.35 D (2H), 2.52 S (3H)

4-chloro-3-methyl-2-butenenitrile **(2-29)**: A mixture of 180 g triethylphosphite (1.1 mol) and 75 g chloroacetonitrile (**2-26**; 1 mol) is heated to reflux for three hours during which ethylchloride evolves from the mixture. In this reaction, triethylphosphite is not only a reagent but it is also an excellent solvent. The remaining triethylphosphite is removed by rotary evaporation under vacuum. In this manner, an intermediate **2-27** is formed that can be distilled under vacuum. Compound **2-27** is dissolved in 500 ml THF. 30 g 80% NaH in mineral oil (1 mol) is added to the solution while stirring (at a temperature of -78°C). The resulting mixture is allowed to heat to -20°C, then 92 g chloroacetone (**2-28**; 1 mol) is added cautiously. The reaction is first cooled, maintaining the external temperature at -20°C, then it is allowed to rise to 0°C for 30 minutes and finally

stirred for 3 hours at room temperature. The mixture is quenched in an aqueous solution of ammonium chloride, extracted with ether and evaporated to dryness. Through vacuum distillation (150°C at 0.1 mbar) the product is purified. Yield 72 g (63%, compound **2-29**). NMR: 5.52 S (1 H, 70%), 5.29 S (1 H, 30%), 4.27 S (2H, 30%), 4.07 S (2H, 70%), 2.15 S (3H, 70%), 2.07 S, (3H, 30%)

4-(Diethylphosphono)-3-methyl-2-butenenitrile (**2-31**): A mixture of 18g (0.11 mol) triethylphosphite and 11.5g (0.1 mol) 3-methyl, 4-chloro crotonitrile (**2-29**) is heated to reflux for three hours during which ethylchloride evolves from the mixture. The remaining triethylphosphite is removed by rotary evaporation under vacuum. In this manner, compound **2-31** is formed. This ester is purified by vacuum distillation at 0.1 mmHg, boiling at about 150°C. Yield is nearly quantitative. NMR: 5.26 D (1H), 2.95 D (J=8.5 Hz, 1H), 4.15 Q (4H), 2.70 D (J=8.5 Hz, 1H), 2.18 D (3H), 1.33 T (6H)

2-32: 24.5g of compound **2-31** (0.1 mol) is dissolved in 150 ml THF. 65 ml N-BuLi (1.6M in hexane) is added to 100 ml THF and 12 g diisopropylamine (0.11 mol) is added as well. The solution is stirred for 30 minutes (at a temperature of -30°C). The resulting LDA solution is allowed to warm up to -20°C, then 6.7 g (0.05 mol) terephtaldehyde (**2-30**) in 100 ml THF is added cautiously. Stirring has to be performed using an external pedestal drill and a propeller in order to achieve sufficient homogenization. The mixture is allowed to assume room temperature, while continuing the stirring. After 3 more hours, the reaction is ended by pouring the solution into 0.1 N aquous HCl hydrolyzing the tough gel out of the reaction vessel with HCl. The remaining liquid is extracted with more water and ether and recrystallized from 1:1 ether:PE mixture. 8.5 g product **2-32** is isolated (65%). NMR: 7.50 S (4H), 6.88 S (4H), 5.36 S (2H), 2.29 S (6H)

2-34: 24.5g of compound 2-**31** is dissolved in 150 ml THF. 65 ml N-BuLi (1.6M in hexane) is added to 100 ml THF and 12 g isopropylamine (0.11 mol) is added as well. The solution is stirred for 30 minutes (at a temperature of -30°C). The resulting mixture is allowed to warm up to -20°C, then 11.0 g (0.05 mol) 4,4'-biphenyldicarboxylic acid (**2-33**) in 100 ml THF is added cautiously. Stirring has to be performed using an external pedestal drill and a propeller in order to achieve sufficient homogenization. The mixture is allowed to assume room temperature, while continuing the stirring. After 3 more hours, the reaction is ended by pouring the solution into 0.1 N aquous HCl and washing the tough gel out of the reaction vessel with HCl. The remaining liquid is extracted with more water and ether and recrystallized from 1:1 ether:PE

mixture. 13.6 g product **2-34** is isolated (81%). NMR: 7.64-7.56 D (4H) 7.62-7.537 D (4H), 6.98-6.84 Qa (4H), 5.36 S (2H), 2.30 S (6H)

2-38: 2.6 g (0.01 mol) 1,4 di (2-methyl, 1,3-butadienenitrile) benzene is mixed with excess fumaryl chloride (6 g was used). This solution is stirred at 150 °C for 30 minutes, then it is allowed to cool down to room temperature and poured into hexane. (anti product) After sonication in ether, 2.2 g beige product was obtained (48%). NMR: (DMSO) 7.23 S (4H), 6.19 S (2H), 4.13 M (4H), 3.73 M (4H), 1.95 S (6H) This product was soluble in warm DMSO and dissolved readily in a dilute sodium hydroxide solution, forming compound **2-38**.

2-37: 2.6 g (0.01 mol) 1,4 di (2-methyl, 1,3-butadienenitrile) benzene is mixed with 6g maleic anhydride and heated so that the maleic anhydride melt acts as a solvent. This solution is stirred at 150 °C for 30 minutes, then it is allowed to cool down (but not allowed to crystallize) and poured into hexane. (*syn* product) After sonication in ether for 30 minutes, 3.0 g light beige product was obtained (69%). This product was soluble in warm DMSO and dissolved readily in a dilute sodium hydroxide solution forming compound **2-39**. NMR: 7.25 S (4H), 6.19 S (2H), 4.12 M (4H), 3.75 M (4H), 1.97 S (6H)

2-42: (4-methylmercapto, 4'-biphenylcarboxaldehyde): A solution of 3.12 g (0.01 mol) biphenyldibromide in 50 ml THF is cooled to -40°C. 6.5 ml n-BuLi (1.6 M in hexane) is added dropwise to the solution under argon. After the addition, the mixture is allowed to warm up to 0°C. It is again cooled to -40°C and 0.73 g (0.01 mol) methylthiocyanate is added. After the addition, the mixture is allowed to warm up to −20°C. 6.5 ml n-BuLi (1.6 M in hexane) is added dropwise to the solution under argon. After the addition, the mixture is allowed to warm up to −20°C. It is again cooled to −40°C and 5 ml DMF is added immediately. After the addition, the mixture is allowed to warm up to room temperature and stirred for 3 more hours. The reaction is quenched with aqueous ammonium chloride and extracted with THF, then ether. Combined organic fractions were dried over $MgSO_4$ and evaporated to dryness. Remaining DMF is removed through vacuum evaporation. The product is recrystallised in ethanol. 0.72 g product is isolated, or 32% yield. A small contaminant consisting of butylated compound is also present. NMR: 10.05 S (1H), 7.94 D (2H), 7.71 D (2H), 7.52 D (2H), 7.33 D (2H), 2.51 S (3H)

2-43: A solution of LDA is prepared by adding 3,5 ml N-BuLi (1.6M in hexane) to 30 ml THF and 600 mg diisopropylamine (0.005 mol). The reaction is instantaneous at 0°C. The resulting mixture is allowed to warm up to −20°C,

then 1.2 g of compound **2-31** in **30** ml THF is added cautiously. 700 mg of compound **2-42** in 5 ml THF is added to the mixture. The mixture is allowed to assume room temperature, while continuing the stirring. After 3 more hours, the reaction is ended by pouring the solution into 0.1 N aqeous HCl. After extraction and workup, 650 mg product **2-43** was isolated or 62% yield. NMR: 7.69 D (2H), 7.59 D(2H), 7.45 M (4H), 6.83 D (2H), 5.26 (1H), 2.51 S (3H)

2-44: 2.6 g of compound **2-32** (0.01 mol) is dissolved in 100 ml THF and 10 ml 1M DIBAL solution is added at −40°C. After addition, the reaction mixture is allowed to assume room temperature, and worked up byadding wet silica, then extracting the liquid with ether. After drying and evaporating, 400 mg product is obtained, or 15% yield. NMR: 9.92 S (2H), 5.37 M (1H), 7.24 S (4H), 3.93 M (4H), 3.45 DD (2H), 3.25 DD (2H), 1.82 S (3H)

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3 Synthesis of (semi)conducting oligothiophenes

3.1 Introduction

This chapter describes the synthesis and characterization of substituted oligothiophenes and related heteroaromatic compounds. There are many synthetic procedures for the synthesis of short and longer oligothiophenes of discrete size with different substituents in different places (see chapter 1), while the development of specific strategies that theoretically offer the chemist the option of functionalizing practically every carbon atom in thiophene oligomers, through heterocycle formation reactions, is important.

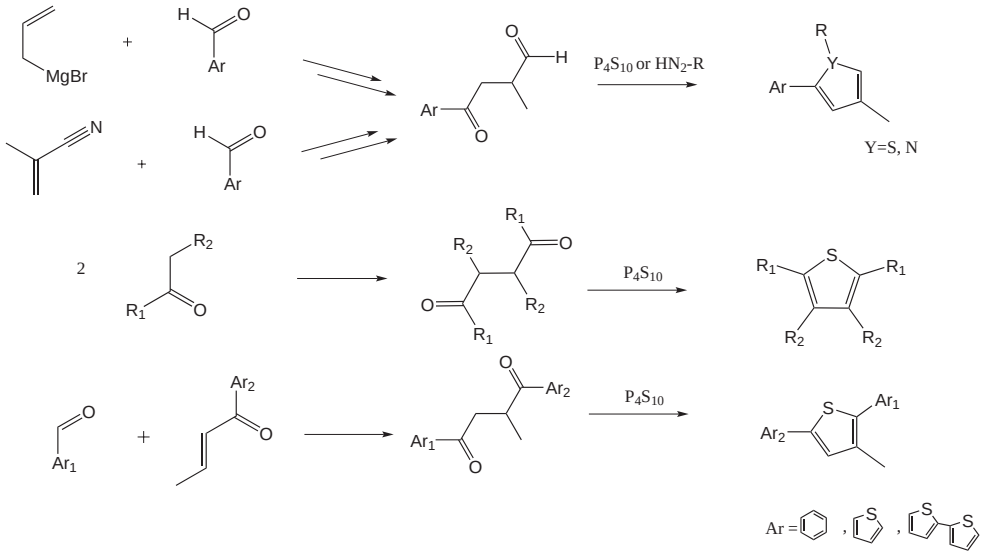
Thiophene oligomers are mostly used as segments of a larger oligomeric compound containing different conjugated structures. In particular, donor-acceptor structures, bulk heterojunction solar cells and organic semiconductors for use in light-emitting diodes have been described. Also, oligothiophene segments are encountered in dendrimers and hyperbranched polymers[1], and liquid crystalline molecules consisting of oligothiophene chains have been reported. It is also feasible to incorporate oligothiophene chains of discrete size into block copolymers. The electronic properties of a structure can be tuned by the addition or removal of functional groups, or altered by adding aromatic rings to the backbone. In addition, computational chemistry has advanced to such a high level that simulations can give insight in - and predict the effect of - specific structural features. To validate these efforts, synthetic strategies that allow the targeted synthesis of oligomers with as much control as possible over nature and position of functional groups are needed.

Polythiophenes and the related oligothiophenes are versatile building blocks in electronically active structures, since thiophenes are stable when capped, their

reactivity is usually quite good and very selective with respect to the carbon atom engaging in a reaction.

Synthetic methods for the production of oligothiophenes are partially analogous to the methods for production of oligophenyls (see chapter 2) although there are possibilities for thiophenes that do not exist for phenyls due to less reactivity and the tendency of phenyls to form regioisomers. The reactivity of all phenyl carbons is similar, whereas thiophene α-carbons, adjacent to the sulfur atom, are more reactive than the distant β–carbons, which explains the selectivity of thiophenes compared to phenyls (scheme 1.6). Similar to oligophenyls, oligothiophenes can be made by coupling reactions and synthesized from non-aromatic precursors.

Scheme 3-1: general mechanism of the heterocycle formation reactions

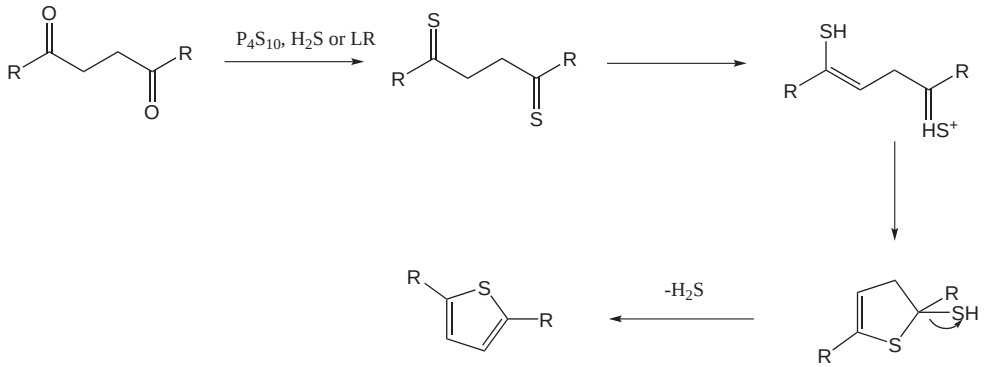


Pathways from simple precursors to oligomers

The coupling reactions for thiophenes are closely related to their phenyl counterparts, and often work for both classes of oligomers. This includes the Kumada, Suzuki and Stille coupling starting from halogenated precursors. Thiophene and oligothiophenes are reactive at the α–carbon, which can be deprotonated by LDA and can be halogenated very selectively by elemental halogen or NBS/NCS. The combination of this reactivity with the versatility of the common coupling reactions allows for a coupling based strategy towards uniform and regioregular oligothiophenes. Repeating the same coupling steps will lead to doubling of the size of a short oligomer.

Thiophene formation reactions usually start with a 1,4-dicarbonyl compound, as in the Paal-Knorr reaction (see scheme 3-3), or alternatively with two carbonyl molecules, such as in the Gewald reaction[2]. If 1,5-dicarbonyl compounds are used, thiapyrane is formed. These reactions are part of a class of cyclization reactions used for the synthesis of heterocycles. There is no true consensus on the mechanism of these reactions. Most likely one or both of the ketone functions is replaced by the heteroatom. The result is a cyclization that leads to a stable 5-ring.

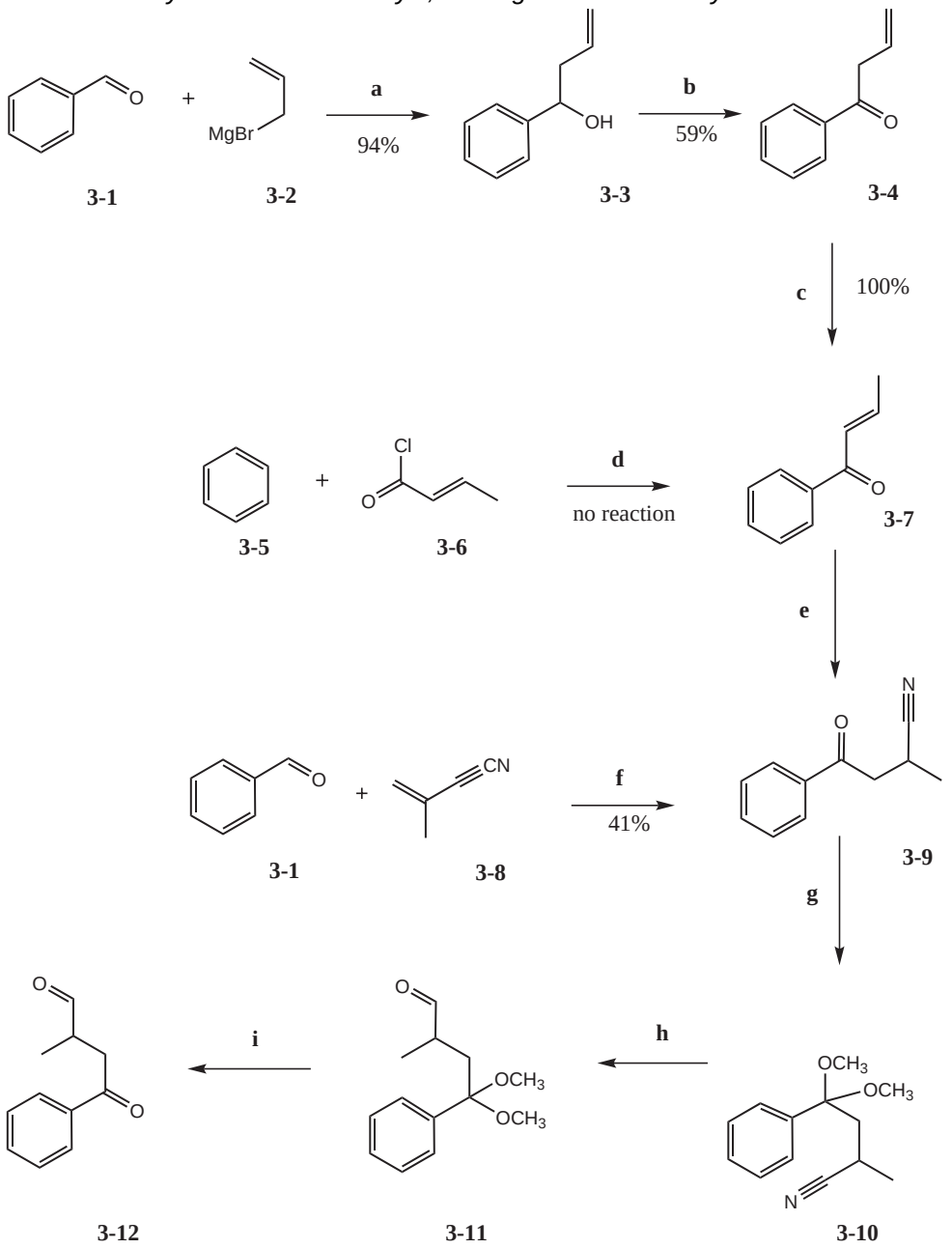
Scheme 3-3: Proposed mechanism of the Paal-Knorr thiophene synthesis



While the actual cyclization reaction is not always providing a good yield, it is experimentally relatively simple to execute. A major challenge is the preparation of the 1,4-dicarbonyl precursor. Several methods to obtain such compounds are described in this chapter. The 1,4-dicarbonyl compound can be converted into thiophene, pyrrole and furan rings. The most reactive 1,4-dicarbonyls are ketones and aldehydes. Even though reactions starting from esters and carboxylic acid salts are known, reactions with such compounds will not be further described. Such reactions require higher temperatures and therefore are limited in their use for the preparation of stable products and reactants.

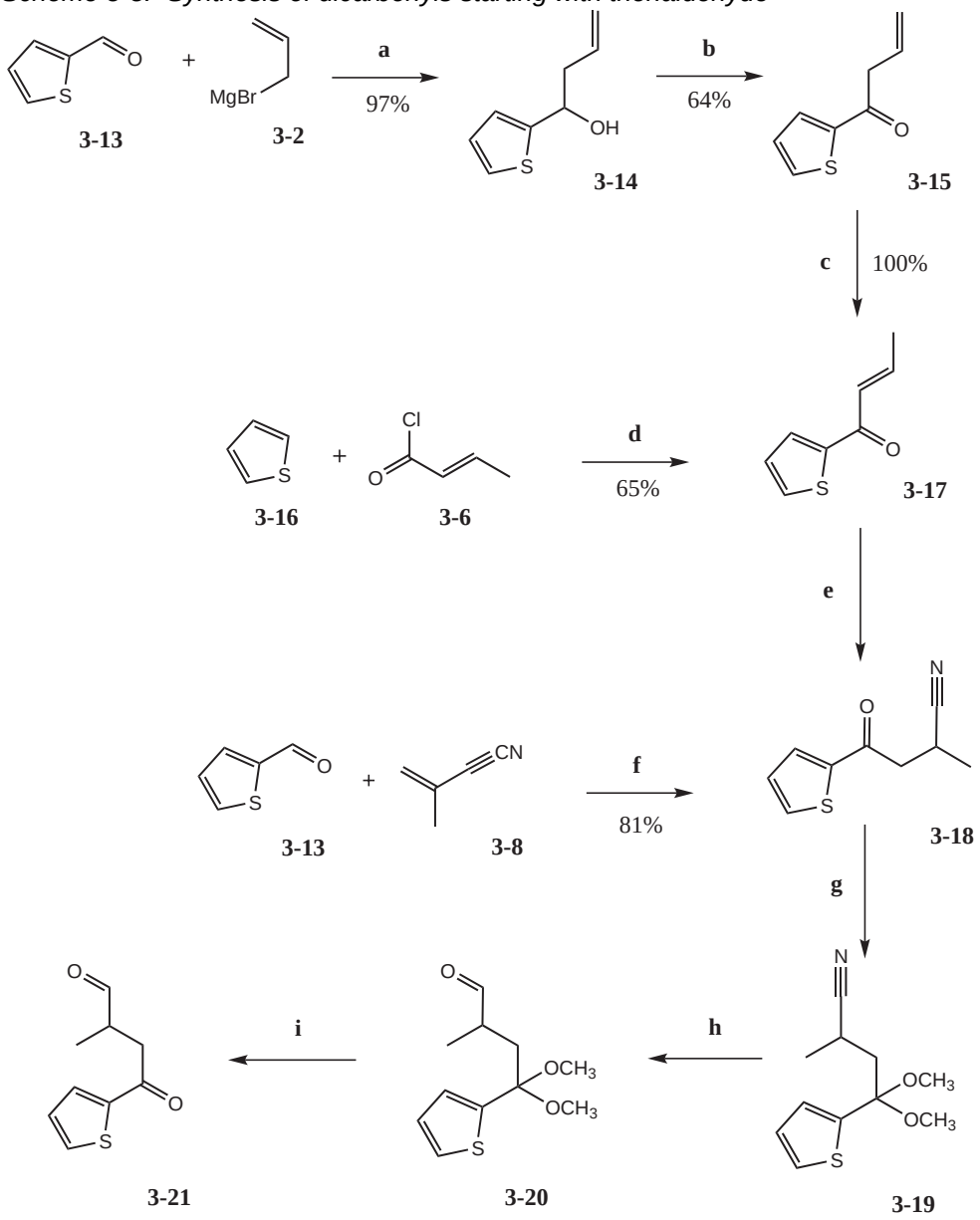
In this chapter, the synthesis of 1,4-dicarbonyls will be discussed, as well as the cyclization reaction that follows, for 1-keto, 4-aldehydes and unsubstituted 1,4-diketones (see scheme 3-1). Synthesis of substituted 1,4-diketones and functionalization of oligomers will be described in chapter 4.

Scheme 3-4: synthesis of dicarbonyls, starting from benzaldehyde



a. diethylether/THF; b. PCC, DCM; c. Al_2O_3; d. $SnCl_4$, DCM; e. KCN, AcOH; f. NaCN, DMF; g. PTS, MeOH, triethylorthoformiate; h. DIBALH, THF; i. H^+, H_2O

Scheme 3-5: Synthesis of dicarbonyls starting with thenaldehyde



a. diethylether/THF; b. PCC, DCM; c. Al_2O_3; d. $SnCl_4$, DCM; e. KCN, AcOH; f. NaCN, DMF; g. PTS, MeOH, triethylorthoformiate; h. DIBALH, THF; i. H^+, H_2O

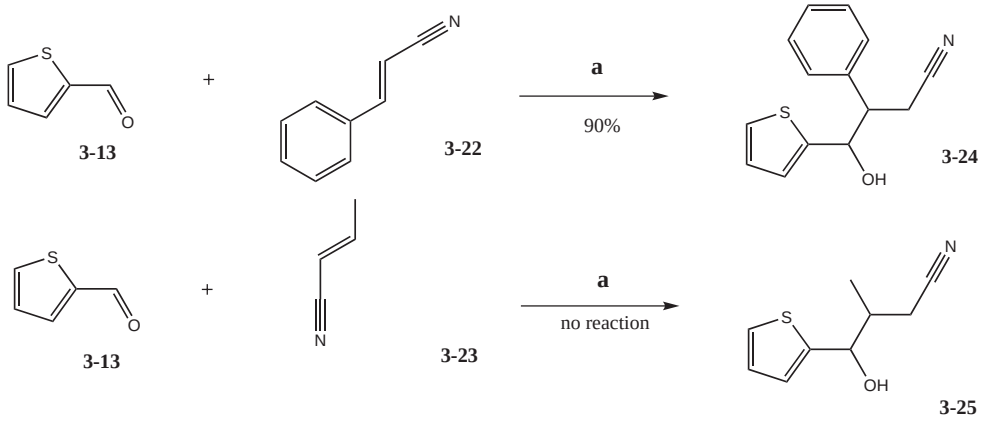
3.2 Results and Discussion

When a protocol can be established for the addition of heterocycles to existing molecules, starting from an aldehyde functionality, in theory a chain of custom made heterocycles can be created. The final product in scheme 3-4 and 3-5, a 1-keto, 4-aldehyde with an aromatic group adjacent to the ketone (compounds **3-12** and **3-23**), can subsequently be cyclicized.

Three major routes have been used to obtain the 1-keto, 4-aldehyde compounds. Both routes start from an aldehyde functionality that is converted to the 1-keto group. In the first route, a Grignard reagent is allowed to react with the aldehyde, followed by oxidation of the hydroxyl group, after which isomerisation takes place. The product obtained so far can also be obtained directly, using a Friedel-Crafts acylation, but only if the substrate is thiophene (compound **3-17**). If the substrate is benzene, no Friedel-Crafts acylation will take place leading to compound **3-7**. Friedel-Crafts acylation is most commonly performed using $AlCl_3$ as Lewis acid but in the case of thiophene, considerable ring-opening takes place. Using $SnCl_4$, no ring opening seems to occur and the Friedel-Crafts reaction of **3-6** and **3-16** to **3-17** proceeds with much better yields.

Compounds **3-7** and **3-17** can be treated with an excess amount of KCN in acetic acid, leading to good yields of compounds **3-9** and **3-18**, respectively. It is also possible to reach compounds **3-9** and **3-18** directly using a different synthetic route, also starting from an aldehyde. In this Stetter reaction scheme, an aromatic aldehyde performs a nucleophilic attack on a Michael acceptor, which in this case is a conjugated nitrile (compound **3-8**). The reaction takes place in the presence of a catalytic amount of NaCN, and 10 mole% was found to be an adequate amount.

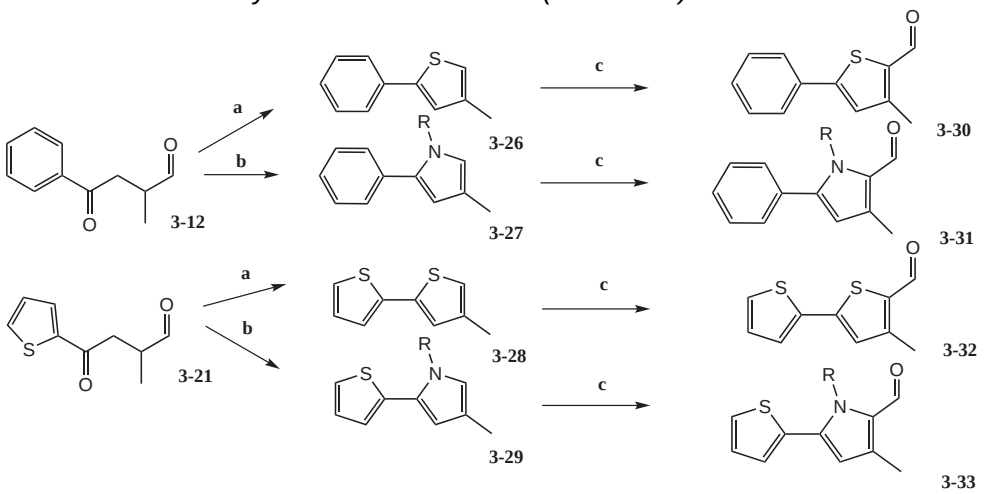
Scheme 3-6: functionalization of the 2-position in the Stetter reaction



a. NaCN, DMF

While it is possible to substitute the 3-methyl group by any alkyl chain from precursors **3-2**, **3-6** or **3-8**, it was found that no 2-alkyl group can be introduced in the 1-keto, 4-aldehydes **3-12** and **3-21**, except perhaps when thiophene is used in the Friedel-Crafts acylation reaction. However, when cinnamonitrile (compound **3-22**) is used instead of methacrylonitrile (compound **3-8**), a phenyl group can be introduced in the 2-position.

Scheme 3-7: Heterocycle formation reactions (Paal-Knorr)



a. P_4S_{10}, toluene; b. NH_4CO_3 (R=H) or allylamine (R=allyl); c. $POCl_3$, DMF, Dichloroethane

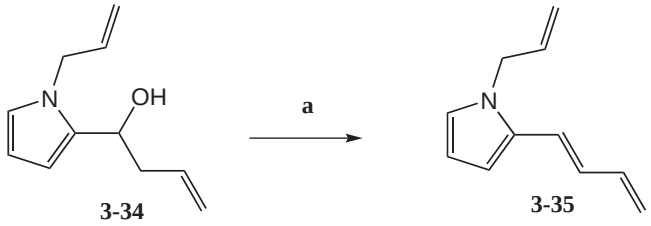
The products of a Stetter reaction with methacrylonitrile are compounds **3-9** and **3-18 (**schemes **3-4** and **3-5)**. In order to obtain a dicarbonyl, the nitrile group must be reduced. DIBAL is a commonly used reagent to perform this reduction, but only after protection of the existing ketone group, by acetalisation. After deprotection of the acetal, the 1-keto, 4-aldehyde compounds **3-12** and **3-21** are formed.

The cyclization reactions (scheme 3-7) proceed without problems for both the pyrrole and the thiophene molecules (compounds **3-26** through **3-29**). P_4S_{10} in toluene and dry NH_4CO_3 were heated with compounds **3-12** and **3-21** to obtain the heterocycle. When the organic amine is used, a protected pyrrole is obtained. The unprotected pyrroles were protected with allylbromide (not shown) after formation. The same result is obtained if not NH_4CO_3 is used as nitrogen donor, but allylamine. There was not much difference between the reactivities of compounds **3-12** and **3-21**.

In both cases, carbonylation is easily achieved using Vilsmeijer-Haack formylation (compounds **3-26** through **3-29**). This is an electrophilic substitution reaction that works very well with electron excessive compounds such as substituted thiophene and pyrrole. Theoretically, the aldehydes **3-26** through **3-29** would take the place of benzaldehyde (compound **3-1**) and thenaldehyde (compound **3-13**) to re-enter the cycle, adding another heterocycle with an alkyl substituent. In practice, however, the Stetter reaction (reaction **f** in scheme 3-4 and 3-5) does not take place on any 3-alkyl substituted heterocyclic carboxaldehyde that has been subject to Stetter conditions before. This indicates that the electron donating effect of the methyl group hinders the addition of cyanide to the aldehyde (see chapter 4 for more about the mechanism of the Stetter reaction). No benzoin condensation was observed either, and the starting compounds were returned without any sign of reaction or side reaction.

When pyrrolealdehyde was used in an analogous pathway as shown in schemes 3-4 and 3-5, a different result was obtained. Pyrrolealdehyde will not participate in a Stetter reaction, thereby excluding pyrrolealdehyde as starting aldehyde, analogous to benzaldehyde and thenaldehyde. Attempts to create a pyrrole based equivalent of compounds **3-7** and **3-17** failed due to dehydration (scheme 3-8). This means that while pyrroles can be the product of a Paal-Knorr reaction, pyrroles cannot be used as starting compounds.

Scheme 3-8: the dehydration behaviour of pyrrole-based precursors



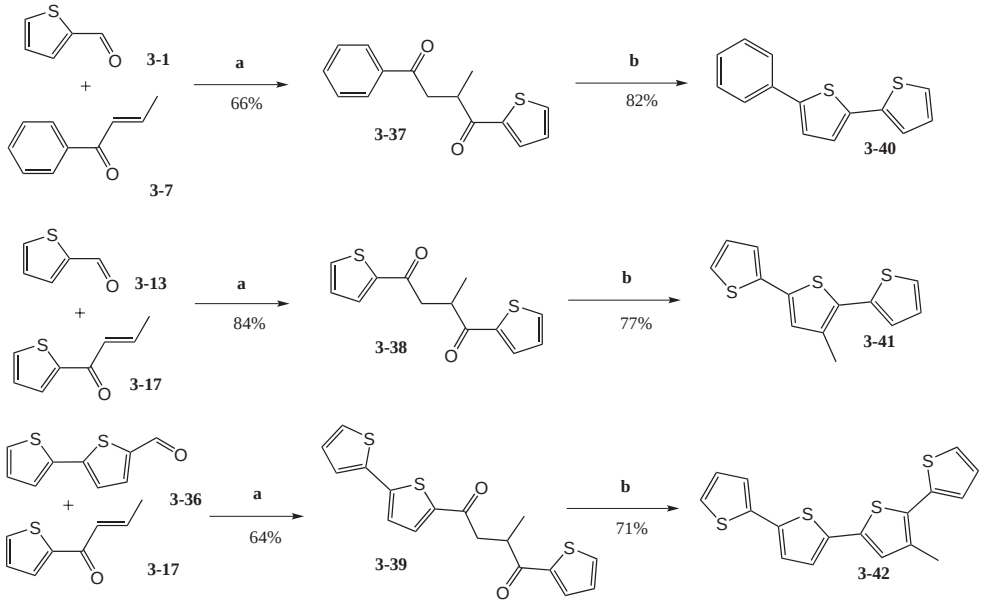
3-34 **3-35**

a. silica / spontaneous reaction

The Stetter reaction (reaction **f** in schemes 3-4 and 3-5) can also be applied in a different manner, in order to obtain 1,4-diketones directly, if a different Michael acceptor is used (scheme 3-7). The compounds **3-7** and **3-17** are Michael acceptors that will react in the same way as methacrylonitrile (compound **3-8**), leading to the formation of a 1,4-diketone in which both R1 and R2 are an aromatic ring (scheme 3-9, reaction a). In fact, this reaction proceeds so well that it can be upscaled with ease, and the resulting 1,4-diketones are stable compounds that can be stored seemingly indefinitely. It was found that the Stetter reaction will proceed with adequate yields of 60-70%, if the reaction is performed with an excess of (recoverable) aldehyde. However, this reaction is deactivated by the presence of a larger dithienyl group (compound **3-32**). Compared to thiophenealdehyde (compound **3-13**) dithienylaldehyde reacts less readily, resulting in a lower yield (48%).

The Paal-Knorr reaction (see scheme 3-9, reaction b) that follows this Stetter reaction will lead to aromatization and the formation of a short oligomer.

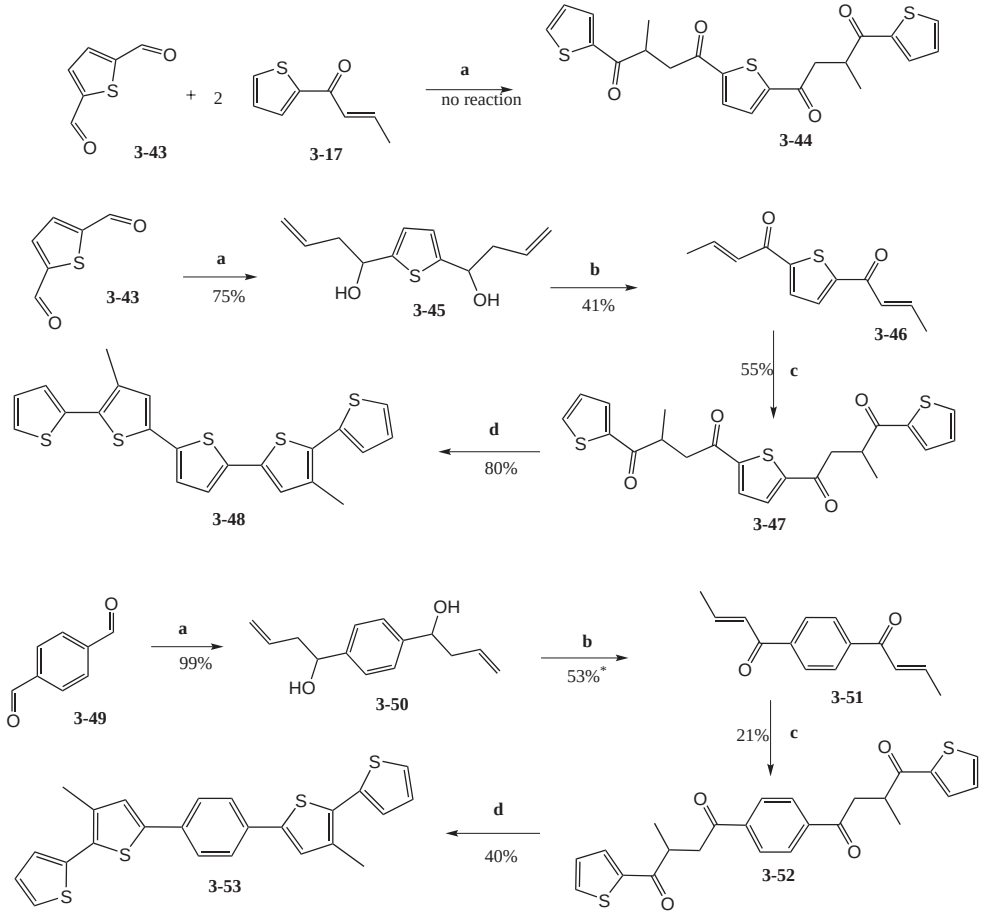
Scheme 3-9: Paal-Knorr heterocycle formations from 1,4-diketones



a. NaCN, DMF; b. P_4S_{10} or Lawesson's reagent, reflux in toluene

Similar to the formation of trimers (scheme 3-9), symmetric pentamers can be made if a symmetric bifunctional Michael acceptor is used in a Stetter reaction with a monofunctional aldehyde (scheme 3-10). No result was obtained when 2,5-thiophenedicarboxaldehyde was used in combination with the regular Michael acceptor compound **3-17**. The Paal-Knorr reaction proceeds in all these cases.

Scheme 3-10: Stetter reactions of doubly functional precursors



a. allylmagnesiumbromide, ether; b. PCC or Dess-Martin periodinane (yields given are PCC yields; use of DM periodinane resulted in near quantitative yield in the conversion from **3-50** to **3-51**) followed by stirring over Al_2O_3; c.thenaldehyde (compound **3-13**), DMF, NaCN ; d. P_4S_{10} in toluene, reflux*

Separation and workup of Paal-Knorr products was possible, although it becomes troublesome at the stage of the pentamers to do any kind of column chromatography. Product **3-53** was destroyed almost completely when loaded on a short silica column, while also for product **3-48** significant losses occurred. Because of this behaviour, recrystallisation procedures were employed to obtain samples of sufficient purity to perform analyses.

The synthesis of the doubly functional Michael acceptors was performed analogous to one of the routes that works for singly functional Michael acceptors (scheme 3-4 and 3-5). It turned out that the oxidation step is the most difficult one. There is significant chain scission at the carbonyl carbon, thus leading to aldehyde formation in step b. Many oxidants were tried, and it was found that only PCC and the Dess-Martin reagent work well[3,4]. The scission side-reaction does not take place when the Dess-Martin reagent is used, thus this procedure is recommended.

3.3 Conclusions:

The Paal-Knorr cyclization reaction has been successfully applied in the synthesis of several heterocyclic dimers, for aldehydes with a 4-methyl substituent in the newly synthesized ring. The reaction requires a 1,4-dicarbonyl compound that can be obtained by several methods.

The most useful pathway towards substituted dimers consists of a Stetter reaction followed by DIBAL reduction and protection/deprotection steps. Unfortunately, the Stetter reaction fails after the first heterocycle, which is most likely due to the electron donating properties of the 4-methyl substituent. This is an important limitation for the use of this reaction sequence in the addition of single heterocycles to existing molecules, since the specific aim of a chain of heterocycles is not reachable. In addition, the Stetter reaction proceeds best when a smaller aldehyde is used. Pyrrole rings can be created by a Paal-Knorr reaction from 1,4-dicarbonyls. Pyrrolealdehyde does not react in a Stetter reaction as thiophenaldehyde does, and neither can a pyrrole-based Michael acceptor be made (compound **3-35** was the unintended product).

Trimers and pentamers can be made using a process that resembles the one used for the addition of dimers. While it is possible to isolate trimers in pure form, it appears that pentamers (**3-48** and **3-53**) degrade upon purification by silica in such a rapid pace that column chromatography is essentially impossible, leaving small amounts of contaminants inseparable.

3.4 Experimental Procedures:

1-phenylbut-3-en-1-ol (**3-3**) : 10.6 g benzaldehyde (0.1 mol) was added to 200 ml of 1M ethereal allyl magnesium bromide solution. The addition was performed in such a manner that the ether solution refluxed gently, and after the addition, refluxing was continued for 3 more hours to ensure complete conversion, and then it was left to cool down to room temperature. The reaction mixture was carefully poured into a large amount of well-stirred saturated aquous ammonium chloride. After extraction of the organic phase by ether, the solvent was dried and removed by rotary evaporation. The compound that remained in the vessel was distilled to obtain the pure compound 3 in about 92% yield (13.4 g). NMR:7.28 M (5 H), 5.79 M (1 H), 5.19 D (J=8.8 Hz, 1 H), 5.13 S (1 H), 4.74 M (1 H), 2.51 M (2 H), 2.11 D (J=3.0 Hz, 1 H)

1-phenylbut-3-en-1-one (**3-4**): 13.4 g of compound **3-3** (0.092 mol) was dissolved in 200 ml dry dichloromethane and vigorously stirred and cooled by ice. To this mixture, a 200 ml dichloromethane solution of 28g pyridinium chlorochromate was added dropwise. The temperature of the solution was kept close to 0º C during the addition, then the temperature was then allowed to rise to room temperature, and the solution was stirred for 3 more hours, then the liquid was decanted. The chrome containing detritus in the flask was washed with dichloromethane, and the liquids pooled, dried over $MgSO_4$ and reduced in volume by rotary evaporation. The resulting dark solution was poured in 100 ml diethyl ether and filtrated over a thin silica pad. The resulting greenish solution was evaporated. There was 6.2 g product remaining (46% yield). NMR: 7.98 D (J=8.3 Hz, 2 H), 7.55 M (1 H), 7.47 M (2 H), 6.09 M(1 H), 5.25 D (J=1.5 Hz, 1 H), 5. 21 DD (J= 9.2 Hz, J=1.5 Hz, 1 H), 3.77 D (J= 6.5 Hz, 2 H)

1-phenylbut-2-en-1-one (**3-7**): 6.2 g of compound **3-4** was dissolved in dichloromethane without much further delay and stirred over 20 g aluminum oxide for three hours. After NMR analysis showed that no more compound **3-3** was present, the liquid was decanted and the alumina was washed with dichloromethane and filtrated. After evaporation and distillation under vacuum, 5.8 g product was isolated, a yellowish transparent oil with a tendency to crystallize. (94% yield). NMR: 7.56 S (3H), 6.88 M (3 H), 6.87 S (1 H), 2.29 S (3H)

1-phenyl, 3-cyanobutanone (**3-9**): 15g (~0.1 mol) of compound **3-7** was added to 100 ml ethanol and stirred with 10 g acetic acid (~0.16 mol). 13 g (0.2 mol) powdered KCN was dissolved in 50 ml water and 10 ml ethanol. The solutions were combined and stirred at 75^{o}C. No temperature effect was observed and the reaction mixture was refluxed for 75 minutes. Workup was done using aqueous ammonium chloride and ethereal extraction. 15.5 g orange oil was obtained (91%) NMR: 7.96 M (2H), 7.59 M (1H), 7.51 M (2H), 3.46-3.32 M (3H), 1.51 S (3H)
Second procedure: 2.5 g pulverized NaCN in 250 ml DMF was stirred at 40 ^{o}C. 53 g benzaldehyde (0.5 mol) was added over the course of 30 minutes. 34 g methacrylonitrile (0.5 mol) was added dropwise over the course of 90 minutes. There was an exothermic spike after an induction period of about 15 minutes. After the reaction, 1 ml acetic acid was added and the reaction mixture was concentrated by rotary evaporation. There was about 80 g of residue that contained little DMF. After purification by a short silica pad and vacuum distillation, 35.5 g red oil was obtained (41% yield). 7. 95 M (1H), 7.65-7.58 M (2H), 7.49 (2H), 3.46-3.18 M (3H), 1.43 S (3H)

1-phenyl, 4-oxobutanon (**3-12**) 15.7 g (0.091 mol) of product **3-9** was dissolved in 100 ml methanol. 0.2 g p-toluene sulfonic acid and 0.2 mol triethylorthoformiate were added to the solution which was refluxed for 12 hours. The solution was quenched subsequently with potash and filtered, poured into 200 ml diethylether and again filtered. The resulting liquid was concentrated in vacuo, and dried. The product was dissolved in 25 ml DCM at 0 ^{o}C cooled by icewater externally and 12 ml DIBALH (1M in DCM) was added in two minutes. The temperature rose to 7 ^{o}C before falling to 0 ^{o}C again. No color changes were observed and the mixture was allowed to reach room temperature. Aquous HCl was added together with silica gel, then the mixture was stirred for 3 more hours. A dark purple solution was obtained after suction filtration. After ethereal workup 11.5 g of a brown-purple oil was obtained (65% yield). NMR: 9.83 S (1H), 7.99 M (1H), 7.57 M (1H), 7.50 M (2H), 3.54 DD (1H), 3.12-2.98 M (2H), 1.26 S (3H)

1-(2-thienyl) but-2-en-1-one (**3-17**): 8.4 g thiophene (0.1 mol) was dissolved in 100 ml benzene. 26 g $SnCl_4$ was added to the well stirred and cooled reaction mixture at 0°C, taking care to keep the temperature no more than a few degrees above zero. After the addition was completed, 0.1 mol trans-crotonylchloride was added slowly, again taking care to keep the temperature from spiking. The reaction mixture was removed from the coolant as soon as the last drop of reagent had been added, then stirred for one more hour. The

reaction mixture was worked up by first pouring it onto crushed ice crystals, then the solids in the reaction vessel were rinsed with diethylether and pooled with the benzene solution. The organic phase was separated, then washed again with water. After separation, the organic phase was dried on $MgSO_4$ and subsequently evacuated to reveal a dark oil that gave 11.2 g clear product after destillation (73% yield). NMR: 7.75 DD (J=3.6 Hz, J=0.8 Hz, 1 H), 7.62 DD (J= 4.6 Hz, J=0.8 Hz, 1 H), 7.11 M (2H), 6.83 D (J=0.8 Hz, 0.55 H), 6.78 D (J=0.8 Hz, 0.45 H), 1.95 D (J=8.5 Hz, 3 H) Note: this product has also been obtained analogous to the sequence described for compound **3-7**, with similar yield.

1-thienyl, 3-cyanobutanone (**3-18**): see the description of compound **3-9**. Compound **3-17** was used instead of compound **3-7**, otherwise conditions and observations were similar. (86% yield) NMR: 7.74 - 7.72 (2H), 7.17 (1H), 3.38-3.19 M (3H), 1.4 S (3H)

1-thienyl, 4-oxobutanon (**3-21**): see the description of compound **3-12**. Compound **3-18** was used instead of compound **3-9**, otherwise conditions and observations were similar. (56% yield) NMR: 9.78 S (1H), 7.77 D (1H), 7.66 D (1H), 7.17 DD (1H), 3.47-2.92 T (2H), 1.27 S (3H)

2-phenyl-4-methylthiophene (**3-26**): 1.76 g compound **3-12** (0.01 mol) was heated with 2 g P_4S_{10} in 10 ml toluene, taking care to heat to a slight reflux. After 3 minutes, heating was ceased and the liquid was dumped in ammonia, and the solids were stirred with ammonia vigorously. The ammonia phases were pooled and extracted with ether. The ethereal fraction was dried and concentrated by rotary evaporation. The resulting liquid was poured on a short silica column (elution solvent 50:50 ether/PE) to remove sulphur containing particles. NMR: 7.65 S (1H), 7.33 M (5H), 7.04 S (1H), 2.49 S (3H)

n-allyl-2-phenyl-4-methylpyrrole (**3-27**): 1.76 g compound **3-12** (0.01 mol) was heated with 5g allylamine to reflux for 10 minutes and extracted with aqueous ammonia, then extracted with ether. After drying, 1.7 g compound **3-27** was obtained (87%). NMR: 7.44 M (2H), 7.35 M (2H), 7.19 M (1H), 6.60 S (1H), 6.35 S (1H), 5.79 M (2H), 5.09 M (2H), 4.61 M (1H), 2.20 S (3H)

4-methyl-2,2'-dithienyl (**3-28**): 8.2 g compound **3-21** (0.045 mol) was heated with 4g P_4S_{10} in 50 ml toluene, taking care to heat to a slight reflux. After 45 minutes, heating was ceased and the liquid was dumped in dilute sodium hydroxide solution, and the solids were stirred with sodium hydroxide solution.

The aqueous phases were pooled and extracted twice with DCM. After evaporation of the organic liquids, 6.7 g crude, yellow-green solid oil was obtained. This oil was subsequently dissolved in 70 ml ethyl acetate and cooled, to obtain a solid fraction that was discarded. After evaporation of the ethyl acetate solution, 6.5 g greenish oil was obtained (80%). NMR: 7.17 M (2H), 7.01 M (2H), 6.78 S (1H), 2.45 S (3H)

n-allyl-2-thienyl-4-methylpyrrole (**3-29**): 1.82 g compound **3-21** (0.01 mol) was heated with 5g allylamine to reflux for 10 minutes and poured into aqueous ammonia, then extracted with ether.
Alternate procedure: 1.8 g compound **3-21** (0.01 mol) was fused with 3.0 g ammonium carbonate (2.5 eq) and heated to about 80-90^{o}C for about 10 minutes. The reaction was quenched by addition of 30 ml DCM. The solution was filtered, dried and evaporated. The intermediate compound was dissolved in 40 ml DMSO then 2.5 g KOH was added. After 5 minutes of stirring, 3 g allylbromide was added and the reaction mixture was heated to about 50^{o}C and stirred at this temperature for 30 minutes then allowed to cool down. Aquous ammonium chloride was added to the reaction mixture followed by ethereal extraction and drying. Ether extracts were evaporated to dryness to yield 1.7 g (first procedure: 84% yield) or 1.3 g (second procedure: 65% yield). NMR: 7.44 M (2H), 7.33 M (1H), 7.19 M (2H), 6.60 S (1H), 6.35 S (1H), 5.98 M (2H), 5.15 D (2H), 4.95 M (1H), 2.20 S (3H)

2-phenyl-4-methyl-5-thenaldehyde (**3-30**): 3.1 g of compound **3-22** (0.018 mol) was dissolved in 10 ml dichloroethane. 1.5 g DMF (0.02 mol) and 2.7g $POCl_3$ (0.018 mol) were mixed at 10°C and left to solidify for 25 minutes. 25 ml dichloroethane was added as well as the solution of compound **3-22**. There was no reaction at room temperature. The mixture was heated to reflux for 15 minutes. Afterwards, an excess of aqueous sodium acetate was added and reflux was maintained for 15 more minutes. The compound was isolated by ethereal extraction and rotary evaporation. No yield was recorded. NMR: 9.81 S (1H), 7.36 S (1H), 7.33 M (5H), 7.02 S (1H), 2.54 S (3H)

n-allyl-2-phenyl-4-methyl-5-pyrrolealdehyde (**3-31**): See compound **3-26** for the procedure, except that 3.0 g of compound **3-23** was used. NMR: 9.59 S (1H), 7.61 D (2H), 7.44 M (3H), 6.43 S (1H), 5.76 M (2H), 5.15 D (2H), 4.95 M (1H), 2.30 S (3H)

4-methyl-2,2'-bithiophene-5-carbaldehyde **(3-32**): See compound **3-26** for the procedure, except that 3.0 g of compound **3-28** was used. The crude product was not purified. NMR: 9.94 S (1H), 7.35-7.00 M (4H), 2.55 S (3H)

1-thienyl, 1-hydroxy, 2-phenyl butanitrile (**3-24**): 10.6 g thiophenaldehyde (**3-13**) was dissolved in 100 ml DMF and degassed with argon. 0.5 g NaCN (0.01 mol) was dissolved in 100 ml DMF and stirred, the thiophenaldehyde solution was added to this mixture in 30 minutes, at 50^{o}C. After this addition, a solution of cinnamonitrile (10 g, or 0.07 mol) in 100 ml DMF was added over the course of 90 minutes. Afterwards the solution was allowed to cool to room temperature and 10 ml acetic acid was added. 5 minutes later, the reaction mixture was poured into water and extracted with DCM many times, followed by rotary evaporation and high vacuum drying. 19.2 g yellow crystals were obtained (81%) yield. NMR: 9.99 S (1H), 7.34 (2H), 7.07 DD (1H), 7.04 S (1H), 2.56 S (3H)

1-thienyl, 1-hydroxy, 2-methyl butanitrile (**3-33**) 1.5 g thiophenaldehyde (**3-13**) was dissolved in 100 ml DMF and degassed with argon. 0.25 g NaCN (0.005 mol) was dissolved in 100 ml DMF and stirred, the thiophenaldehyde solution was added to this mixture in 30 minutes, at 50^{o}C. After this addition, a solution of crotonitrile (0.67 g or 0.01 mol) in 100 ml DMF was added over the course of 90 minutes. Afterwards the solution was allowed to cool to room temperature and 10 ml acetic acid was added. 5 minutes later, the reaction mixture was poured into water and extracted with DCM many times, followed by rotary evaporation and high vacuum drying. The reaction was unsuccessful.

1-n-allylpyrrole, 1-hydroxy, 3-butene (**3-34**): 4 g KOH was suspended in 80 ml DMSO and a solution of 2.5 g pyrrolealdehyde (0.037 mol) in 25 ml DMSO was added while stirring vigorously. There was a small exothermic effect (about 5 degrees). After 15 minutes, 5 g allylbromide was added, There was another exothermic effect (about 10 degrees). After about 30 minutes, the mixture was heated to 50 ^{o}C. Aqueous ammonium chloride was added and the liquid was extracted with ether. After washing the ethereal layer thoroughly, it was dried in vacuo. 3.1g of a red oil (n-allyl pyrrolealdehyde) was obtained (66%). NMR: 7.37-7.29 M (5H), 6.02 S (1H), 5.81 M (2H), 5.10 M (2H), 4.85 M (2H), 4.61 S (1H), 2.75 M (1H), 2.64 M (1H), 2.18 S (3H)

3.0 g n-allyl pyrrolealdehyde (0.022 mol) in 20 ml ether was added to x ml of 1M ethereal allyl magnesium bromide solution. The addition was performed in such a manner that the ether solution refluxed gently, and after the addition, refluxing was continued for 3 more hours to ensure complete conversion, and then it was left to cool down to room temperature. The reaction mixture was carefully poured into a large amount of well-stirred saturated aquous ammonium chloride. After extraction of the organic phase by ether, the solvent was dried and removed by rotary evaporation. The compound that remained in the vessel was distilled to obtain the pure compound **3-34** in about 92% yield (3.6 g). NMR: 7.37 M (5H), 6.02 S (1H), 5.84 M (2H), 5.16 M (4H), 4.86 M (1H), 4.60 S (1H), 2.78-2.60 DM (2H), 2.28 S (3H)

1-n-allyl-2-phenylpyrrole, 1,3-butadiene (**3-35)**: The same procedure was used as described for compound **3-4**, but 1.77 g (0.01 mol) of compound **3-34** was used. The result of this reaction was the formation of compound **3-35**. No yield was recorded because although **3-35** was the major product of this reaction, it was not the intended one. NMR: 7.32 M (5H), 6.47 S (2H), 6.13 S (1H), 5.24 M (2H), 5.24-5.01 M (4H), 4.50 S (2H), 2.24 S (3H)

2,2'-dithienyl-5-carboxaldehyde (**3-36**): 10 g dithiophene (0.060 mol) was weighed off and dissolved in 100 ml DMF and 9.20 g phosporylchloride (0.060 mol) was added dropwise to a stirred solution of 100 ml DMF at 0°C. The dithiophene solution was added to the reaction mixture in one minute, then the reaction mixture was stirred for one more hour, allowing the mixture to assume room temperature. The mixture was poured onto 300 g ice, then vigorously shaken and then extracted with diethylether. After drying and evaporation of the solvent, the yield was 72% (8.4 g). NMR: 7.67 D (J=4.3 Hz, 1 H), 7.36 D (J= 4.3 Hz, 1 H), 7.25 M (J=4.6 Hz, 2H), 7.08 D (J=4.4 Hz, 1 H)

1-phenyl, 3-methyl, 4-thienyl 1,4-butadione (**3-37**): 0.0075 mol NaCN was dissolved in 150 ml DMF at 70°C and 5.6 g thiophenealdehyde (0.05 mol) was added dropwise in about 30 minutes during which the solution was stirred under argon. When the addition was completed, a solution of 0.03 mol (4.3 g) of compound 17 in 40 ml DMF was added over the course of two hours. There was no temperature effect visible but the color changed from green through brown to red. 3 ml acetic acid was added, turning the solution orange. The solvents were evaporated under vacuum, then 100 ml dichloromethane was added to the residue and washed by an equal amount of water several times. The remaining residue was purified by column chromatography (ether:PE) and

6.9 g of compound **3-17** was isolated (88%). NMR: 7.98 D (5.6 Hz, 2 H), 7.87 D (4.3 Hz, 1 H), 7.66 D (5.5 Hz, 1 H), 7. 57 M (3), 7.46 M (2), 7.17 DD (4.7 Hz, 20 Hz, 1 H), 4.00 M (2 H), 3.70 M (1 H), 3.12 DD (3 H)

1,4-(2-thienyl)-2-methyl-butane-1,4-dione (**3-38**): 3.0 g of compound **3-7** (0.02 mol) was dissolved in 20 ml DMF. 0.1 g NaCN was dissolved in 100 ml DMF and 3.4 g thiophenealdehyde was added to the NaCN solution in 30 minutes. Temperature was maintained at 30°C. The solution of compound 1 was then added over the course of three hours, and then stirred for three more hours. After this time, 0.5 ml acetic acid was added to the reaction mixture, turning the brown solution into a bright red one. The solvent was evaporated under vacuum and the residue was dissolved in 100 ml dichloromethane, then washed with an equal amount of water 10 times. The organic fraction was subsequently dried and the solvent evaporated. 4.1 g product was isolated (78%). NMR: 7.85 D (4.0 Hz, 2 H), 7.77 D (4.0 Hz, 2 H), 7.64 T (5.6 Hz, 2 H), 7.14 M (2 H), 3.99 M (2 H), 3.60 M (2 H), 1.34 DD (6.8 Hz, 6 H)

1-(2,2'-dithiophen-5-yl), 4-(2-thienyl)-2-methyl-butane-1,4-dione (**3-39**):
3.0 g of compound **3-7** (0.02 mol) was dissolved in 20 ml DMF. 0.1 g NaCN was dissolved in 100 ml DMF and 3.4 g 2,2'-dithienyl-5-carboxadehyde was added to the NaCN solution in 30 minutes. The temperature was maintained at 30°C. The solution of compound 1 was then added over the course of three hours, and then stirred for three more hours. After this time, 0.5 ml acetic acid was added to the reaction mixture, turning the brown solution into a bright red one. The solvent was evaporated under vacuum and the residue was dissolved in 100 ml dichloromethane, then washed with an equal amount of water 10 times. The organic fraction was subsequently dried and the solvent evaporated. 4.1 g product was isolated (68%). NMR: 7.70 M (2 H), 7.29 D (1 H), 7.11 M (3 H), 6.85 S (1 H), 3.95 M (1 H), 3.57 M (1 H), 3.30 M (1 H), 3.14 M (1 H), 1.40 D (1 H)

3-phenyl, 3 methyl 2,2' dithienyl (**3-40**): 2.58 g (0.010 mol) compound **3-38** was dissolved in 10 ml toluene and boiled vigourously with P_4S_{10} (1.2 g) for 30 minutes. The liquid was allowed to cool to room temperature and poured in a 100 ml aquous solution of 10 g NaOH. After extraction of the water layer with diethylether, the combined organic fractions were dried with $MgSO_4$ and concentrated in vacuo. 2.1 g product was obtained (83% yield). NMR: 7.68 D (8.4 Hz, 2 H), 7.58 D (7.7 Hz, 1 H), 7.37 M (3 H), 7.268 M (2,5 H), 6.59 S (0.5 H), 2.34 D (J=35 Hz, 3 H)

3'-methyl 2,2':5',2''-terthiophene (**3-41**): 2.6 g of compound **3-17** was dissolved in 10 ml toluene. 2.6 g P_4S_{10} was added to the solution and the reaction mixture was heated to reflux. The reflux column was protected with a drying tube. After the reaction was finished (frothing had subsided), the liquid was decanted and the black residues were washed with diethylether under sonication. All organic layers were mixed with a copious amount of water and washed several times. Then the organic phase was separated and dried, and the solvent was removed by rotary evaporation. 2.2 g product was obtained. (86% yield) NMR: 7.12 DD (J=3.10 Hz, J=1.00 Hz, 1H), 7.06 DD (J=3.10 Hz, J=5.20 Hz, 1 H), 7.28 DD (J=5.10 Hz, J=1.00 Hz, 1H), 6.96 (1 H), 7.19 DD (J=3.10 Hz, J=1.00 Hz, 1 H), 6.99 DD (J=3.10 Hz, J=5.20 Hz, 1 H), 6.96 DD (J=5.20 Hz, J=1.00 Hz), 2.37 S (3H)

3'-methyl 2,2':5',2'':5'',2'''-tetrathiophene (**3-42**): 0.6 g of compound **3-39** was dissolved in 3 ml toluene. 0.6 g P_4S_{10} was added to the solution and the reaction mixture was heated to reflux. The reflux column was protected with a drying tube. After the reaction was finished (frothing had subsided), the liquid was decanted and the black residues were washed with diethylether under sonication. All organic layers were mixed with a copious amount of water and washed several times. Then the organic phase was separated and dried, then the solvent was removed by rotary evaporation. 0.400 mg product was obtained (67% yield). NMR: 7.18 DD (3.5 Hz, 1.04 Hz, 1 H), 7.03 DD (3.5 Hz, 5.15 Hz, 1 H), 7.23 DD (J=1.04 Hz, J=5.15 Hz, 1 H), 7.13 D (J=3.88 Hz, 1 H), 7.05 D (J=3.88 Hz, 1 H), 6.97 S (1 H), 7.21 DD (J=5.10 Hz, J=0.96 Hz, 1 H), 7.01 DD (J=5.10 Hz, J=3.60 Hz, 1 H), 7.15 (J=0.96 Hz, J=3.6 Hz, 1 H), 2.38 S (3 H)

1,1'-(2,5-thienyl) dibut-3-en-1-ol (**3-45**) : A solution of 0.1 mol (13.9 g) 2,5-thiophenedicarboxaldehyde in 150 ml THF was added dropwise to 0.3 mol well-stirred ethereal allylmagnesiumbromide. Care was taken to keep the reaction temperature below 30°C. After the addition was completed, the mixture was refluxed for two more hours and then stirred overnight at room temperature. A thick reddish suspension suspension resulted which was poured slowly into 300 ml ice cold ammoniumchloride solution. After separation of the organic upper layer, the water layer was extracted five times with 50 ml portions of diethylether. The combined fractions were dried over $MgSO_4$, filtrated and concentrated in vacuo; this resulted in an orange oil in almost quantitative yield. Some impurities were removed over a short silica pad with CH_2Cl_2 as an eluent. The pure compound was obtained by eluting with 20%

methanol as a lightyellow oil, 18.2g (81% yield). NMR: 6.82 S (2 H), 5.81 M (1 H), 5.21 D (J=1.8 Hz, 1 H), 5.15 DD (3.4 Hz, 1.8 H), 4.91 T (5.8 Hz 1 H) 2.59 T (7.0 Hz, 2 H)

1,1'-(thiophene-2,5-diyl) dibut-2-en-1-one (**3-46**): To a well stirred suspension of 0.16 mol (29.2 g) pyridinium chlorochromate in 250 ml dry CH_2Cl_2 was added dropwise in about 20 minutes (at room temperature) 0.04 mol (8.8g) of compound **3-45** in 50 ml CH_2Cl_2. A slight exothermic effect of about 5°C was observed. After the addition was complete, stirring was continued during 2 hrs. The dark brown liquid was decanted from the chromium solids. The solids were washed several times with 50 ml CH_2Cl_2. To the combined CH_2Cl_2 solution was added 200 ml diethylether which resulted in some clouding of the solution (chromium salts precipitated). These solids were removed by filtration over a short silica pad. A light-green-yellow solution was obtained. After concentration in vacuo, 6.2g of off-white crystals were obtained (about 70% yield). NMR: 7.70 S (2 H), 6.04 M (1 H), 5.29T (J=2.5 Hz, 1 H), 5.24 DQ (7.5 Hz, 2.5 Hz, 1H), 3.70 D (6.9 Hz 2 H). To a well stirred solution 4.4 g (0.02 mol) of the intermediate compound, 10 g (~0.1 mol) Al_2O_3 was added in 10 intervals of about 2 minutes. After stirring for some extra 10 minutes, the light yellowish suspension was filtrated over a short silica pad and eluted with about 200 ml CH_2Cl_2. After concentration in vacuo, 3.2 g of light yellow crystals remained (70% yield, mp 154-156 °C). NMR: 7.74 S (2 H), 7.20 M (2 H), 6.85 D (1.3 Hz, 2 H), 2.02 DD (6.7 Hz, 1.3 Hz, 6 H)

3', 4''' dimethyl 2,2':5',2'':5'',2''':5''',2''''-quinquethiophene (**3-48**): To a stirred solution of 3.3 g compound 11 in 80 ml toluene was added in one portion 1.7 g P_4S_{10} (5 mol eq.). This brownish suspension was refluxed during 2 hours during which the color changed from yellowish to a deep green. After cooling to RT, the toluene solution was decanted from the solids. The solids were washed with 50 ml ether twice and the combined fractions poured into 50 ml 1M NaOH. After separation of the layers, the organic layer was washed several times with water, then dried over $MgSO_4$ and concentrated in vacuo. The residue was purified over a silica column (10: 90 ether: petroleum ether, proceeding to 20:80) and finally recrystallized from hot ethanol. The yield was 2.5 g orange-brownish crystals (78% yield). Mp 152-154. NMR: 7.28 DD (J=3.60 Hz, J=5.13Hz), 7.13 DD (J=3.60 Hz, J=1.16Hz), 7.06 Dd (J=3.60 Hz, J=5.13Hz), 7.01 S (1 H), 6.94 S (1 H), 2.36 S (6 H)

4,4'-(2,5-thienyl) bis (2-methyl-1-(2-thienyl)) butane-1,4-dione (**3-47**): 0.1g NaCN (~0.002 mol) was suspended in 40 ml dry DMF, stirred and heated to 35°C. A solution of 4.5 g (0.04 mol) 2-thiophenealdehyde in 20 ml dry DMF was added over the course of 30 minutes. A dark green color developed rapidly, after a short retention period. After the temperature had fallen to 20°C, a solution of 2.2 g compound **3-17** dissolved in 80 ml DMF was added dropwise, over the course of 1 hour. The color darkened from dark green to dark brown with a reddish hue over the course of the addition. No exothermic or endothermic effects were observed. After stirring overnight at room temperature, 0.5 ml glacial acetic acid was added. The color changed from brownish to a much clearer light yellow. This solution was concentrated in vacuo as much as possible. 200 ml diethylether was added and the ether extract was washed with a saturated ammonium chloride solution. The ethereal extract was then dried over $MgSO_4$, evaporated and subsequently purified over a silica column (10: 90 ether: petroleum ether, proceeding to 20:80). The compound (**3-47**) is obtained in almost pure form in 77% yield (yellow oil 3.3 g). NMR: 7.83 D (3.85 Hz, 2 H), 7.73 S (2 H), 7.64 D (4.0 Hz, 2 H), 7.15 T (4.5 Hz, 2 H), 3.95 M (2 H), 3.60 M (2 H), 3.06 D (3.8 Hz, 2.1 H), 3.00 D (3.8 Hz, 1.9 H), 1.32 D (7.0 Hz, 6 H)

1,4-phenyl-bis-1-hydroxy-3-butene (**3-50**): 50 g 1,4 terephthaldehyde was dissolved in 1l THF and added to 1000 ml of 1M ethereal allyl magnesium bromide solution. A heavy precipitate formed, an external stirring device was used to ensure vigourous homogenization of the liquid until addition was complete. The mixture was refluxed for 3 hours to ensure complete conversion, and then it was left to cool down to room temperature. The reaction was then quenched by carefully pouring the liquid into a large amount of well-stirred saturated aquous ammonium chloride. After extraction of the organic phase by ether, the solvent was dried and removed by rotary evaporation. The compound that remained in the vessel was carefully distilled under a vacuum of 0.05 mbar using a short column with only two glass joints in the system, to keep thermal degradation of the product to a minimum, then redistilled to obtain pure compound 2 in about 82% yield based on terephtalic aldehyde. NMR: 7.31 S (H), 5.77 M (1 H), 5.13 M (2 H), 4.70 M (2 H), 2.48 S (2 H), 1.95 (J=8.3 Hz)

1,4-phenyl-bis-1-oxo-2-butene (**3-51**): 22.4g of compound **3-50** was dissolved in 1l dry dichloromethane and vigorously stirred and cooled by ice. To this mixture, a 500 ml dichloromethane solution of 60 g pyridinium chlorochromate

(2.8 eq) was added dropwise, while the temperature of the solution was kept close to 0º C. The temperature was then allowed to rise to room temperature, and the solution was stirred for 3 more hours. The remaining solids were extracted from the dark solid with dichloromethane. The resulting dark solution was poured in 1l diethyl ether and filtrated over a thin silica pad in order to remove the solids. The resulting greenish solution was evaporated. 9.9 g product was obtained. 30 g aluminum oxide was added to a solution of this compound and the resulting suspension was stirred at room temperature for about 3 hours. From this liquid, samples were taken and evaluated by NMR to follow the isomerisation to the conjugated ketone. Compound **3-51** can be purified by distillation, if a microdistillation setup is used, greased well and evacuated to 0.1 mbar. By distilling the remaining wax, 9.6 g of compound **3-51** was finally obtained (50%). NMR: 7.98 S (4 H), 7.11 M (1 H), 6.92 S (1 H), 6.88 S (0.55 H), 6.78 D (J=1.5 Hz, 0.45 H), 2.02 S (0.8 Hz)

4,4'-(1,4-phenyl) bis (2-methyl-1-(2-thienyl)) butane-1,4-dione (**3-52**): 0.2 g NaCN was dissolved in 40 ml DMF and 2.3 g thiophenealdehyde in 10 ml DMF was added dropwise, in about 30 minutes at 40º C. To this dark green solution, 2.1 g (about 0.7 eq) of compound **3-51** dissolved in 10 ml DMF was added in about 180 minutes at a temperature of 35º C. After the addition, heating was removed and stirring continued. After one more hour, 0.5 ml glacial acetic acid was added to the mixture and after 5 minutes of stirring, the mixture is added to 200 ml water and extracted twice with 100 ml DCM. The organic phase was washed repeatedly with water, then dried on MgSO4, filtered off and the solvent removed by rotary evaporation. The remaining DMF was partially removed under a high vacuum at about 40º C, and then the product was purified by column chromatography. Starting with 90% hexanes and 10% diethyl ether, gradually using a larger fraction of diethyl-ether, compound **3-52** was obtained in about 38% yield based on compound **3-51**. The DMF mentioned in this synthesis is dried on activated molsieves and purified by filtration through a pad of active alumina. NMR: 7.85 s (4 H), 7.78 D (J= 4.4 Hz, 2 H), 7.64 T (J=6.3 Hz, 2 H), 7.14 M (2 H), 4.01 Q (J= 7.0 Hz, 2 H), 3.6 M (2 H), 3.09 D (J=5.3 Hz, 1.15 H), 3.03 D (J=5.3 Hz, 0.85 H), 1.35 D (J=7.2 Hz, 3.5H),1.33 D (J=7.2 Hz, 2.5 H)

1,4-phenyl-bis-(3-methyl)-2,2'-dithiophene (**3-53**): 1 g of compound **3-52** was dissolved in 5 ml of dry toluene in a 25ml flask and 2.5g P_4S_{10} was added to the flask. The flask was gently heated with a heat gun in such a manner that

slight frothing was observed. The heating was continued until no more gases evolved, then the toluene was separated. The solid residue was sonicated with 10 ml toluene to free any remaining product from the detritus that is inside the reaction flask. The toluene fractions were combined and poured in 25 ml aquous 1M HCl to dissolve any remaining phosphorus compounds. The organic layer was dried on $MgSO_4$ and filtered, then evaporated off. The product **3-53** was obtained in about 85% yield after column chromatography, starting with 90% hexanes and 10% diethyl ether, gradually using a larger fraction of diethyl-ether. NMR: 7.31 D (J=21 Hz, 4H), 7.15 D (J=14 Hz, 4 H), 7.08 DD (J=14 Hz, 2.2 H), 7.07 D (3.5 Hz, 1.8 H), 7.05 S (4 H) 6.97 S (2 H), 2.39 S (6 H)

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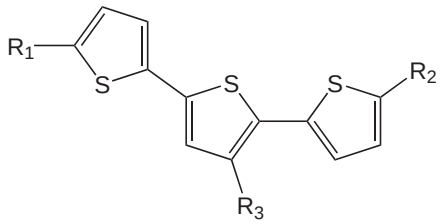
4 Synthesis of symmetric and asymmetric oligothiophenes

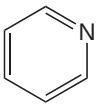
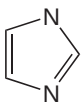
4.1 Introduction

Symmetrically substituted oligothiophenes are usually easier to synthesize than asymmetrically substituted homologues (see chapter 1). However, asymmetric oligothiophenes are interesting building blocks from an engineering point of view, and this chapter deals with synthetic strategies to obtain those as the principal product of the formation reaction. In figure 4-1, the asymmetry of interest is in the difference between R_1 and R_2. In chapter 3, terminally unsubstituted oligothiophenes with a methyl side-chain substituent (R_3) have been described. Although the procedure may work as well for longer alkyl chains, longer chains were not necessary for solubility of the relatively short oligomers described in this thesis. In this chapter, compounds will be described that possess different terminal substituents. In particular two different substituents on one oligomer molecule are synthetically important.

Scheme 4-1: target compound



R_1=SMe or $PO(OH)_3$

R_2=  or 

R_3=Me

Interesting functionalities on asymmetric oligomers are a pyridine-type nitrogen on one end to coordinate with metalloporphyrins, and sulfur on the other side to bind to different metals. Phosphate instead of sulfur is also of interest. While

incorporating protected sulfur on a thiophene chain has been described in the literature, incorporating pyridine or imidazole has received less attention.

The main part of this chapter deals with the Stetter reaction that was also mentioned in chapters 1 and 3 of this thesis, since it is very suitable also for the incorporation of different side-groups on thiophene trimers. Starting from the asymmetric intermediates that were made with the Stetter procedures in chapter 3, the pyridine terminated oligothiophene has been synthesized using two different procedures. Different strategies for the coupling of imidazole to oligothiophenes were explored as well.

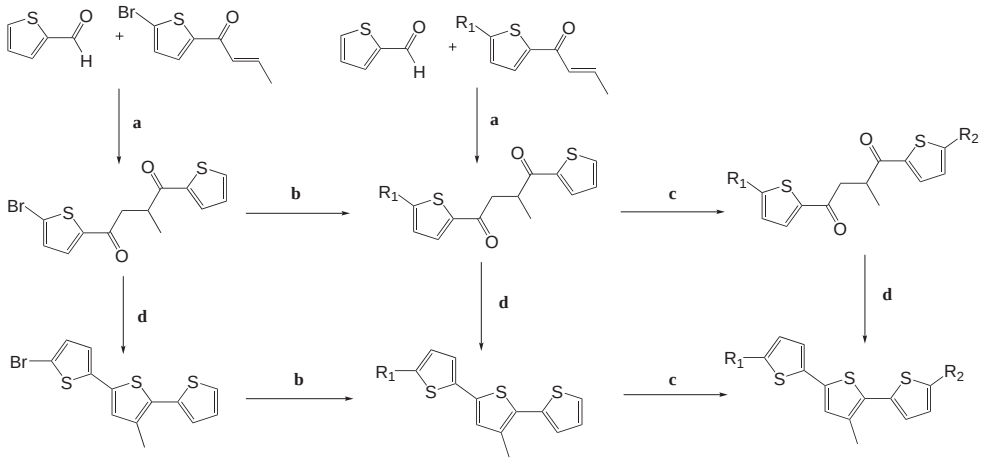
4.2 Results and Discussion

In scheme 4-1, the different phases of the asymmetric oligomer synthesis are shown. The first phase concerns the Stetter reaction (a) that leads to the intermediate diketone, the second phase concerns the subsequent Paal-Knorr reaction (d) that leads to the fully formed oligomer. This two-step sequence has been described in detail in chapter 3. Adding substituents can in theory be done in three different stages.

For instance, substituted aldehydes or Michael acceptors can be used in reaction a. In practice, however, there were synthetic difficulties with many substituents, in particular when present on the aldehyde. Depending on the nature of the aldehyde substituent, the Stetter reaction may or may not proceed. In contrast, it has been possible to incorporate the bromine atom in a Michael acceptor that leads to a reasonably high-yield Stetter reaction. The resulting intermediate is capable of reacting in many types of substitution reactions (b). After the substitution reaction, a Paal-Knorr reaction may still be performed resulting in a monosubstituted oligomer. It is also possible to continue with the Paal-Knorr reaction and perform a similar substitution reaction after the second phase, leading again to a monosubstituted oligomer. After the first substituent has been incorporated, differences in reactivity enable the introduction of a second substituent on the other side by several methods (reaction c).

Scheme 4-2 summarizes the degrees of freedom in the synthesis of asymmetrically substituted oligomers. This versatility is much needed, because some methods are only moderately successful, or not at all. R_1 and R_2 here are functional groups that can be introduced at specific points in the synthesis pathway.

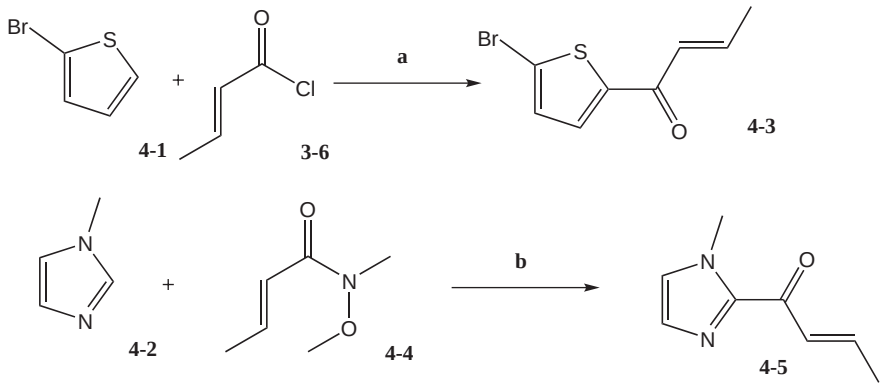
Scheme 4-2: Possible routes to functionalized oligothiophenes



a. Stetter reaction; b. substitution reaction (Ullmann or Suzuki reaction); c. Polar organometallic reaction; d. Paal-Knorr reaction

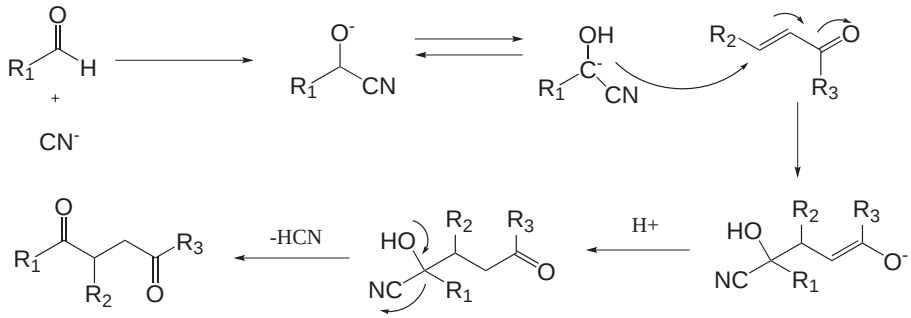
Michael acceptors can be synthesized in a number of ways (see chapter 3). The most useful method is a Friedel-Crafts acylation of thiophene to produce compound **3-17**. This procedure also works to produce compound **4-3**. Michael acceptors that cannot be produced using the Friedel-Crafts acylation can also be prepared using the Danishevski reaction[1, 2] involving a nucleophilic attack on compound **4-4** (see scheme 4-3). In chapter 3 (see schemes 3-4 and 3-5) a three step method for the synthesis of Michael acceptors was introduced that may work in specific cases where neither the Danishevski nor Friedel-crafts approach provide the desired result. This method was not used, however, if not strictly necessary, due to the laborious procedure involved.

Scheme 4-3: Michael acceptor synthesis techniques



a. $SnCl_4$/DCM; b. LDA/THF

Scheme 4.4 Stetter reaction taking place between a Michael acceptor and an aldehyde in the presence of a cyanide ion.

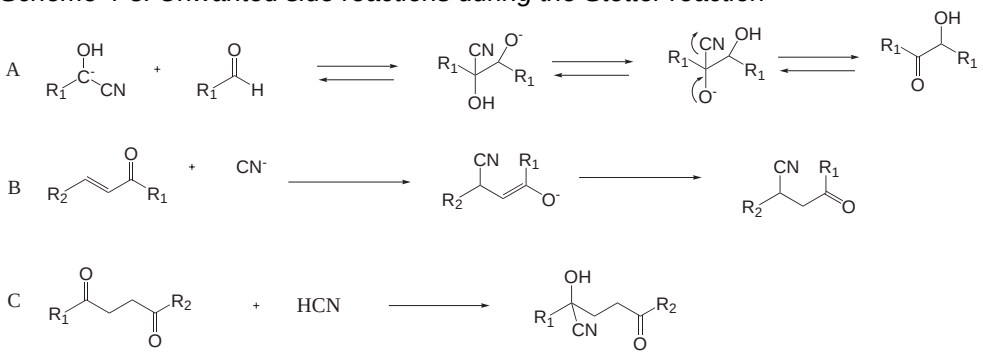


The Stetter reaction as described in chapter 3 and scheme 4-2 is a Michael addition, a conjugate addition of an aldehyde to an 1,4-unsaturated acceptor. While the aldehyde is normally subject to nucleophilic attack and not a nucleophile, it is turned nucleophilic through the reversible addition of a cyanide ion or thiazolium ion to the aldehyde carbon (see scheme 4-4). The thiazolium is not further discussed in this thesis. The R groups in this scheme can be varied (See *e.g.* scheme 4-6).

The cyanide remains after the Stetter reaction has completed and plays a catalytic role. Since the cyanide ion can also add to Michael acceptors and ketones irreversibly (see reactions B and C in scheme 4-4), it is important that the cyanide concentration remains low during the reaction. Stetter reactions are always

executed with excess aldehyde to make sure that most of the cyanide is 'occupied' in the catalytic form and not present as detrimental free CN^-.

Scheme 4-5: Unwanted side reactions during the Stetter reaction



A. Benzoin condensation. B. 1,4-addition of cyanide to michael acceptor. C. Cyano addition to ketone

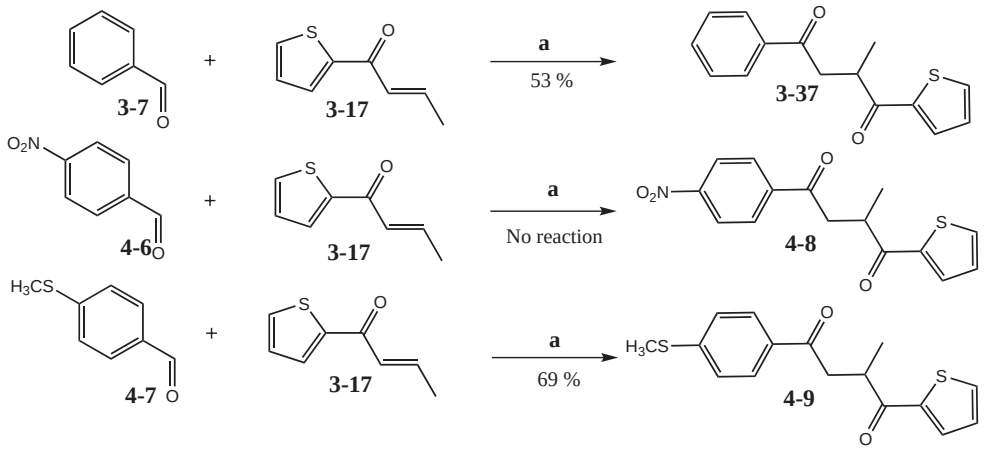
When a cyano-aldehyde complex attacks an unmodified aldehyde, which is always the major fraction of aldehyde in the reaction mixture, reversible benzoin condensation takes place. If the cyanide ion attacks the Michael acceptor, both can be considered lost, and when cyanide scavenges the reaction product, the diketone, it decreases the overall yield. The color of the reaction mixture is a good indicator of the status of a Stetter reaction. All Stetter reactions described in this thesis show a characteristic color change that occurs when cyanide and aldehyde are both present in DMF solution, and the retention time appears to depend on the purity of the aldehyde. For example, thiophenaldehyde will change from greenish yellow to a deep bluish-green color after a few minutes contact with cyanide. For benzaldehyde, the color changes from yellow to blue, and always there is a strong intensification of the color.

Adding a Michael acceptor to the solution before the color change has occurred inevitably resulted in low yield. Adding too much Michael acceptor at once or at a too slow pace causes the color to change back and results in a poor conversion. This indicates that a loss of catalyst due to addition to the product or to the Michael acceptor is the cause of these events. In any case, both benzaldehyde and thenaldehyde need to be distilled immediately before use in order to achieve a good result. In addition, it is imperative to work in scrupulously dry conditions, for optimal yield.

In scheme 4-5 the R groups can have an effect on the course of the reaction. In particular, varying the nature of the aldehyde has a profound influence on the yield

obtainable in a Stetter reaction, and in many cases, the intended product is not formed at all. The effect of substituents on the Michael acceptor is less pronounced. This can be attributed to the formation of the cyano-adduct. If the Stetter reaction does not proceed, neither does the benzoin condensation, since both require a reactive cyano-adduct. For electron-rich aldehydes this adduct is probably not formed. When electron withdrawing groups are present, but the negative charge is distributed over the molecule, the aldehyde carbon is not sufficiently reactive to engage in a Michael addition and the reaction does not proceed. The differences in reactivity are shown in schemes 4-6 for substituted benzaldehydes and in schemes 4-7 for substituted thenaldehydes.

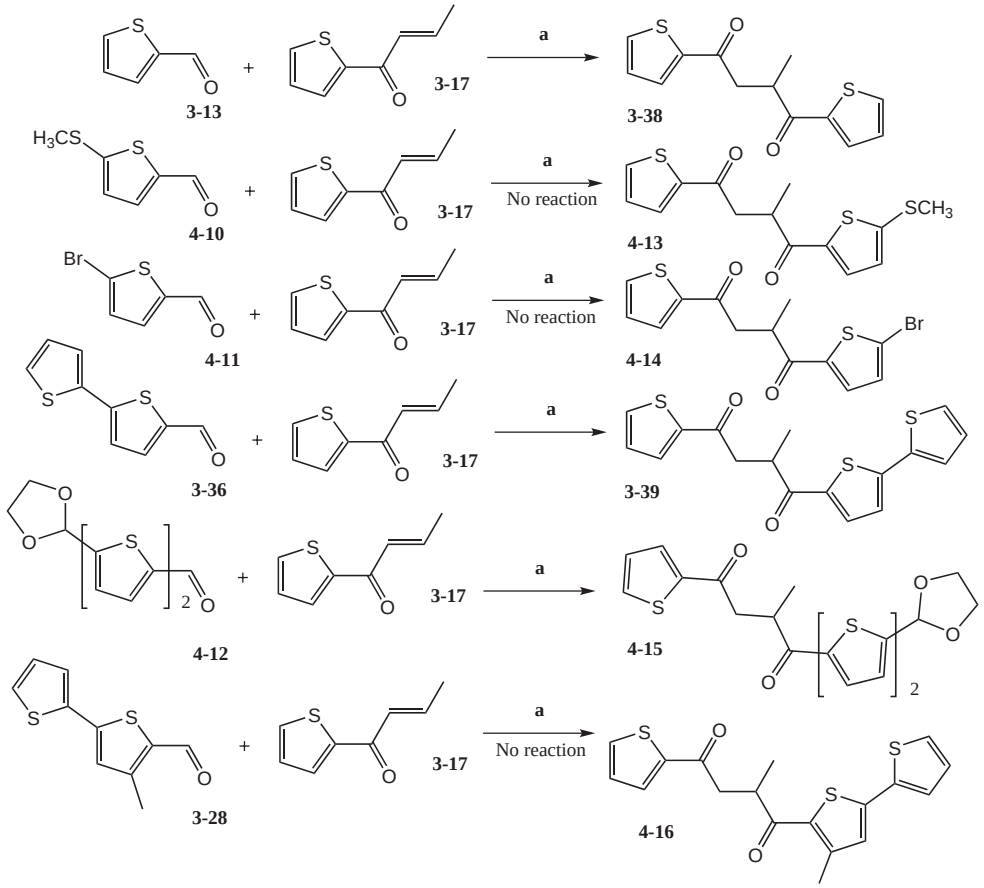
Scheme 4-6: Stetter reactions starting with benzaldehydes



a. 10% NaCN, DMF

The Stetter reaction that has been applied in chapter 3 to make doubly functionalized, symmetric oligomers can be performed using monoprotected dialdehydes. In this way, asymmetric products can be obtained.

Scheme 4-7: Stetter reactions starting with thenaldehydes



a. 10% NaCN, DMF

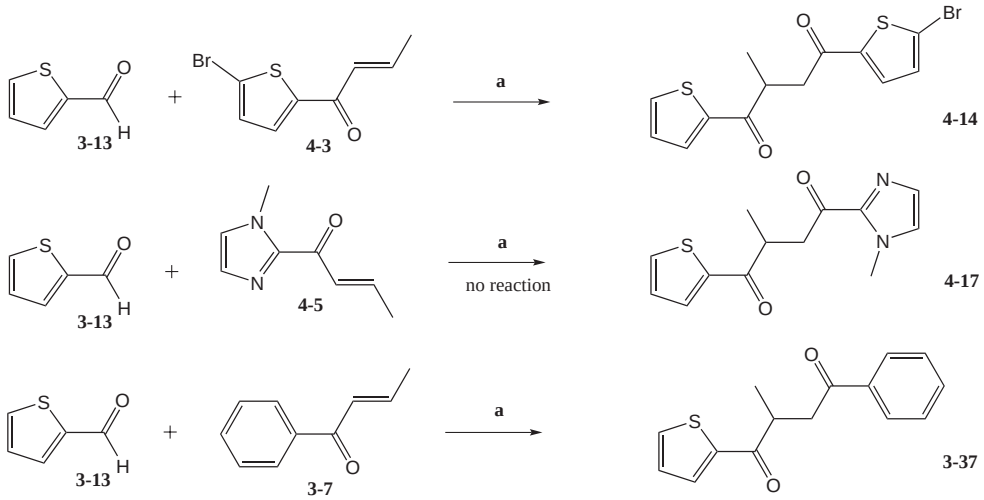
There are some striking differences between thenaldehydes and benzaldehydes with respect to the reactivity in a Stetter reaction. Para-substituted benzaldehydes with electron withdrawing groups such as chlorine or bromine, provide very effective Stetter nucleophiles, better than benzaldehyde, and comparable with para-mercaptomethyl benzaldehyde (**4-7**). In contrast, the 2,5 substituted thenaldehyde analogons **4-10** and **4-11** are very inert under comparable conditions.

The synthesis of substituted 1,4-diketones starting from substituted aldehydes would be better than starting with substituted Michael acceptors. Many thenaldehydes are commercially available or can be prepared in one step, while Michael acceptors are more laborious to prepare. However, since Stetter reactions

with substituents on the aldehyde are difficult, introducing the substituents with the Michael acceptor is the only possible route to a successful synthesis scheme for the functionalized oligomers.

While the Stetter reaction does not proceed well with all Michael acceptors, (see scheme 4-8), it was possible to functionalize the proto-oligomer with bromine (compound **4-14**).

Scheme 4-8: Stetter reaction with different Michael acceptors

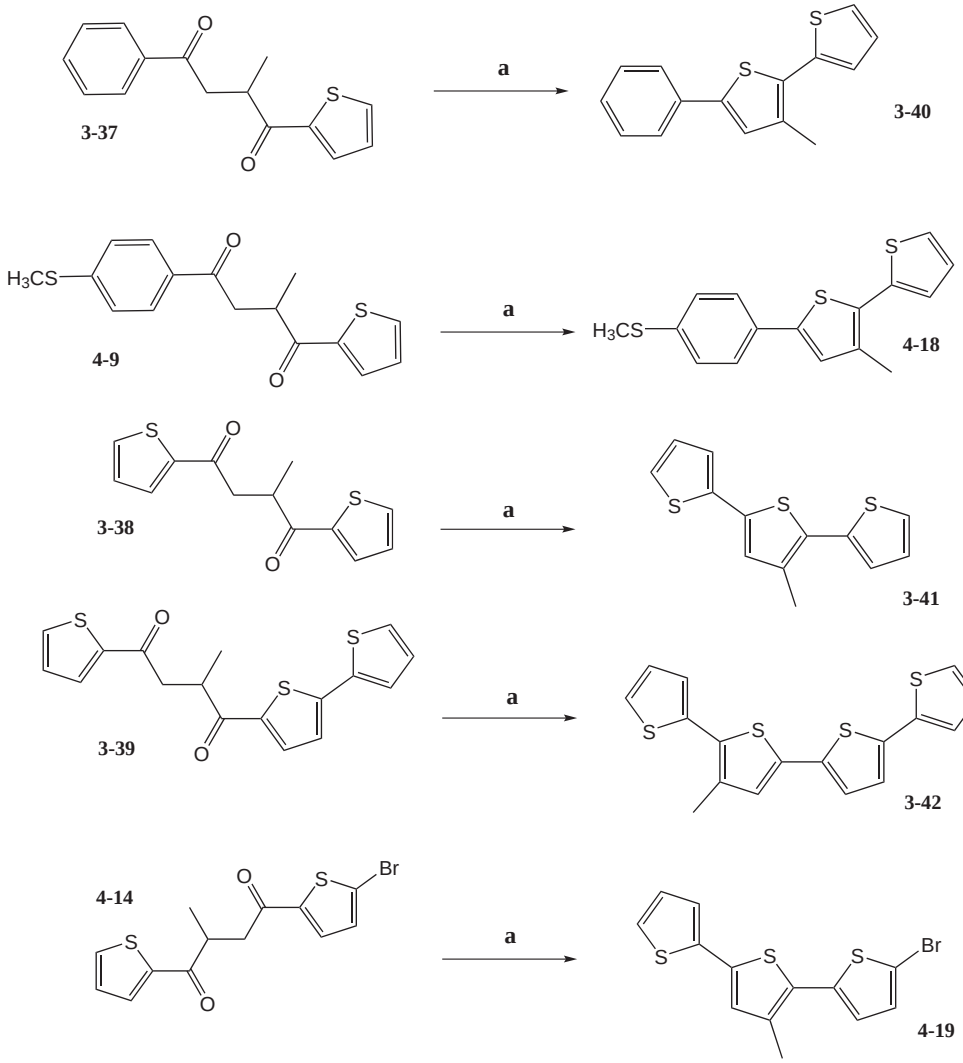


a. 10% NaCN, DMF

Although it was possible to synthesize compound **3-37** by using the Michael acceptor, the more interesting compound **4-17** was not formed. This is remarkable, since the aldehyde **3-13** is capable of participating in a successful Stetter reaction with several Michael acceptors, and indicates a negative influence on the reaction caused by the Michael acceptor **4-5**.

In summary, Stetter reactions offer the possibility of building functionalized (proto) oligomers, while their performance is unpredictable with respect to the substituents that can be incorporated. Terminal substituents can be present on either the aldehyde or the Michael acceptor. Side groups can be present as well. In this thesis the methyl-group is used, and longer alkyl chains are a possibility as well . Protected imidazole could not be introduced in this reaction.

Scheme 4-9: Paal-Knorr cyclizations following the Stetter reactions



a. P_4S_{10} or Lawesson's reagent

Since Stetter reactions are precarious and optimal conditions vary strongly depending on the substituent, the best way to incorporate a desired substituent is by starting from compound **4-14** or after the Paal-Knorr procedure, starting from compound **4-19**. In scheme 4-8, a number of Paal-Knorr follow-up reactions are given for successful Stetter reactions (see schemes 4-6 to 4-8). The successful synthesis of intermediate **4-14** gave rise to the possibility of performing substitution reactions, since thienylbromides can react in many different ways. In addition, the

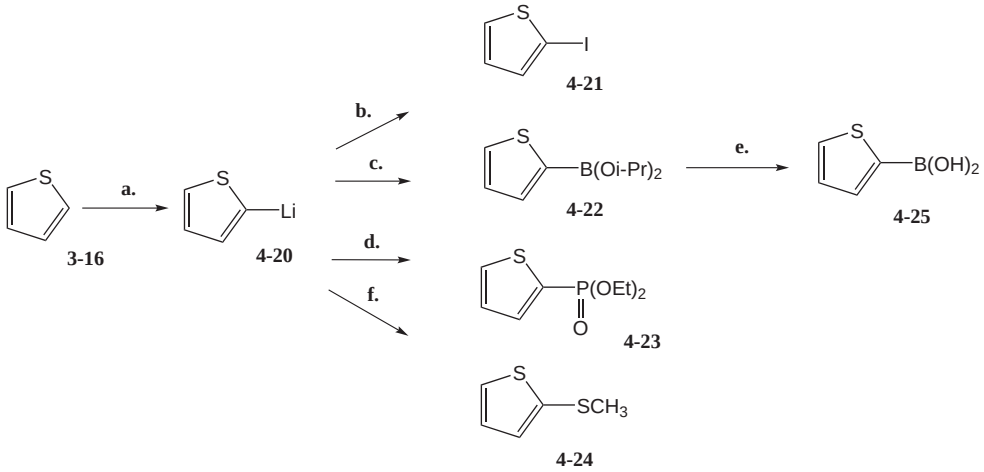
intermediate **4-14** can be obtained pure, in bulk and in adequate yields from the Stetter reaction followed by recrystallisation or column chromatography.

The Paal-Knorr reactions (scheme 4-9) proceeded usually with a very good spectroscopic yield. However, there are difficulties obtaining any of these products in pure form. The best results were obtained using Lawesson's reagent as a sulfur donor.

4.2.1 Functionalization of oligomers

The oligomers that have been described in scheme 4-9, or the precursor 1,4-diketones that have been described in schemes 4-5 through 4-8, may theoretically be modified with functional groups. There are many possibilities, and the ones that will be addressed here are limited to head or tail positions on the oligomer backbone. The substituents of particular interest are phosphonic acids, protected thiols, imidazoles and pyridines.

Scheme 4-10: Polar organometallic reactions of thiophene

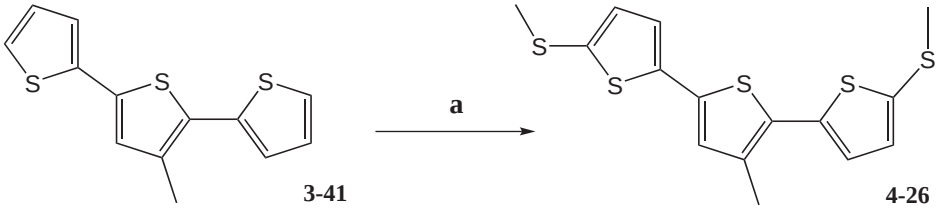


a. n-BuLi or LDA (THF); b. I_2; c. $B(Oi\text{-}Pr)_3$; d. $PO(OEt)_2CN$; e. H^+; f. MeSCN

The reactivity of thiophene and analogues on the 2 and 5 carbon atom is usually quite good. Halogenation has already been described, as well as selective Friedel-Crafts acylation. It is also possible to deprotonate this carbon atom with LDA or stronger bases. Thienyllithium is a relatively stable anion that will attack several substrates. Boronic acid, iodide and mercaptomethyl groups were introduced on thiophene (see scheme 4-10). The Danishevski reaction can be applied to arrive at

product **4-3**, and **4-5** can be made directly using a Friedel-Crafts reaction. Instead of thienyllithium, the Grignard reagent thienylmagnesium bromide can be used in mechanistically similar reactions. When the trimer is treated with butylllithium, the same type of reaction occurs, but it is hard to achieve monolithiation and subsequent reaction, since usually both the 2 and 5 positions of thiophene are attacked (scheme 11).

Scheme 4-11: Polar organometallic chemistry of oligothiophenes



3-41 **4-26**

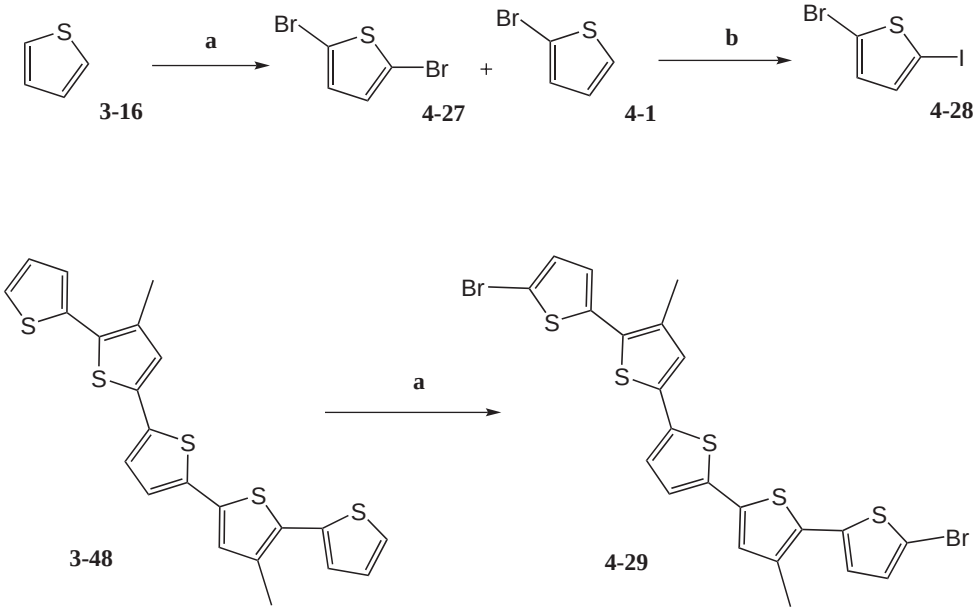
a. n-BuLi followed by MeSCN (2eq)

It is possible to brominate (scheme 4-10) thiophene with some selectivity using bromine in acetic acid or other solvent, or more selectively, using NBS in DMF at temperatures below room temperature. The order of bromination of unsubstituted thiophene is towards the α-carbons first (see chapter 1). If one equivalent of bromine donor is added, the monobrominated 2-bromothiophene is the major product. If two equivalents of bromine are added, the product is 2,5-dibromothiophene. The 3 and 4 carbon atoms are brominated sequentially if more bromine is added.

This behaviour is largely conserved when oligomers are subjected to brominating conditions although the selectivity towards monobromination and dibromination decreases with increasing mass. However, NBS bromination seems to take place preferentially on carbon atoms adjacent to alkyl-substituted carbon atoms.

Iodine can be introduced on a thiophene using a strong base to deprotonate the thiophene, followed by treatment with elemental iodine.

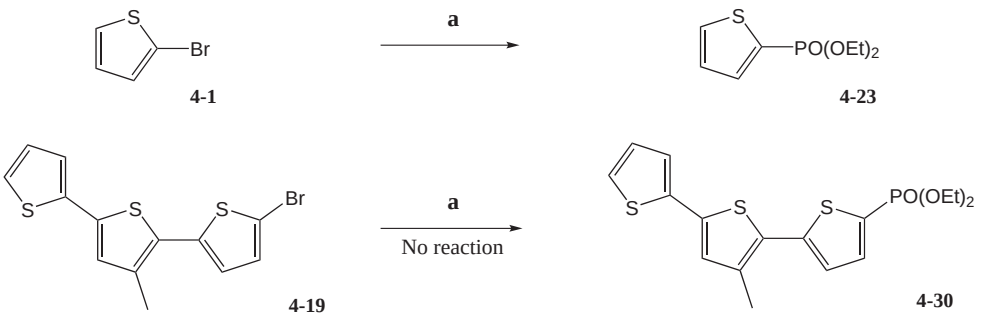
Scheme 4-12: Halogenation of thiophene and oligothiophenes



a. Br_2 (AcOH) or NBS (DMF); b. LDA, I_2

Phosphorus can be introduced at an alkyl halide using an Arbusov reaction: when triethylphosphite is heated with the alkyl halide acting as solvent and under reflux, the halide is substituted by a phosphonate group. In the case of aryl halides, this reaction does not take place normally, but in the presence of nickel salts, arylphosphonates do form in refluxing triethylphosphite. Alternatively, phosphonates can be introduced using polar organometallic reagents (see scheme 4-10) in which the anion acts on diethyl cyanophosphonate.

Scheme 4-13: Fosfonation reactions



a. $P(OEt)_3$, $NiCl_2$

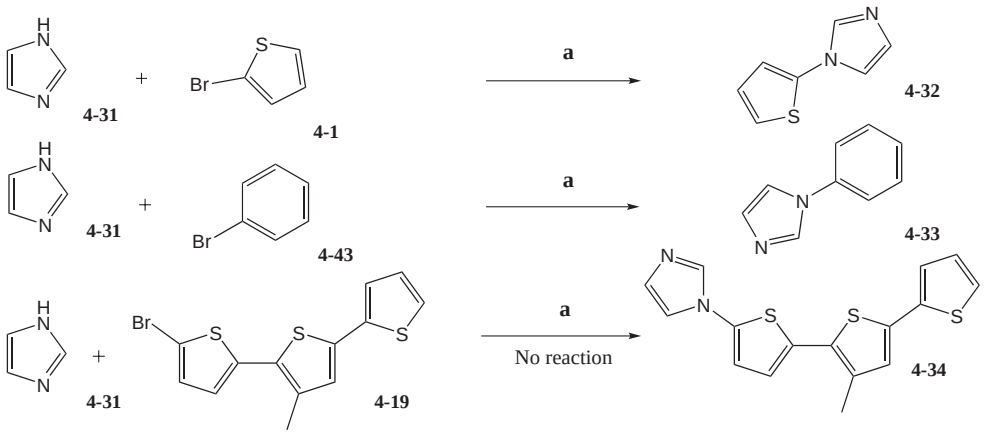
When the nickel catalyzed Arbusov reaction was attempted with compound **4-19**, no result was obtained. A 50/50 mixture of compound **3-41** (the 3'-methyl substituted terthiophene) and **4-19** (the brominated analogue, see scheme 4-13) was subjected to the nickel catalyzed Arbusov conditions. The result was that compound **4-19** had disappeared while compound **3-41** remained apparently untouched. The conclusion of this experiment is that the phosphonated terthienyl derivate or an intermediate of this reaction is unstable enough to be destroyed at the temperatures involved (140^{o}C).

4.2.2 Nitrogen ligand incorporation

The pyridine-type nitrogen atom is capable of coordinating with metalloporphyrins. This coordinating behaviour takes place in the photosystem using the histidine residue, which is a 4-substituted imidazole. Imidazole is a heterocycle that contains two nitrogens, one of which is called ‘pyrrole type’, the other ‘pyridine type’. The pyrrole type nitrogen does not coordinate to metalloporphyrins, and neither does pyrrole itself show any ligating properties. The pyridine-type nitrogen of imidazole, and pyridine and its analogues, show strong complexing properties.

Imidazole, like thiophene, has slightly acidic hydrogens. Apart from the pyrrole hydrogen, its C-2 hydrogen and C-4/C-5 hydrogen can be abstracted, in that order. Strong base is required, such as n-BuLi. Deprotonated imidazole reacts readily with alkylhalides to form alkylated imidazoles. The pyrrole-type nitrogen can be coupled to an aryl ring using the copper-catalyzed Ullman reaction[3, 4]. The Ullman reaction is a rather brutal aryl-aryl coupling reaction in which copper(0) bronze is heated with arylbromides to temperatures exceeding 200^{o}C. This type of conditions is unsuitable for the rather fragile thiophene oligomers. The name ‘Ullman reaction’ is also used for ligand and cuprous salt catalyzed coupling reactions that take place in ionic liquids or polar aprotic solvents at temperatures in the order of 110^{o}C. It is this kind of Ullman reaction that was used in this thesis. 3’-methylated terthiophene and the bromo derivative **4-19** can be heated to this temperature without any apparent degradation.

Scheme 4-14: Ullman Couplings of imidazole to aryl compounds

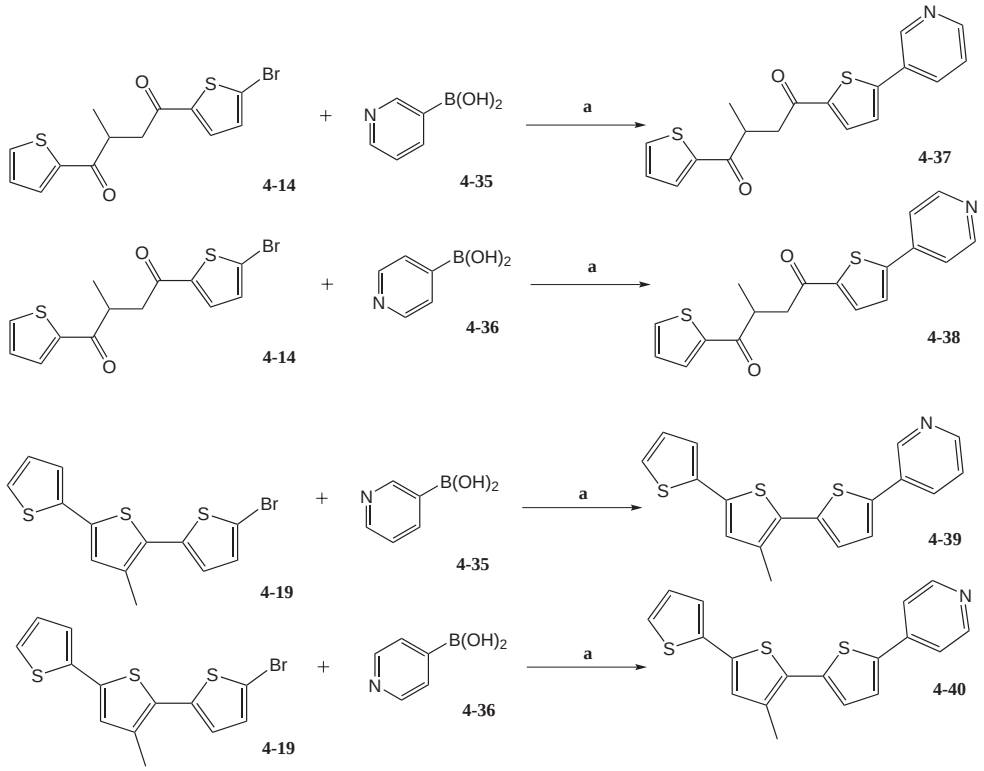


a. $CsCO_3$, CuI, proline, DMF

Under Ullman conditions (scheme 4-14) the simple arylimidazoles **4-32** and **4-33** are formed. Unfortunately, this is not true for the trimer **4-34**. The starting compound is returned with no visible losses. Only at a higher temperature (around 180°C) in the ionic liquid $BMIMBF_4$ there is visible conversion of the starting compound **3-41** – unfortunately, not into the desired product but probably into a polymeric compound.

Because pyridine is also an acceptable nitrogen ligand, it was attempted to incorporate pyridine into an oligomer that resembles product **4-34**. Pyridine boronic acids are commercially available, and the Suzuki reaction is a coupling reaction that is very applicable for coupling heteroaryls to each other (scheme 4-15). This includes pyridine. The Suzuki reaction has been applied in order to synthesize simple biaryls without problems, from pyridine boronic acid. When this was apparently successful, pyridines were coupled to compound **4-14**. Yields for this reaction seemed to be excellent. When pyridine boronic acid was coupled to compound **4-19**, problems occurred and there was pronounced apparent degradation.

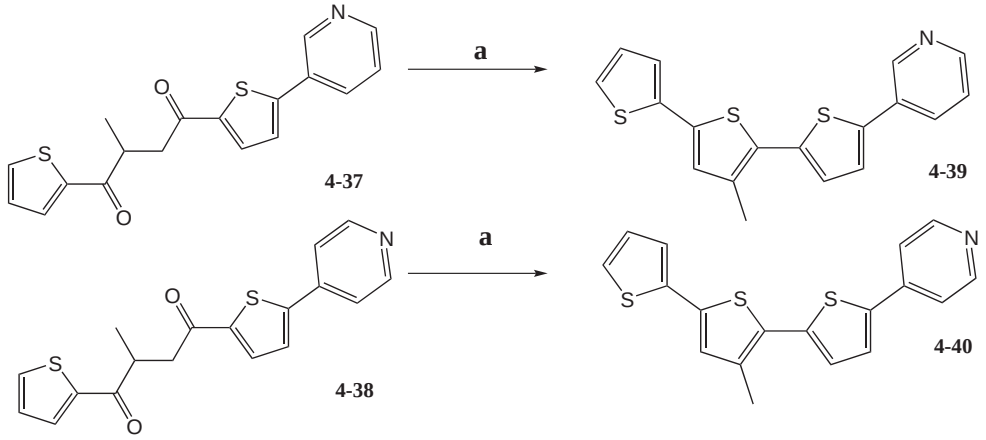
Scheme 4-15: coupling of pyridine boronic acids to thiophene oligomers and precursors



a. $Pd(PPh)_3$ or $PdAc_2$, DME, water, $NaHCO_3$

Compounds **4-37** and **4-38** have been subjected to Paal-Knorr conditions with dismal results. Even though there is a significant conversion detectable through NMR spectroscopy, the product is rapidly destroyed during the reaction. Column chromatography of pyridinated oligomers resulted in complete loss of product while unconverted compound **4-38** could be recovered, similar to the pentamers described in chapter 3. It is assumed the same problem would occur for compound **4-37**). This instability of the oligomers is a counter intuitive result, especially because their 1,4-diketone precursors are very stable and easily purified over silica. Nevertheless, the destruction of the oligomers occurred repeatedly and reproducibly.

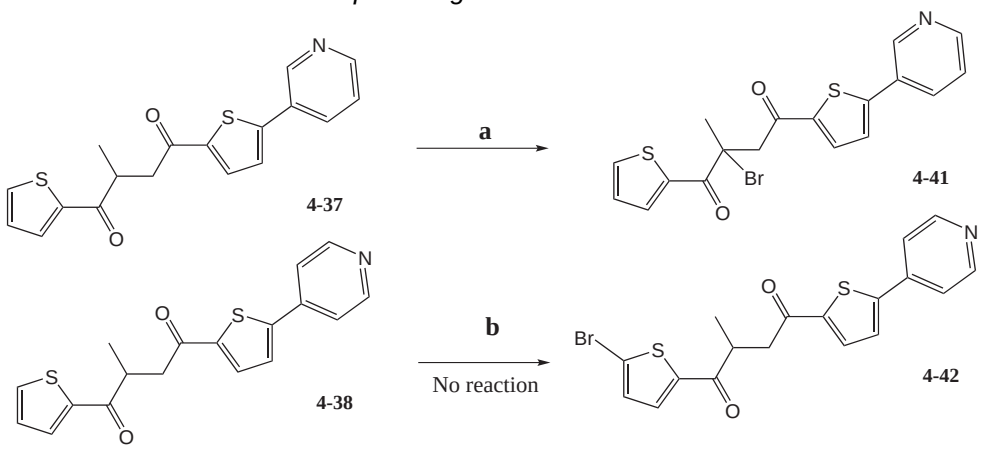
Scheme 4-16: Paal-Knorr cyclizations of pyridine-terminated terthiophenes



a. toluene, Lawesson's reagent

Substituting the backbone of oligothiophene may have a stabilizing effect. In an attempt to functionalize both sides of the molecule before performing the Paal-Knorr reaction, two different bromination procedures were applied to the stable intermediates **4-37** and **4-38** (scheme 4-17). Using $AlCl_3$ in DCM together with bromine caused selective bromination on the alkyl chain, while NBS bromination did not seem to work at all on these intermediates. Although the conditions for NBS bromination used in this reaction were more than adequate for simple thiophene, compound **4-38** remained unconverted.

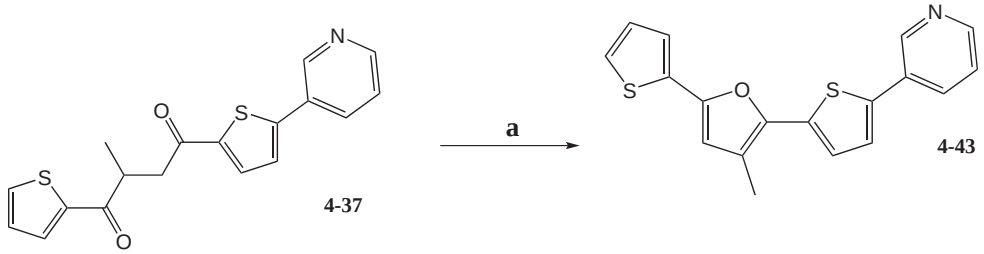
Scheme 4-17: Bromination of proto-oligomers



a. $AlCl_3$, Br_2 in DCM; b. NBS in DMF or $HgCl_2$, Br_2

Since product **4-41** was formed in the bromination reaction and only traces of the desired product **4-42** were obtained, it was attempted to protect the diketone **4-37** by acetalisation and then brominate the terminus. This procedure resulted in the formation of a furan ring during the protection step (see scheme 4-18).

Scheme 4-18: protection of diketone by acetalisation resulted in furan formation



a. PTS, triethylorthoformiate

4.3 Conclusions

The Stetter reaction followed by the Paal-Knorr reaction offers a good way to produce asymmetric halogenated oligomers. The products of the Stetter reaction are very stable, and they can be purified over silica with good results. These intermediates show little undesirable reactivity, and they are 100% regiopure, inherent to the synthetic technique used.

Unfortunately, oligomers formed from these intermediates by Paal-Knorr cyclization are unstable. While terminally alkylated or arylated thiophenes are more stable than 'bare' oligothiophenes, a pyridine functionalized trimer is much more unstable than an unfunctionalized one, to such a degree that pyridine-functionalized thiophene oligomers can be considered impractical.

The degradation of the oligomers is apparent during the Paal-Knorr cyclization. This problem is not inherent to the Paal-Knorr cyclization; if a precursor is made leading to a more stable oligothiophene such as compound **3-41**, the Paal-Knorr cyclization has a very good yield. Continued boiling and overheating with P_4S_{10} caused little degradation of compound **3-41**. Hence, it may be advantageous to postpone the cyclization reaction after the introduction of functional groups.

Deprotonation of oligomers followed by reaction with a nucleophile, and halogenation by NBS tend to become aselective with increasing molecular mass

when one equivalent of reagent is used. Both reactions proceed very well, and if the molecule is already asymmetric, they can be used without problems.

Ullman reactions between imidazole and bromothiophene proceed well, while the analogous Ullman reaction between imidazole and brominated 3'-methylterthienyl does not take place.

In summary, it has been shown that while it is possible to cap a side-chain functionalized thiophene oligomer with pyridine, such compounds are less stable than the bare oligothiophenes, and obtaining pure samples is difficult.

4.4 Experimental Section

1-(p-mercaptomethyl)phenyl, 3-methyl, 4-thienyl 1,4-butadione (**4-8**): 1,51 g p-nitro benzaldehyde was added dropwise to a solution of 0.25 g NaCN in 20ml DMF at 30°C. This solution was stirred for 20 minutes, and the color of the solution became dark brown. 1.2 g of compound **3-17** (0.8 eq) dissolved in 20 ml DMF was added dropwise in 90 minutes with the temperature at 60°C. The solution was stirred for 24 hours, then the solvent was removed by rotary evaporation, the residue dissolved in DCM and washed with water five times. There did not seem to be any 1,4-diketone product in the remaining organics, nor any starting compound **3-17**. Nevertheless, no peaks associated with a 1,4-diketone could be identified.

1-(p-mercaptomethyl)phenyl, 3-methyl, 4-thienyl 1,4-butadione (**4-9**): 1,52 g p-thiomercapto benzaldehyde was added dropwise to a solution of 0.25 g NaCN in 20ml DMF at 30°C. This solution was stirred for 20 minutes, and the color of the solution became bright yellow seconds after the first drops of aldehyde had been added. After the 20 minutes, a suspension of yellow solids had formed. 1.2 g of compound **3-17** (0.8 eq) was added dropwise in 90 minutes with the temperature at 60°C. The solution was stirred for 24 hours, then the solvent was removed by rotary evaporation, the residue dissolved in DCM and washed with water five times. The solid that had formed was prepurified over a column of sephadex beads to remove polymeric side-product. The fraction that came off the column with DCM as solvent was concentrated and recrystallized from diethylether to obtain 2.1g yellow crystals (69%). NMR: 7.94 D (J=4.3 Hz, 1H), 7.78 D (J=1.9 Hz, 1H), 7.63 D (J=2.25 Hz, 1H), 7.123 M (3H), 3.945 M (1H), 3.517 Q (J=x, 1H), 3.285 Q (J=x, 1H), 2.52 S (3H), 1.318 D (3H)

1-((2-mercaptomethyl)-5-thienyl), 3-methyl, 4-thienyl 1,4-butadione (**4-13**): see compound **4-9**, except that 2.0 g of 2-methylmercapto, 5-thenaldehyde (**4-10**) was used together with 1.2 g of compound **3-17**. The color that appears from the beginning is reddish and dark, instead of green as is the case when 2-thenaldehyde is used. No reaction seems to occur upon addition of compound **3-17**.

1-(2-thienyl) but-2-en-1-one (**4-14**): see compound **4-9**, except that 1.9 g of 2-bromo, 5-thenaldehyde was used together with 1.2 g of compound **3-17**. The color effects are similar to the ones observed for compound **4-9**, but the initial bluish green color turns to nearly black and stays this way throughout the addition of Michael acceptor **3-17**. This procedure was not successful.
Alternate (successful) procedure: 6 g thenaldehyde (**3-13**) is added to a solution of 250 mg NaCN in 200 ml DMF and heated to 50^{o}C. A solution of 4.6 g of compound **4-3** in 100 ml DMF is added dropwise over 90 minutes. The reaction is stirred until a red color appears, upon this color change the reaction mixture is quenched in 30 ml acetic acid turning the mixture bright yellow. Subsequently 300 ml DCM is added together with increasing volumes of water. Through repeated extraction with water, the yellow liquid is purified of DMF and acetic acid. The organic fraction is dried and evaporated, after which crystallization from ether or ethanol delivered 3.4 g nearly pure compound **4-14**. Column chromatography of the remaining mixture with petroleum ether/EtAc resulted in another 1.5 g, total yield or 72% total. NMR: 7.83 D (J=2.2 Hz, 1H), 7.66 D (J=2.4 Hz, 1H), 7.51 D (J=2.0, 1H), 7.16 (J_1=2.2, J_2=2.0), 7.10 D (J=2.0, 1H), 3.96 M (1H), 3.53 (J_1=4.2Hz, J_2=4.3Hz, 1H), 2.96 (J_1=2.5Hz, J_2=8.7, 1H), 1.33 (J=3.6 3H)

1-(5-(1,3-dioxolan-2-yl)thiophen-2-yl)-2-methyl-4-(thiophen-2-yl)butane-1,4-dione (**4-15**): See compound **3-37**, except that 2.5 g of compound **4-12** was used (0.01 mol). The resulting product was observed in the NMR spectrum (identifiable without any doubt by telltale peaks 3.56 DD (1H) and 3.11 DD (1H). Judging from the integrals, the product is formed in about 30% yield), but not further purified (all attempts at purification of small samples were unsuccessful).

2-methyl-1-(4-methyl-2,2'-bithiophen-5-yl)-4-(thiophen-2-yl)butane-1,4-dione (**4-16**): see compound **4-14**. The same procedure was performed, but there were remarkable differences. There was a color effect but not nearly as intense as is common for Stetter reactions involving thiophenealdehydes. No product at all was formed, the aldehyde was mostly present in unconverted form.

1-(5-bromothiophen-2-yl)but-2-en-1-one (**4-3**): 16.3 g 2-bromothiophene (0.1 mol) and 11.2g trans-crotonylchloride (0.11 mol) were dissolved in 400 ml dichloromethane. 26 g $SnCl_4$ was added to the well stirred and cooled reaction mixture at 0°C, taking care to keep the temperature no more than a few degrees above zero. The reaction mixture was removed from the coolant as soon as the last drop of reagent had been added, then stirred for 10 minutes. The reaction mixture was worked up by pouring all of it into water. The organic phase was separated, then washed again with water. After separation, the organic phase was dried on $MgSO_4$ and subsequently evacuated to reveal a transparent brownish oil that were crystallized out of diethylether to yield 7.1g white crystals. (32% yield). NMR: 7.47 D (J=2.0,1H), 7.12 M (2H), 6.75 S and 6.70 S (cis/trans, 1H), 1.99 DD (J_1=3.7 Hz, J_2=0.9 Hz, 3H)

N,O-methylmethoxycrotylamide (**4-4**): 4.85 g N-methoxymethylamine hydrochloride (0.05 mol) and 5.25 g trans-crotonylchloride (0.05 mol) were dissolved in 50 ml DCM and cooled to 0º C. 6.5 g triethylamine (2.2 mol) was added dropwise while stirring, taking care not to overheat the mixture. After the addition, the mixture was stirred at room temperature for 1h, after which the solution was poured into 100 ml diethylether and the crystals were filtered off. The filtrate was evaporated to dryness, then vacuum distilled to give 3.8 g clear oily liquid (58%). NMR: 6.96 M (1H), 6.41 D (J=0.045 ppm, 1H), 3.69 S (3H), 3.24 S (3H), 1.89 S (3H)

N-methyl, 2-crotylimidazole (**4-5**): 1.7 g N-methylimidazole (0.02 mole) was dissolved in 50 ml THF at -78°C, and 13 ml n-BuLi (1,6 M) (0.021 mole) was added slowly under stirring. N,O-dimethylhydroxylamino trans-crotonylchloride was added to the solution slowly. The pure product was obtained by evaporation and then vacuum distillation of the reaction mixture. 1.01 g product was obtained (66%)

2-methyl-4-(1-methyl-1H-imidazol-2-yl)-1-(thiophen-2-yl)butane-1,4-dione (**4-17**): see compound **4-14**, except that 1.5 g thenaldehyde (**3-13**) (0.0135 mol) was used and 1.5 g of compound **4-5** (0.01 mol). No reaction took place.

3-methyl-5-(4-(methylthio)phenyl)-2,2'-bithiophene (**4-18**): 500 mg (1.6 mmol) of compound **4-9** was added to 5ml toluene and 500 mg Lawesson's reagent was added. A condensor was added and the mixture was brought to a gentle reflux, and 320 mg of compound **4-18** (64% yield) was isolated in moderate purity, through 'oiling out' the impurities, and a short silica column separation.

Compared to the other Paal-Knorr products described in this chapter, compound **4-18** is more stable on silica. NMR: 7.40 D (J=4.2 Hz, 2H), 7.29 M (3H), 7.20 D (J=2.5Hz, 1H), 7.16 D (J=2.2Hz, 1H), 7.02 M (2H), 2.52 S (3H), 2.30 S (3H)

5-bromo-3'-methyl 2,2':5',2''-terthiophene (**4-19**) 500 mg of compound **4-14** was used, and instead of P_4S_{10}, Lawesson's reagent was used. 350 mg of a yellow oil was obtained after 'oiling out' some impurities. The reaction was also performed using P_4S_{10}, which resulted in a mixture of **4-19** and **3-41**, that seems to be about 50/50 ratio, judging from the NMR spectra, while the procedure with Lawesson's reagent as a sulfur donor does not produce this debrominated compound. NMR: 7.31 D(J=2.2 Hz, 1H), 7.14 D (J=1.7, 1H), 7.07 (J_1=2.6 Hz, J_2=1.8 Hz, 1H), 6.96 D (J=1.7, 1H), 6.9 S (1H), 6.88 D (J=2.2, 1H), 2.36 S (3H)

(**4-20**) Thienyllithium in THF/hexane was prepared as follows. 8.4 g thiophene (**3-16**) (0.1 mol) was added to 100 ml THF and 65 ml 1.6 M n-BuLi in hexane was added at -20^{o}C. The addition is performed in such a manner as to keep the temperature below 0^{o}C. The thienyllithium solution that results from this procedure is stored at 4^{o}C or used immediately. Thienyllithium is not isolated from solution or characterized.

2-iodothiophene (**4-21**) was prepared from thienyllithium solution (**4-20**). 0.01 mol thienyllithium in 16 ml hexane/THF was cooled to -78^{o}C. A solution of 2.5g iodine in a minimum amount of THF was added to the solution slowly enough to keep the temperature below -60^{o}C. After adding about 2/3 of this solution, the color of the mixture was dark, indicating a serious side reaction was taking place. The reaction mixture was allowed to reach room temperature, then poured in aqueous ammonium chloride. After standard workup followed by vacuum distillation, 0.5g 2-iodothiophene was obtained (24% yield). NMR: 7.32 D (J=2.3 Hz, 1H), 7.21 D (J=2.0 Hz, 1H), 6.70 DD (J_1=2.3, J_2=2.0, 1H)

2-thiopheneboronic acid (**4-25**) was prepared from thienyllithium solution (**4-20**). 0.01 mol thienyllithium in 16 ml hexane/THF was cooled down to -40^{o}C. 2.0 g triisopropyl borate (0.011 mol) was dissolved in 10 ml THF and added all at once. The mixture was allowed to assume room temperature and was stirred, then the reaction mixture was added to an excess of 10% aqueous HCl in ice water and stirred for one more hour. Ammonium chloride was then added to the reaction mixture together with more THF. THF was used as extraction solvent (three successive extractions were performed). After drying of the

organic fraction followed by evaporation, 0.9 g beige solid was obtained that was shown to be mainly compound **4-25** (not further purified). NMR: 7.38 D (J=2.6 Hz, 1H), 7.07 D (J=1.9, 1H), 6.96 DD (J_1=2.6, J_2=1.9, 1H)

diethyl, (2-thienyl)phosphonate (**4-23**) was prepared from 2-thienyllithium solution (**4-20**). 0.01 mol thienyllithium in 16 ml hexane/THF was cooled down to -40^{o}C and 1.6 g diethylcyanophosphonate in 5 ml THF was added dropwise. After the addition, the temperature was allowed to reach room temperature. The reaction mixture was poured into aqueous ammonium chloride and worked up using ethyl acetate as extraction solvent. 0.7 g of a clear oil was obtained after vacuum distillation (32% yield).
Alternate procedure: see compound **4-30.** NMR: 8.59 D (J=2.2, 1H), 7.67 D (J=3.8, 1H), 7.28 (J_1=3.6, J_2=2.9, 1H)

2-methylmercaptothiophene (**4-24**) was prepared from thienyllithium solution (**4-20**). 0.05 mol thienyllithium in 80 ml hexane/THF was cooled down to -40^{o}C. 5 g methylthiocyanate (0.075 mol) was added to the reaction mixture. The coolant was removed and the reaction mixture stirred at room temperature for 15 minutes, after which it was poured into aqueous ammonium chloride. Using ethyl acetate, the brownish organic compound was extracted from the watery layer and dried, followed by evaporation and vacuum distillation. A clear distillate with a light brown hue was obtained, totaling 5.9 g or 91% yield. This compound turned dark upon extended storage. NMR: 7.28 D (J=2.2 Hz, 1H), 7.07 (J=1.8 Hz, 1H), 6.95 DD (J_1=2.2 Hz, J_2=1.8 Hz), 2.48 S (3H)

2,5''-bis(mercaptomethyl)-3'-methyl 5,2':5',2''-terthiophene (**4-26**) 300 mg of compound **3-41** (0.0011 mol) was dissolved in 20 ml THF and cooled to -50 ^{o}C and 1.3 ml n-BuLi (1.6 M in hexanes) was added. The solution was allowed to attain -20^{o}C and 200 mg methyl thiocyanate (0.0026) was added. The solution was stirred and allowed to reach room temperature, then it was poured into aqueous ammonium chloride. Using ethyl acetate, the organic fraction was extracted and dried. 360 mg of black tar was obtained, containing product **4-26**. No yield is known because the product was not further purified. NMR: 7.05-6.95 M (5H), 2.48 S (3H), 2.38 S (3H)

(**4-27**) and (**4-1**) 42 g thiophene (0.5 mol) was dissolved in 200 ml DCM. 160g bromine (1.01 mol) in 500 ml DCM was added to the mixture at 0^{o}C, taking care to stay at a temperature below 5 ^{o}C. Strong evolution of HBr gas was observed. The mixture was allowed to reach room temperature after the addition. A mixture of 2-bromo and 2,5-dibromothiophene was obtained after

washing, drying and rotary evaporation. Through vacuum distillation, the products were separated. 11 g 2,5-dibromothiophene (**4-27**) (9%) was obtained and 56 g 2-bromothiophene (**4-1**) (70%). Yields are given with respect to thiophene usage. 2-bromothiophene NMR: 7.20 DD (1H), 7.06 DD (1H), 6.89 DD (1H)

2-iodo, 5-bromothiophene (**4-28**) 8.0 g 2-bromothiophene (0.05 mol) was dissolved in 150 ml THF and 0.05 mol LDA solution in 100 ml hexane/THF mixture (1:2) was added at a temperature of -40 ^{o}C. 12.5 g iodine dissolved in 100 ml THF was added slowly at a temperature of -70 ^{o}C. The reaction proceeded much better than the one described for compound **4-21**, evident from the fact that no iodine coloring was present in the reaction mixture until the end. After washing with water and dilute aqueous sodium sulfite until the liquid had lost most of its dark coloring, with ethyl acetate as extraction solvent followed by drying, the brownish liquid was concentrated and vacuum distilled. 10.9 g liquid (that turned black rapidly) was obtained (66% yield). NMR 7.04 D (1H), 6.74 D (1H)

5,5''''-dibromo, 3', 4'''-dimethyl-2,2':5',2'':5'',2''':5''',2''''-quinquethiophene (**4-29**) 100 mg (0.22 mmol) of compound **3-48** (see Ch. 3) was dissolved in DMF and 90 mg NBS (0.5 mmol) was added at room temperature, in the dark. After 24 hours of stirring, the DMF solution was poured into water and the organics were recovered by extraction with DCM followed by drying. After rotary evaporation, a red oil was obtained. High vacuum was applied for 24 hours. 120 mg compound **4-29** was obtained (91%). NMR: 7.01 M (3H), 6.92 S (2H), 6.87 M (3H), 2.32 S (6H)

3'-methyl 5,2':5',2''-(2-terthiophenephosphonate) (**4-30**) 300 mg of a 50:50 mixture of compound **4-19** and **3-41** (obtained as such by a later abandoned procedure to perform the Paal-Knorr reaction by using P_4S_{10} instead of LR) was mixed with 50 mg $NiCl_2$ (catalytic amount) in triisopropylphosphite and heated to 140^{o}C. Compound **3-41** was recovered together with traces of compound **3-41**. No phosphonated compounds were detected, the preparation seems to have failed.

n-(3'-methyl-5,2':5',2''-terthiophen-2-yl)-imidazole (**4-34**) See procedure for compound **4-32**, except that 300 mg of compound **4-19** (0.001 mol) was used, 0.068 g imidazole (0.001 mol) and 300 mg K_2CO_3, 0.046 g proline (0.004 mol) and 0.038 g CuI were added to 1 ml dry DMF. There was no apparent change

in the NMR spectrum of the compound isolated, with compound **4-19**. This means there has been no reaction.

2-methyl-4-(5-(pyridin-3-yl)thiophen-2-yl)-1-(thiophen-2-yl)butane-1,4-dione (**4-37**) 120 mg 3-pyridineboronic acid (0.001 mol) and 350 mg (0.001 mol) of compound **4-14** were suspended in 5 ml DME and 250 mg (0.003 mol) sodium bicarbonate in 4 ml demi water is added. The suspension is degassed with argon for 10 minutes, then 50 mg $Pd(PPh)_4$ is added (catalytic amount). The mixture is stirred under reflux for 16 hours and poured into water. The organic compounds are extracted with ethyl acetate and dried. Recrystallisation from ethanol or diethylether resulted in 290 mg translucent off-yellow crystals (84%). 8.95 S (1H), 8.63 D (J=2.4 Hz, 1H), 8.03 D (3.8 Hz, 1H), 7.87 D (1.9 Hz, 1H), 7.80 D (1.9 Hz, 1H), 7.68 D (2.1 Hz, 1H), 7.48 DD (J_1=3.6 Hz, J_2=2.6 Hz, 1H), 7.43 D (1.9 Hz, 1H), 7.37 S (1H), 7.19 DD (J_1=5.0 Hz, J_2=3.6 Hz, 1H), 4.02 M (1H), 3.64 DD (J_1=4.0 Hz, J_2=8.6 Hz, 1H), 3.06 DD (J=2.4 Hz, J=8.6 Hz, 1H), 1.39 D (J=2.2 Hz, 3H)

2-methyl-4-(5-(pyridin-4-yl)thiophen-2-yl)-1-(thiophen-2-yl)butane-1,4-dione (**4-38**) See compound **60**. 4-pyridineboronic acid was used instead, otherwise the procedure was the same. 81% yield was obtained. 8.65 D (J=3.0 Hz, 2H), 7.85 D (J=2.0, 2H), 7.776 D (J=2.3 Hz, 1H), 7.67 (J=2.6 Hz, 1H), 7.5 D (J=3.9 Hz, 1H), 7.17 D (J=4.7 Hz, 1H), 4.00 M (1H), 3.64 Q (J=x, 1H), 3.04 DD (J=x, 1H), 1.35 D (J=x, 3H)

3-(3'-methyl-5,2':5',2''-terthiophen-2-yl)-pyridine (**4-39**) See compound **4-37**. Palladium acetate was used as a catalyst, and compound **4-19** instead of **4-14**. The procedure was the same. Product **4-39** was detected from NMR, although the estimated (spectroscopic) yield was around 40% judging from integrals, no product could be obtained in purer form.
B. 350 mg of compound **4-37** was dissolved in dry toluene, and 500 mg Lawesson's reagent was weighed off and divided in two portions. One portion was added to the reaction mixture right away. The reaction mixture was refluxed for one minute, then the remaining Lawesson's reagent was added and the reflux was continued for two more minutes. The reaction was followed on NMR. Even though compound **4-39** was formed, it was evident from this data that it was being destroyed as well. The optimal yield was spectroscopically estimated to occur at a conversion rate of about 60 %, falling rapidly afterwards. NMR: 8.89 D (J=0.9 Hz, 1H), 8.53 DD (J_1=3.0, J_2=0.3 Hz, 1H), 7.88 D (J=4.2 Hz, 2H), 7.71 M (3H), 7.47 M (3H), 7.30 M (3H), 7.08 DD (J_1=2.5 Hz, J_2=2.8 Hz, 2H), 7.03 S (1H), 2.40 S (3H)

4-(3'-methyl-5,2':5',2''-terthiophen-2-yl)-pyridine (**4-40**) See compound **4-39**, only 4-pyridine boronic acid was used instead. The same problems occurred, resulting in an even smaller spectroscopic yield than described for compound **4-39**.
B. See compound **4-39**, procedure B. 350 mg of compound **4-38** was used instead. The same observations were done. 8.85 D (J=4.2 Hz, 2H), 7.88 D (J=4.2 Hz, 2H), 7.73 M (2H), 7.45 M (1H), 7.33 M (1H), 7.08 DD (J_1=2.5 Hz, J_2=2.8 Hz, 1H), 7.02 S (1H), 2.40 S (3H)

2-bromo-2-methyl-4-(5-(pyridin-3-yl)thiophen-2-yl)-1-(thiophen-2-yl)butane-1,4-dione (**4-41**) 350 mg compound **4-37** was dissolved in 5 ml DCM and cooled to 0^oC. 150 mg $AlCl_3$ and 160 mg Br_2 were added and the reaction mixture was stirred in the dark, with the coolant removed. After 30 minutes, the reaction mixture was poured into water and 300 mg sodium sulfite was added. The organic compounds were extracted with DCM and dried. After evaporation, some brown paste was obtained which was revealed to contain about 50% compound **4-41** (not isolated) together with compound **4-37**. More importantly, no significant bromination of the thiophene terminus was observed.

1-(5-bromothiophen-2-yl)-2-methyl-4-(5-(pyridin-4-yl)thiophen-2-yl)butane-1,4-dione (**4-42**) 350 mg compound **4-38** was dissolved in 5 ml DMF and 180 mg NBS was added, stirring in the dark at room temperature for 24 hours. After workup using ethyl acetate, compound **4-38** was recovered (unchanged).

3-(5-(3-methyl-5-(thiophen-2-yl)furan-2-yl)thiophen-2-yl)pyridine (**4-43**) 350 mg compound **4-37** was dissolved in 10 ml methanol and 1 ml triethylorthoformiate. 40 mg dry PTS was added (catalytic amount) and the mixture was refluxed for 24 hours. After aqueous extraction with ethyl acetate, compound **4-43** was obtained in crude form as a dark brown crystalline paste. It was spectroscopically determined that the conversion was nearly 100%, judging from the spectrum. The identity of 4-43 is postulated because of the facts that ring closure has taken place and an NMR peak exists in the region 6.45 ppm which is in accordance with simulations (even though it has to be stated that this simulation is usually in error within a range of to 0 to +0.5 ppm in predicting the peaks in oligothiophenes.). Evidence that pleads against the furan ring formation is the fact that the peak at position 6.45 is a well-developed quartet (which means unusually strong coupling with the methyl group would have taken place). The product was not isolated because **4-43**

was not the intended product. NMR: 7.30 S (1H), 7.12 DD (J=2.0, 1H), 7.06-7.00 M (2H), 6.45 Q (J=2.4 Hz), 2.29 S (3H)

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[2] de Luca, L., Glacomelli, G., Taddei, M., J. Org. Chem., 2001, 66, 2534
[3] Lv, X., Wang, Z., Bao, W., Tetrahedron, 2006, 4756
[4] Chen, Y. J., Chen, H. H., Org. Lett., 2006, 8, 24, 5609

5 Surface Chemistry of Imidazole Derivatives

5.1 Introduction

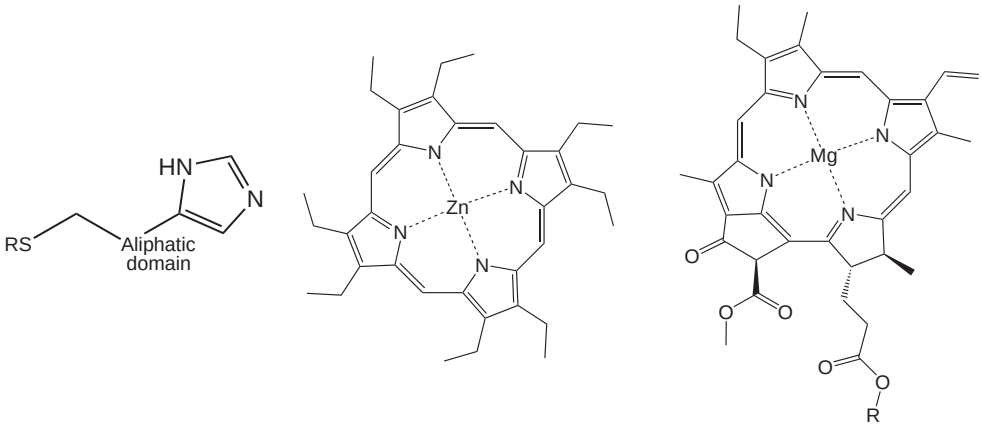
Metalloporphyrins (being chromophores) and imidazole derivatives (being powerful coordinating ligands that immobilize porphyrins) play a central role in this research. Especially imidazole has been mentioned in chapters 2 and 4, and ultimately pyridine as well. These moieties are difficult to incorporate into conjugated oligomers when compared to aliphatic molecules. In this paragraph, two methods of obtaining aliphatic, saturated analogues will be described.

These aliphatic ‘oligomer analogues’ are asymmetric, they can bind to a surface and they possess a histamine or imidazole group that is capable of binding porphyrins. They lack the conjugated structure, otherwise they are a model system for the more complicated proposed oligomers.

5.2 Aliphatic histamine and imidazole surfactants

Histidine is the residue responsible for coordination-binding with most chlorophylls in the photosynthetic system. The imidazole moiety is the active part. In order to study the coordination behaviour of metalloporphyrins in artificial systems, derivatives of imidazole have been prepared that are capable of binding to a metal surface. Although they do not occur in the photosynthetic system of normal plants, pyridine derivatives can play a similar coordination role.

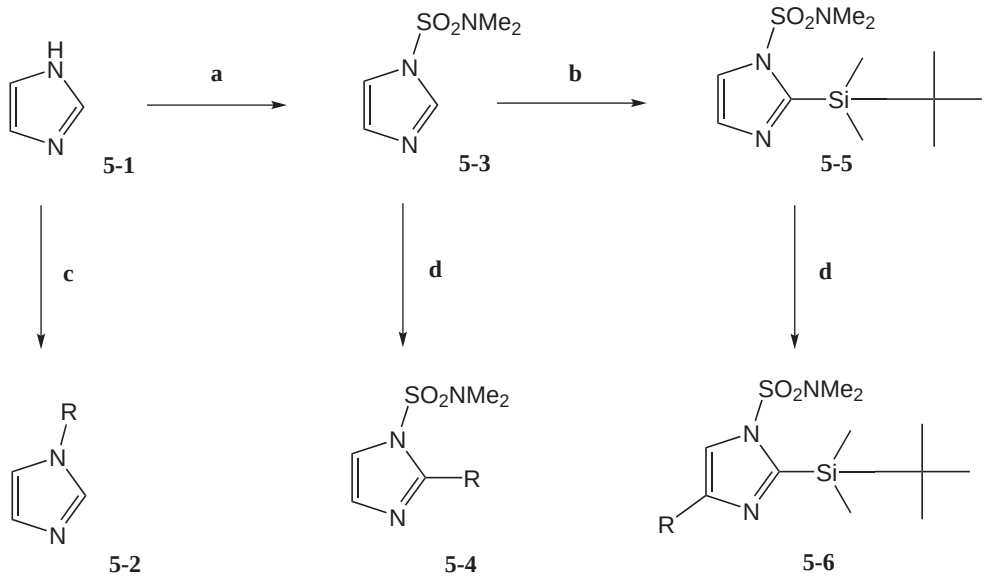
Scheme 5-1: left: target ligand; middle: Zn-OEP; right chlorophyll a



5.2.1 Synthesis of aliphatic imidazole derivatives

Synthetic procedures starting from imidazole, such as the procedures used by Vollinga[1], can be used to produce N-substituted, 2-substituted as well as 4/5-substituted imidazoles. Apparently there is no difference between N-methylimidazole and imidazole with respect to ligation, and probably N-alkylimidazoles will behave in a similar way as 4/5-substituted imidazoles, such as histamine, with the major difference that there is no mesomerism that renders two nitrogen atoms potentially binding. 2-substituted imidazoles have two chemically indistinguishable nitrogen atoms, both of which can assume the role of pyridine-type nitrogen. The different general structures and preparation are summarized in scheme 5-2.

Scheme 5-2: synthetic procedures for the preparation of substituted imidazoles



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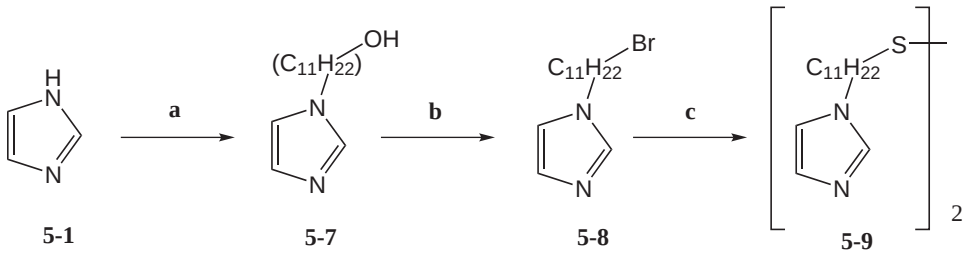
a. dimethylchlorosulphonamide, TEA; *b. n-BuLi, THF followed by TBDMS-Cl; c. R-Br, K_2CO_3 d. n-BuLi, THF followed by RI*

In order to be useful, the R-group in scheme 5-2 must be ω-functionalized, preferentially with a halogen atom. The reaction from halogen to disulfide is relatively simple (see compound **5-2**). It is possible to use, for example, I-$(CH_2)_n$-Cl or similar molecules in reaction d, since the I atom will be substituted first, leaving a terminal Cl atom for the next step, or simply to use a large excess of dichloroalkane followed by separation of the products.

An alternative that works only for reaction **c**, but not **d**, is to use Br-$(CH_2)_n$-OH, followed by bromination of the alcohol described by Wei *et al*. This approach (scheme 5-3) led to unsatisfactory results in our hands and in the original article, no yield was specified either.

Scheme 5-3: Alternate procedure for the preparation of N-functionalized imidazole disulfides



5-1 **5-7** **5-8** **5-9**

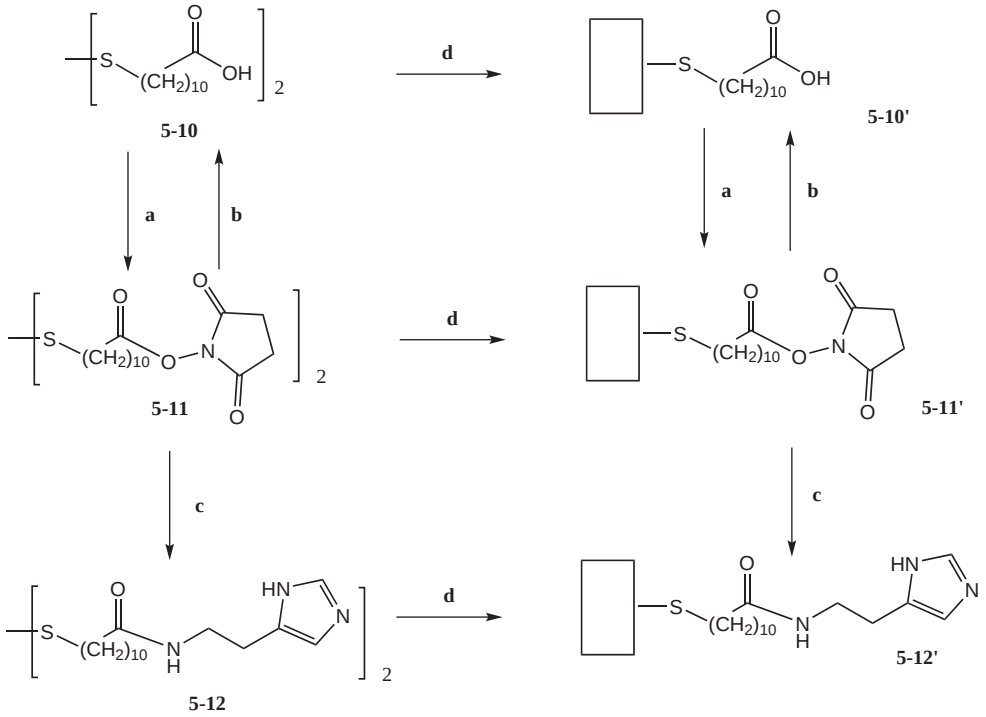
a. R-Br, K_2CO_3; b. HBr; c. NaS_2O_3 followed by HBr

5.2.2 Surface chemistry of imidazoles

Self-assembled monolayers on gold (SAMs) can be used for detailed characterization of molecular interactions. Alkanethiols are commonly used because of their excellent adsorption behaviour into monomolecular layers. For a comprehensive review on the preparation of these compounds, see the article of Witt et al.[2] The Au-S bond is strong, and it takes vigorous and destructive means to completely remove a layer from the metal surface. Alkanethiols that are unbranched and asymmetrically ω-functionalized will adsorb into well-ordered layers with their sulfur side oriented to the metal and their other functional group outward exposed. The chemical and physical properties of a surface modified by such molecules will be determined almost completely by the nature of the exposed functional group. If the layer thickness is ten or more methylene groups, the adsorbents will assume a crystalline orientation.

A common adsorbent class are the N-hydroxy succinimide (NHS) alkylesters such as DSU (**5-11**)[3]. The NHS ester can be considered a reactive ester that will form amide bonds with primary amines and it will hydrolyze quickly in an alkaline medium. Histamine and other amines can be bound to this ester irreversibly, both in a solid-state reaction as well as in solution. The precursors for compound **5-11** and similar molecules of different chain length are easily prepared from the terminally brominated carboxylic acid.

Scheme 5-4: Formation of surface active ligand



a. DCC, NHS; b. OH^-; c. histamine.HCl, triethylamine; d. EtOH, Au (surface)

It is also possible to perform solid-support reactions on a metal surface, if the exposed moiety is reactive. Reactions **a** and **b** in scheme 5-4 have been performed both on a surface, as well as in solution, although reaction **a** may not proceed to completion due to the increased bulk of the reaction product compared to the precursor. Reaction **b** leads from a moderately hydrophobic, sterically hindered molecule to a very hydrophilic species and this reaction is not hindered. Reaction **c** results in a rather insoluble compound **5-12**, while compound **5-11** also requires considerable time in a sonicator to dissolve well in ethanol. Histidine, being a primary amine, will bind quickly to compound **5-11** on a surface exclusively with its primary amine functionality to form compound **5-12**.

Surface adsorption and the formation of crystalline and relatively defect-free monolayers is a complex matter, especially if two or more different classes of adsorbent are present (a mixed SAM). There may be a difference in adsorption kinetics between thiol/disulfide adsorbents and the resulting surface ratio will likely be different from the ratio in solution. It is also possible that microdomains are formed if the compounds are sufficiently dissimilar, the result of phase

separation on the surface. Therefore, all the possibilities in scheme 5-4 may have their own specific advantages. Another similar experiment was done by Yang et al.[4], who used short peptide chains beginning with Cys and ending with His and let these peptides bind to gold. Covalently bound metalloporphyrins on gold and ITO electrodes[5,6] produce current under illumination.

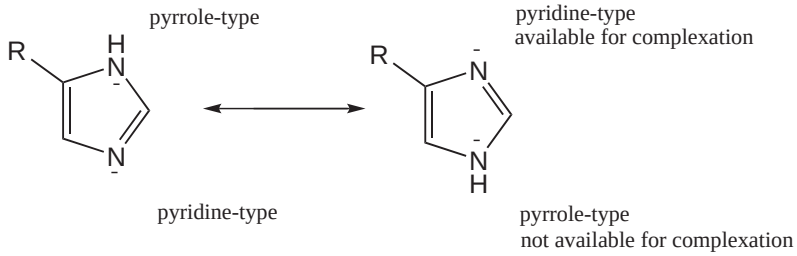
5.2.3 Coordination behaviour of pyridines and imidazoles with metalloporphyrins

Chlorophylls and related chromophores belong to the porphyrin class, as do the commonly used phthalocyanin dyes. These molecules are characterized by a conjugated tetrapyrrole ring and they can coordinate several metal ions. In the case of chlorophylls, the metal is the five-coordinate Mg^{2+}, though other metals such as the six-coordinate Zn^{2+} are readily coordinated. In fact, magnesium porphyrins are less stable than their zinc counterparts. Metals such as iron and copper are also coordinated by porphyrins, but in this thesis, the focus is on porphyrins that resemble the dyes in photosynthetic systems, with central M^{2+} ions.

Histidine forms a strong coordination bond with the central metal ion in porphyrins. A good model compound to study ligand effects on porphyrin bonding is Zn-OEP (OEP stands for octaethylporphyrin). Zinc is a more stable central metal than magnesium and the porphyrin itself is far more stable than chlorophylls due to the alkyl substituents.

The ligands that bind to Zn-OEP and other porphyrins are those who posess a ‘pyridine-type’ nitrogen. This means, pyridine and derivatives, as well as imidazole and N-methyl imidazole, but not pyrrole. Imidazole has two nitrogen atoms, one of the pyridine type, the other of the pyrrole type. Even though the role of each nitrogen can change due to mesomeric structures, only one of them leads to strong coordination. Also N-methylimidazole coordinates. Here the pyrrole-type nitrogen is neutralized by a methyl substituent and there is only one, pyridine-type, nitrogen atom.

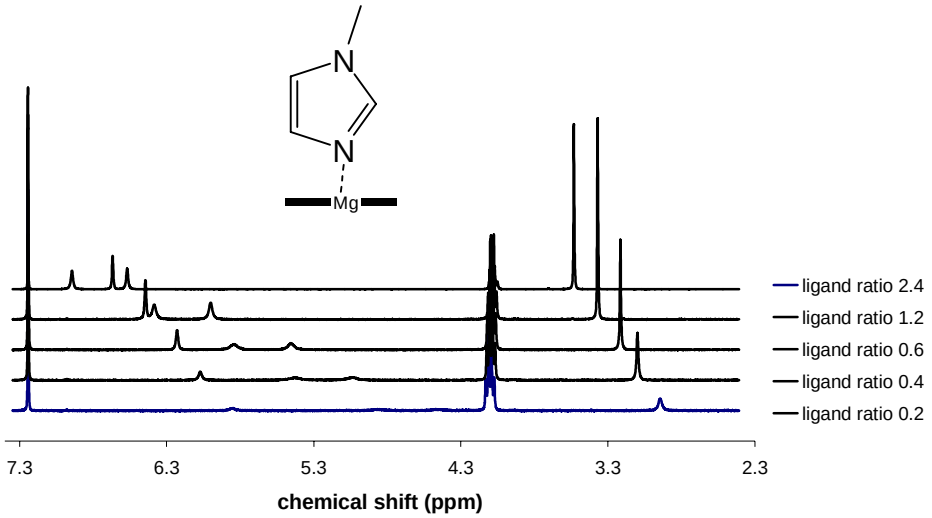
Scheme 5-5: pyrrole- and pyridine-type nitrogen in imidazole derivatives



The effect of the ligand on Zn-OEP can be quantitatively characterized. The UV-VIS spectrum of ligand-porphyrin complexes changes with increasing ligand to porphyrin ratio. The chemical shifts in a proton NMR spectrum also change with the ligand to prophyrin ratio[7]. In scheme 5-6, the NMR spectra of different mixtures of Zn-OEP and N-methylimidazole in $CDCl_3$ are plotted. Not shown is the change in chemical shift for the porphyrin hydrogen atoms. The peak belonging to the hydrogen atoms in the meso-position was shifted -0.2 ppm when excess ligand was present, compared to free Zn-OEP.

It is obvious from the graph that there is considerable interaction between ligand and porphyrin. Similar effects are observed for pyridine, imidazole and substituted imidazoles. However, if thiophene or pyrrole are present instead of N-methylimidazole, the NMR spectrum is simply a superposition of the responses of the individual components in the mixture and concentration dependent changes are not detected.

Scheme 5-6: Effect of MeIm ligand – Zn-OEP porphyrin coordination on chemical shift



The proton-NMR shift is an indicator of complexation in solution. Barring steric hindrance, the complexation is assumed to take place on solid surfaces as well, where the imidazole functionality is exposed and allowed to contact a solution of porphyrins.

5.3 Conclusion:

Imidazole (and assumedly pyridine) derivatives are effective coordinating ligands for metalloporphyrins. Imidazole derivatives that are capable of self-assembly on gold surfaces have been prepared using several methods. The most useful method of producing these surface binding ligands seems to be the reaction between active esters and histidine or histamine.

5.4 Experimental

N,N-dimethyl-1H-imidazole-1-sulfonamide (**5-3**)[8]: 9.54 g imidazole (0.14 mol) and 13 ml dimethylchlorosulphonamide (0.12 mol) were stirred in 200 ml toluene and 18 ml triethylamine was added (0.13 mol). The reaction mixture was stirred at room temperature for 16h, then filtrated. The solids were rinsed with toluene once. The combined filtrate was washed with water and then dried and concentrated in vacuo. The remaining slurry was vacuum distilled at 0.1 mmHg. 17.7g compound **5-3** was obtained (82%). NMR: 7.88 S (1H), 7,26 M (1H), 7.01 S (1H), 2.65 S (6H)

2-(dimethylhexylsilyl)-N,N-dimethyl-1H-imidazole-1-sulfonamide (**5-5**): 2.6 g compound **5-3** (0.015 mol) was dissolved in dry THF (50 ml) under a blanket of argon in an acetone - dry ice cooling bath. 10 ml n-BuLi in hexane (0.016 mol) was added slowly, not allowing the temperature to exceed -60^{o}C. After the addition and 15 more minutes, 2.5 g t-butyldimethylsilylchloride (0.017 mol) is added in the same manner as the n-BuLi solution. After the addition, the coolant was removed and the mixture was stirred for one more hour. The solution of compound **5-5** was stored in a sealed contained. NMR: 7.88 S (1H), 7,26 M (1H), 7.01 S (1H), 2.65 S (6H)

11-(1H-imidazol-1-yl)undecan-1-ol (**5-7**): Imidazole (0.68 g; 0.01 mol), 2.76 g K_2CO_3 (0.02 mol) and 2.51 g 11-bromo-1-undecanol (0.01 mol) were added to 25 ml DMF under argon. This mixture is sealed and stirred for 60 hours at room temperature. The mixture was poured in 50 ml ice water. The solids were collected and recrystallized from ethanol. The resulting wax was dried under high vacuum. 1.43 g product **5-7** was obtained (55%). NMR: 7.51 S (1H), 7.04 S (1H), 6.96 S (1H), 3.92 M (2H), 3.62 M (2H), 1.72 M (2H), 1.55 M (2H), 1.27-1.22 M (14 H)

11-(imidazol-1-yl)undecan-1-ylbromide (**5-8**): 500 mg product **5-7** (0.002 mol) was added to 2.5 ml HBr solution (48%) and refluxed for 24 hours. An excess amount of K_2CO_3 was added and extracted with chloroform twice. The chloroform fraction was evaporated resulting in 330 mg of an oily compound that solidified after lyophilizing (0.00115 mol). NMR: 7.50 S (1H), 7.04 S (1H), 6.95 S (1H), 3.93 T (2H), 3.39 M (2H), 1.82 M (2H), 1.55 M (2H), 1.29-1.21 M (14 H)

11-dithiobis-(1-undecyl)--imidazole (**5-9**): See the article of Wei et al[9]. for a synthetic protocol. This experiment was performed but the results of Wei et al. could not be reproduced.

dithiobis undecanoic acid (**5-10**) 5.3 g 1-bromoundecanoic acid (0.02 mol) was dissolved in 30 ml dioxane. 3.2 g sodium thiosulfate (anhydrous) was dissolved in 30 ml water. These solutions were combined and heated to reflux under stirring for 6 hours. Iodine crystals were added until the iodine color did not disappear anymore, then the solution was refluxed for 15 minutes. A dilute sodium sulfite solution was added in sufficient quantity to make the iodine color disappear. The reaction mixture was extracted using ethyl acetate and washed with water several times. After drying and evaporation, the resulting beige wax was dissolved in warm ethanol and recrystallized twice to reveal 3.9 g white waxy powder (89 % yield). NMR: 2.69 T (2H), 2.28 T (2H), 1.71 M (2H), 1.62 M (2H), 1.40-1.28 M (12 H)

Dithio-bis-succinimidyl-undecanoate (**5-11**): 2.18 g dithiobis undecanoic acid (0.005 mol) was dissolved in 50 ml THF along with 2.1 g DCC (0.01 mol) and stirred for 16 hours. After that time, 1.3 g N-hydroxy succinimide was added. (0.012 mol) and the stirred mixture was heated to 40^{o}C. After 4 hours, the mixture was filtrated to remove the waste product DCU. The filtrate was concentrated until it was a wet solid, dissolved in 100 ml hot ethanol and the liquid was cooled to 4^{o}C to recrystallize the product. After three successive recrystallisations, 760 mg of a slightly salmon compound was obtained (23%). Some DCU remained in the sample but it is inert and considered a harmless contaminant. NMR: 2.82 S (4H), 2.68 T (2H), 2.61 T (2H), 1.80-1.60 M (4H), 1.45-1.25 M (12H)

Dithio-bis-histidyl-undecanoate (**5-12**): 180 mg histamine hydrochloride (1 mmol) and 200 mg triethylamine (2 mmol) were suspended in 10 ml THF. A solution of 250 mg compound **5-11** (0.00038 mol) in THF was added to the histamine solution. The THF solution was subjected to rotary evaporation, the solid residue was refluxed in water. The remaining solids (200 mg or 81%) were collected after lyophilizing. NMR: 7.51 S (1H), 7.04 S (1H), 6.96 S (1H), 3.92 M (2H), 3.62 M (2H), 1.72 M (2H), 1.55 M (2H), 1.27-1.22 M (14 H)

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6 Conclusions and Future Prospects

From the choices that have been made in this research, and the results that have been obtained, a number of suggestions can be made to improve on what has been achieved so far.

There are many procedures to produce and functionalize oligothiophenes and oligophenyls. Most currently applied syntheses have been reviewed in chapter 1. Of these, several have been employed in this research.

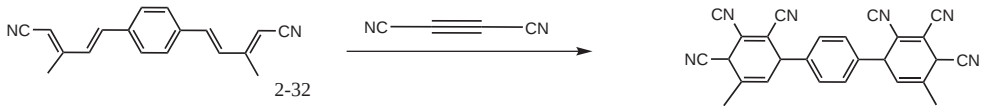
In chapter 2, phenyl coupling reactions resulted in symmetric conjugated molecules that have the potential to self-assemble on a surface, but these compounds suffered from poor solubility. To combat this problem, side-chains were to be introduced. A number of Friedel-Crafts additions have been described in order to form the oligomers with side-chains, and many more had been attempted. Compound **2-35** did not react with any dienophile except maleic anhydride and fumaryl chloride, powerful dienophiles that result in a cyclohexane but not a cyclohexadiene. Thus, the problem with this synthetic route was that substituted acetylenes would not react with the diene. Decarboxylation of the adducts that could be formed (using non-acetylene dienophiles) proved to be unsuccessful.

The bottom line is that the not-so-reactive diene requires a very powerful dienophile that contains a triple bond, since decarboxylation of these adducts was not possible. Powerful dienophiles are scarce, and dienophiles with a triple bond tend to be less powerful than dienophiles with a double bond: the latter may have more electron withdrawing groups on them.

However, a compound that is certainly one of the most powerful dienophiles around and contains a triple bond exists: carbon subnitride or

dicyanoacetylene. It seems possible that the addition of this compound to the diene **2-35** would succeed, and because a cyclohexadiene is the product of the addition, aromatization to a phenyl ring would be likely to succeed.

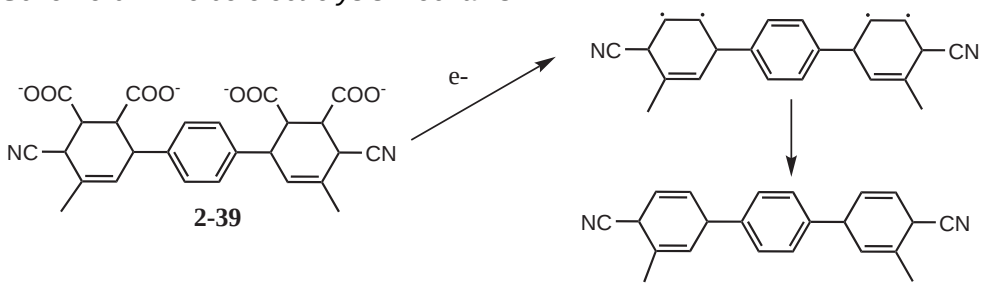
Scheme 6-1: reaction of diene with carbon subnitride



An alternative procedure to remove carboxylate groups that has not been attempted is the Kolbe decarboxylation[1]. This is an electrochemical procedure that sometimes leads to success. The Kolbe reaction was originally applied to produce ethane from two equivalents of acetic acid; the carboxyl group is lost as CO_2. The Kolbe reaction is also successfully applied to decarboxylate fatty acids of n carbon atoms and produce a paraffin of 2n-2 carbon atoms. The coupling of acetate and similar compounds is assumed to proceed via a radical mechanism.

The compound **2-29** that failed to decarboxylate (see chapter 2) has its carboxyl groups adjacent to each other. Decarboxylation leading to the formation of a biradical (or tetraradical) should result in immediate formation of a double bond. See scheme 5-9.

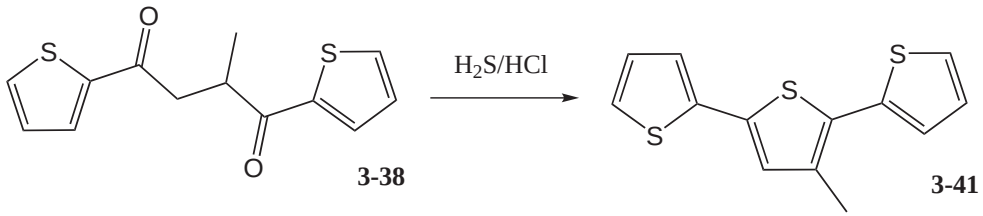
Scheme 6-2: Kolbe electrolysis mechanism



Thiophene oligomers have been made with some success in a short synthetic procedure using Paal-Knorr methodology in chapter 3 and 4. In chapter 3 terthienyl, quaterthienyl and quinquethienyl have been prepared with one or two methyl groups on the side chain. Larger alkyl groups can be introduced instead of methyl, but precursors which lead to methyl substituents are cheaper to produce. A problem arose when the oligomers were purified. Using phosphorus sulfides, purification is required or there will always be

contaminants present in the product. Using hydrogen sulfide as sulfur donor, it might be possible to produce the oligomers without need for purification, or a different sort of contamination.

Scheme 6-3: proposed hydrogen sulfide cyclization: purification should be different using H_2S gas as sulfur donor



3-38 **3-41**

In chapter 4 the oligomers produced with the technique from chapter 3 were used to incorporate not only a side-chain but also asymmetric end groups. This led to the successful synthesis of the versatile synthons **4-19** and **4-14**. These compounds have high potential for any synthetic route involving thiophene oligomers, because of the asymmetric functionalization. Many different substituents can be added asymmetrically to alkyl-substituted terthiophene starting with these precursors. Also, the oligomer can be modified to participate in many of the catalyzed coupling procedures, most likely Stille and Suzuki coupling, to form highly regioregular polythiophene, with a substituent alkyl group on each third thiophene ring.

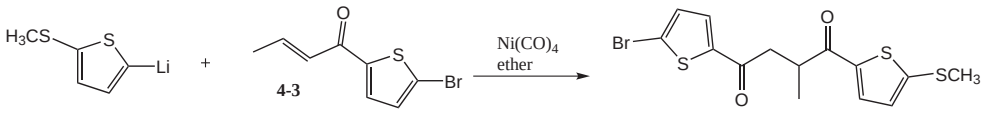
Scheme 6-4: the asymmetric synthons

4-14 **4-19**

The Stetter-Paal-Knorr reaction sequence seemed like a good candidate in theory for producing asymmetric short oligomers, because of the alkyl side-chain. While this is synthetically relevant, the side chain also has a negative impact on the purification of the oligomer. Unsubstituted thiophene chains, if not very long, may well remain soluble enough to be processible and they will certainly be easier to purify through recrystallization than the oily oligomers described in this thesis.

The Stetter reaction is only one available route to 1,4-diketones. Another procedure that has not been attempted due to time constraint is the addition of thienyllithium reagent and nickel carbonyl to a Michael acceptor of the type used in chapters 3 and 4. A precedent has been published[2], although with aliphatic side-groups. This procedure may succeed where the Stetter reaction fails in producing a bifunctional trimer. The -CH_3S group inhibits the Stetter reaction but it is unlikely to inhibit this reaction, and it uses the same precursor that is needed for the production of the asymmetric synthon **4-14**.

Scheme 6-5: nucleophilic attack on a Michael acceptor with a ketone precursor leading to a 1,4-diketone



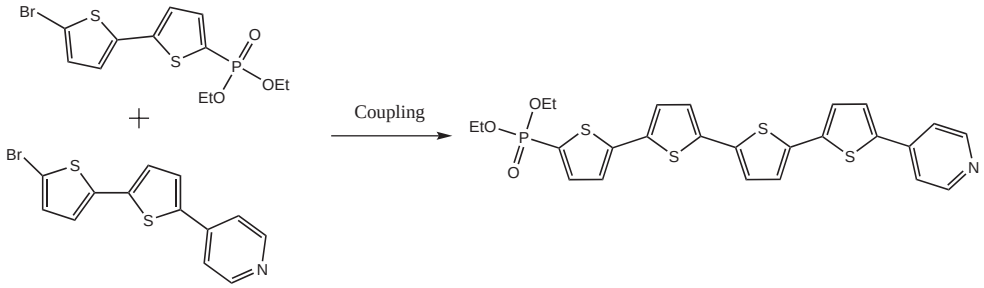
In chapter 5, the synthesis of surfactant molecules has been described as well as the coordination interactions between imidazoles and metalloporphyrins. If metalloporphyrins are actually deposited on imidazole-functionalized surfaces, specialistic surface characterization techniques are required. For example, Fourier transform infrared spectroscopy reflection FTIR (GIR-FTIR) and also ATR-FTIR are useful for the chemical characterization of hydrocarbons on the surface, SPR (surface plasmon resonance) for the monolayer characterization and especially XPS (X-ray Photon Scattering) which is an elemental analysis technique that works well for surfaces. Metalloporphyrins that remain behind on a histidine-modified surface can be imaged using XPS because the metal atom in the porphyrin will usually not be present in the sample in any other form, therefore, the metal content is a direct indicator of porphyrin loading.

The use of mixed SAMs for binding porphyrins seems to be the most likely way to successful binding. A mixed SAM is a multicomponent SAM. In this case, one component would be inert, the other would contain the imidazole group, and be slightly exposed from the surface (due to a longer carbon skeleton). The use of mixed SAMs as binding surface and even electron-transfer site has been performed by Sek et al.[3]

The adsorption of imidazole or pyridine-terminated conjugated oligomers on surfaces can be accomplished if the oligomers are asymmetrically functionalized. A realistic route to terminally substituted, asymmetric

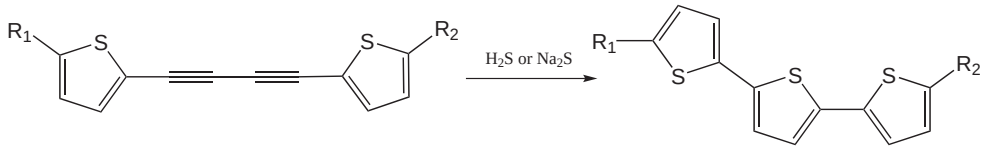
tetrathiophenes without side-chain substituents would be to produce the dithienyl with a single substituent, followed by one of the coupling reactions described in chapter 1 (see scheme 6-6). A phosphate-bipyridine terminated oligothiophene that binds to ruthenium dyes was made in this manner[4].

Scheme 6-6: Concept of using bimolecular heterocoupling reaction for the synthesis of a short, asymmetric oligomer



In this thesis, cyclization reactions were used starting with diketones. The other major cyclization route uses substituted butadiynes. Unlike the Stetter reaction that suffers from lower yields when larger oligomers are required to react, butadiynes in such large chains are reported to form with better yield[5]. Obviously, no side-chains can be present on oligomers formed from butadiynes. Since some homogeneity in oligomers may be desirable, this procedure is better suited for the production of asymmetric unsubstituted oligothiophenes. However, for reasons mentioned above, a side-chain may be undesirable for surface applications. In such a case, the procedure sketched in scheme 6-7 may be ideal.

Scheme 6-7: Butadiyne as (unsubstituted) thiophene precursor in oligomers



Conjugated oligomers are likely to play a role in nanochemistry for the years to come. Their optical and electronic properties are fascinating to scientists. Even if organic molecules should never surpass inorganic semiconductors in performance and stability, their flexibility and potential cheap production make it worth to investigate them.

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Summary

Conjugated aromatic oligomers constitute a class of organic molecules that in molecular mass are inbetween small aromatic molecules like benzene and polymers.
In chapter 1, currently available well-described synthetic techniques to produce and functionalize such conjugated oligomers have been reviewed. Emphasis has been placed on oligothiophenes.
In chapter 2, the synthesis of several phenyl-type oligomers is described. Two methods have been explored: coupling of substituted phenyls and construction of oligomers from non-aromatic precursors. The conclusions from this work were that poor solubility is an virtually intractable problem in the case of phenyl oligomers, especially if pyridine or imidazole substituents are present.
Chapter 3 deals with the novel synthesis of heterocycles that possess an alkyl side-chain. The synthesis of soluble substituted oligothiophenes was achieved using simple precursors via the Stetter and Paal-Knorr reactions.

In chapter 4, the successful technique developed in chapter 3 was made more versatile by adding terminal functional groups asymmetrically to oligomers. The side-chains (introduced in chapter 3) are also present, leading to the synthesis of compounds **4-14** and **4-19**. These compounds (and similar ones) have wide potential in nanotechnological applications but were previously hard to obtain using existing oligomer syntheses. Purification remained an issue yet to be resolved, since routine column separations do not give satisfactory results.
Chapter 5 deals with the preparation of porphyrin binding molecules, and assembly of these molecules on metal surfaces. Also, an NMR based method to characterize the coordinating strength of imidazole derivatives and metalloporphyrins has been demonstrated.
The final chapter 6 contains the conclusions of this research, as well as an outlook for further work on conjugated oligomers. The main problems that were unresolved and possible solutions for them are presented in this chapter.

Samenvatting

Geconjugeerde aromatische oligomeren vallen tussen simpele moleculen en polymeren met betrekking tot moleculaire massa. In hoofdstuk 1 wordt beschreven wat voor synthetische technieken er bekend zijn in de literatuur om dergelijke oligomeren te synthetiseren en analyseren. De nadruk ligt hierbij op oligothiophenen. In hoofdstuk 2 wordt de synthese van een aantal phenyl-type oligomeren beschreven. Twee methoden zijn hierbij aan de orde: koppeling van gesubstitueerde phenyls en het opbouwen van oligomeren uit niet-aromatische precursors. De conclusies uit dit werk waren dat slechte oplosbaarheid leidt tot vrijwel onoverkomelijke problemen in het geval van phenyl oligomeren. In het bijzonder wanneer pyridine of imidazole substituenten aanwezig zijn.
Hoofdstuk 3 gaat over de nieuwe syntheseroute om heterocyclische verbindingen te maken waarbij een alkyl zijketen aanwezig is. De synthese van oplosbare gesubstitueerde oligothiophene is gelukt door middel van Stetter en Paal-Knorr reacties toe te passen op simpele precursors.

In hoofdstuk 4 is de in hoofdstuk 3 ontwikkelde techniek gebruikt en uitgebreid door functionele groepen toe te voegen aan het einde van de ketens, hetgeen heeft geleid tot asymmetrische oligomeren. De zijketens (in hoofdstuk 3 geintroduceerd) zijn nog steeds aanwezig, hetgeen heeft geleid tot de synthese van stoffen **4-14** en **4-19**. Deze stoffen (en vergelijkbare analogen) hebben ruimte toepasbaarheid in nanotechnologische applicaties, maar waren voorheen lastig te verkrijgen met gangbare synthesetechnieken. Zuivering blijft problematisch, omdat routine kolomseparaties niet tot succes hebben geleid.
In hoofdstuk 5 wordt de bereiding en assemblage van porphyrine-bindende stoffen op oppervlakken beschreven. Een NMR-gebaseerde methode wordt gebruikt om het coordinerende vermogen van imidazolderivaten en metalloporphyrines te karakteriseren.

In het laatste hoofdstuk 6 worden de conclusies van dit werk opnieuw samengevat, evenals een vooruitzicht op verder werk in geconjugeerde oligomeren. De belangrijkste problemen die niet zijn opgelost en mogelijke antwoorden hierop worden in dit hoofdstuk uiteengezet.

Curriculum Vitae

Geerten Herman Degenhart werd op 5 augustus 1977 geboren te Rotterdam. Na het behalen van het Gymnasium-diploma aan het Coornhert te Gouda in 1996 werd in september dat jaar begonnen met de studie Technische Natuurkunde aan de Universiteit Twente. In september 1997 werd begonnen met de studie Chemische Technologie. In 2003 werd in het kader van de doctoraalopdracht onderzoek gedaan bij de vakgroep Material Science and Technology of Polymers naar oppervlaktemodificatie en dip-pen nanolithography van dendrimeren op chemisch bindende oppervlakken. In november 2003 werd het doctoraaldiploma verkregen. Vanaf februari 2004 tot september 2008 werd als Assistent in Opleiding het in dit proefschrift beschreven onderzoek uitgevoerd bij de vakgroepen SSNMR, BOF en BIOSYN onder leiding van de hoogleraren de Groot, Lugtenburg en Overkleeft.

Acknowledgements

This thesis has been the product of several turbulent years, with changes taking place to the workgroup almost as often as the assignment itself. I was a member of three groups within five years. Working at Leiden University is as much adventure as it is science. As adventures go, unusual circumstances give unusual friendships between people and memories that will never go away. Because most of my memories are positive ones, I hope that the memory I leave behind will also be mostly positive.

The beginnings of my assignment were full of uncertainties and I appreciate Frans for being there for me when needed and his eye for the social side of an AIO's life. It was also Frans who taught me certain pieces of wisdom in life that proved valuable.
I sincerely hope that, one day, Huub's multidisciplinary group will produce its biological solar cell or fuel cell and that I get an invitation for the celebrations.
A group of passing students, AIO's and post-docs would not have been a group at all if Liesbeth, who is far more than just our secretary, had not been present. She is the mother of the SSNMR group and one of the crucial members that keeps it together. Speaking of members who keep the group together, Fons, Johan and Kees taught me the use of advanced NMR spectroscopy. Several times one or more of them have helped me with problems and produced excellent spectra that ultimately led to my analytical protocols for chapter 4 of this thesis. A crucial part of the SSNMR experience was certainly the quality time spent together with colleagues where the terms colleague and friend became indistinguishable. Adriaan, Prashant, Anna, Richard, Ania, Esha, Arjan & Arjan, Shipra, Ido, Niels, Eugenio, Swapna, Ramona, Samira, Piotr and Karthick were all an important part of the good group cohesion SSNMR experienced in Leiden and I already missed those who left before me, and I will miss a lot more after leaving this group. Those were fun times.

After my initial year, changes were forced upon us and the path to be taken was organic synthesis, a relatively new field for me. I am thankful to Thijs for his support during my early work and it hurts that this part of the project was ended prematurely from our side. But events have a way of catching up with us and I became part of a group that had always been close to SSNMR, the BOF group of Johan. It was the cooperation with Johan that finally led to the results, described in this thesis. It cannot be stressed enough that Johan was the one who led me to the work that ultimately became this thesis. Of course, the practical part of this cooperation was largely the responsibility of Rob. We shared the same enthusiasm for old-school chemistry and our lab has always been an interesting place. Besides Rob, of course there is another Rob. He is one of the most helpful people I know and also one of the most social ones. Another helpful neighbour and informal reading committee member is Reinier, colleague and by virtue of coincidence also my coach in the sports centre. He kept us physically fit as well as mentally by his scientific discussions.

During my final year in Leiden, I moved to a lab owned by the BIOSYN group, led by Hermen and Gijs. I had already followed a much needed, comprehensive course in advanced organic chemistry under their dual tutelage. It was with their help that the existing myriad of ideas was expanded with new ideas and channelled into a workable plan.
A lot of gratitude is also due to the chief of my new lab, Richard, who not only accepted me as his charge but also showed me some new lab skills. And then there are the fellow co-workers in my new lab, who are easy-going as well as being generally helpful. Erwin, Amar, Dima and Annemiek are people I will not easily forget. Hardcore chemistry is so much better practiced in a social group than alone in a small lab. But besides thanking all my co-workers, let me mention the AMA’s of both buildings whose efforts to keep our equipment running is highly appreciated by me and everyone else who does any lab work at all.
Special thanks go to mom and dad who were extremely supportive in general and a great help during the more difficult hours of my time in Leiden. Dad’s help and example have been instrumental in getting me to the point where I am defending a scientific thesis of my own.