Selective Synthesis of $\alpha$-Substituted Oligothiophenes

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An improved synthesis of selectively mono- and dibrominated oligothiophenes using the system N-bromosuccinimide/dimethylformamide is reported together with the preparation of the corresponding $\alpha$-alkyl and $\alpha,\alpha$-diacyl derivatives which represent potent biologically active agents.

Oligothiophenes are among the best investigated model compounds for electrically conducting polymers. The stepwise synthesis using defined key building blocks leads to a well-defined structure. On the contrary, the corresponding polymers involve interruptions of the conjugated system due to mislinkages and other defects. $\alpha$-Conjugated thiophene oligomers represent not only intriguing model compounds, moreover, they are frequently applied as semiconducting materials in molecular electronic devices or optical devices. Furthermore, the biological activity of bi- and terthiophenes which frequently occurs in plants belonging to the class of Compositae has launched numerous synthetic efforts. Many of the isolated and synthesized $\alpha$-conjugated oligomers exhibit phototoxic activity against nematodes, larvae and eggs of insects, bacteria, algae, and fungi, respectively. Among this class of compounds, e.g. 5-methyl-2,2':5',2''-terthiophene was found to be particularly effective.

Oligothiophenes monobrominated in $\alpha$-position represent very valuable key building blocks for the defined synthesis of longer $\alpha$-conjugated thiophene oligomers on one hand, and $\alpha$-substituted bi- and terthiophenes on the other hand. In general, the preparation of the mono-substituted compounds is rather difficult. Electrophilic substitution as well as metathesis of the heterocyclic $\pi$-system lead to $\alpha,\alpha$-disubstituted products in considerable amounts. In the case of electrophilic formylation, $\alpha$-functionalized products can be obtained in moderate yields because separation is possible from starting material and the twofold substituted oligothiophene by chromatography.

In this respect, pure $\alpha$-bromobithiophene and $\alpha$-bromothiophene have been synthesized up to now only by indirect methods and in low yields. For example, Rossi et al. obtained 5-bromothiophene by palladium-catalyzed cross-coupling of 5-bithiophenylmagnesium bromide and 2,5-dibromothiophene in 38% yield relative to 5-bromobithiophene, which is produced in 50% yield by analogous coupling of 2-bromothiophene and 2,5-dibromothiophene, respectively. Several research groups therefore investigated the selective monobromination of oligothiophenes using bromine or N-bromosuccinimide in various solvents. Experiments run in our laboratory confirmed that bromination of oligothiophenes with e.g. N-bromosuccinimide in chloroform/acetic acid always results in dibrominated products to a larger extent (25%) which cannot be separated even by multiple recrystallization.

Similarly, the synthesis of $\alpha$-alkyl substituted ter- and quaterthiophenes turns out to be problematic. The direct formation of 5-methyl-2,2':5',2''-terthiophene via methylation of $\alpha$-lithioterthiophene expectantly leads to a mixture of 5-methyl-, 5,5''-dimethylterthiophene, and unreacted starting material. In the series of corresponding quaterthiophenes, 5-methyl-2,2':5',2''-5',2''-quaterthiophene represents the only derivative reported, synthesis and characterization has not been detailed so far. The preparation of symmetrically $\alpha,\alpha$-diacylated oligothiophenes turns out to be somewhat simpler, and higher members of the series up to sexithiophene have been described. Likewise, the series of $\beta$-substituted oligothiophenes has recently been extended up to the dodeca-

$\alpha$-lithioterthiophene. However, due to the synthetic strategy, isomeric mixtures of the various oligomers have been obtained, and the absolute position of the alkyl substituents remains ambiguous.

We now report on the selective synthesis of monobrominated and dibrominated oligothiophenes in high yield and high purity employing the system N-bromosuccinimide/dimethylformamide. The successive reaction of the monobrominated key building blocks with $\alpha$-alkylated bromothiophene results in a series of novel $\alpha$-alkylated and $\alpha,\alpha$-diacylated oligothiophenes.

$\alpha$-Bromosuccinimide dissolved in dimethylformamide has been successfully used in the monobromination of reactive aromatic hydrocarbons. This method has now been applied to the bromination of oligothiophenes, although these heteroaromatic systems exhibit much lesser selectivities. In the Table the product ratios of equimolar bromination of oligothiophenes 1b-d with N-bromosuccinimide/dimethylformamide are presented (Scheme 1).

![Scheme 1](image-url)
Table. Product Ratio for the Reaction of Oligothiophenes 1 with NBS/DMF (homogeneous solution) to the x-Bromoooligothiophenes 2 and Dibromoooligothiophenes 3.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Temp. (°C)</th>
<th>T₄ (%)</th>
<th>Br/T₄ (%)</th>
<th>Br₂T₄ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>2</td>
<td>-20</td>
<td>9</td>
<td>81</td>
<td>10</td>
</tr>
<tr>
<td>1c</td>
<td>3</td>
<td>-20</td>
<td>12</td>
<td>73</td>
<td>15</td>
</tr>
<tr>
<td>1b</td>
<td>3</td>
<td>20</td>
<td>13</td>
<td>72</td>
<td>15</td>
</tr>
<tr>
<td>1c</td>
<td>3</td>
<td>-20</td>
<td>12</td>
<td>84</td>
<td>4</td>
</tr>
<tr>
<td>1d</td>
<td>4</td>
<td>20</td>
<td>20</td>
<td>60</td>
<td>20</td>
</tr>
</tbody>
</table>

* Calibrated by GC.
* Calibrated by HPLC.
* Concentrated solution from which product 2c precipitates.

Evidently, the selectivity of the bromination decreases with increasing chain length of the oligothiophenes. Under these conditions, 5-bromothiophene (2b) is formed in 81% yield. Due to the electronic decoupling of the terminal thiophene rings, the portion of 5-bromothiophene (2c) is reduced to 73%, that of the corresponding quaterthiophene 2d even to 60%, respectively (Table). Lowering the reaction temperature to -20°C does not improve the selectivity which could be demonstrated in the case of terthiophene 1c. On a preparative scale, 5-bromothiophene (2b) is obtained in 70% isolated yield after distillation. The highest yields of pure 5-bromothiophene (2c) (86%) are attained by operating in concentrated solution and by stepwise addition of N-bromosuccinimide in a slight deficit. With this, the desired compound 2c crystallizes from the reaction mixture. In contrast, monobromination of quaterthiophene 1d is problematic since the dibrominated product is instantaneously formed at low turnovers.

Dibromination of oligothiophenes 1 with two equivalents N-bromosuccinimide in dimethylformamide (Scheme 1) proves less difficult. Pure x,x-dibrominated products are isolated in 76–88% yield employing portionwise addition of N-bromosuccinimide and a reaction time of 3 hours at room temperature. Isomeric products which have been found, e.g., for the bromination of terthiophene in the system N-bromosuccinimide/tetrachloromethane, do not occur in detectable amounts under the conditions used. The high selectivity of the bromination towards the x-position allows the synthesis of dibromoquaterthiophene 2d at an elevated temperature which is necessarily due to the low solubility of quaterthiophene 1d. Ultimately, the melting points of all monobromo- and dibromoooligothiophenes synthesized according to our procedure are without exception higher than those reported in literature so far.

Monobromoooligothiophenes 2b,c are ideally suited halogen components in metal-catalyzed Grignard cross-coupling reactions for the assembly of unsymmetrically x-substituted oligothiophenes. Whereas the reaction of x-halothiophenes with alkyl Grignard reagents leads almost exclusively to dehalogenation of the heterocycle, the coupling of aryl or heteroaryl Grignard reagents proceeds smoothly in good yields. In this way, bromooligothiophenes 2b,c were coupled to the novel x-dodecyloligo-
The formation of the novel symmetric α,α-didodecyloligothiophenes 6c,d was likewise realized by the 'Kumada' coupling of two equivalents of Grignard reagent of 5 with dibromothiophenes 3a,b (81 and 61 %, respectively) (Scheme 4). The homologous dialkylbithiophene 6b was isolated in pure form as byproduct (6%) of the reaction leading to alkylthiophene 4c (Scheme 3). Homo-coupling products of this type are formed in metal-catalyzed Grignard cross-coupling reactions to a considerable extent by dimerization of the Grignard reagent. This reaction path represents a side reaction in the catalytic cycle. The related chemical constitution renders them often to components which are difficult to separate.

$$2 \text{H}_2\text{S}_2\text{C}_2\text{Br} + \text{BrS} \rightarrow \text{Ni(dpdp)}\text{C}_2 \rightarrow \text{H}_2\text{S}_2\text{C}_2\text{Br}$$

Scheme 4

Following the above mentioned bromination method, we were able to obtain α-bromooligothiophenes 2 and α,α-di-substituted oligothiophenes 3 in one step and in high yields and purity, respectively. Transition metal catalyzed Grignard coupling reactions of the valuable building blocks lead to novel α-alkylated and α,α-dialkylated oligothiophenes 4 and 6, respectively. The bromination with the system N-bromosuccinimide/dimethylformamide proceeds with unexpected high selectivity also in the case of β-alkylated oligomers allowing the preparation of isomer free dialkylselenothiophene and tetraalkylthiophene, respectively.

1H NMR were obtained with a Bruker AC-F 250 or a Bruker CXP 300 operating at 250 and 300 MHz, respectively. Chemical shifts are measured relative to TMS in CDCl₃ as solvent. Melting points were carried out on Elektrotherm 9100 and Büchi SMP-20 and are not corrected. Preparative column chromatography was performed using glass columns of different size, packed with silica gel A 60, grain size 0.032–0.063 mm (Riedel de Haen). Analytical HPLC was performed with a Shimadzu LC-9A/SPD-M6A instrument fitted with a Nucleosil NO 5 μm column (Knauer). GC were taken on Carlo Erba Auto-HRGC, combined with FID detector EL 580, integrator DP 700 (Spectra-Physics), glass column OV 1701 (20 m), and hydrogen as carrier gas. All experiments were performed under N₂ as inert gas with absolute solvents in flame-dried apparatus. Et₂O was distilled from sodium under N₂, DMF from CaH₂ under N₂; NBS was recrystallized from nitromethane prior to use. The known 2-dodecythiophene (4a) [bp 178–178°C/13 Torr, Lit. 181–182°C/13 Torr; GC > 99%] was prepared analogous to 2-buthylthiophene in 80% yield. All new compounds gave satisfactory microanalyses: C ± 0.25, H ± 0.15, Br ± 0.23, 5 ± 0.25.

5-Bromo-2,2'-bithiophene (2b):
In the absence of light, NBS (44.5 g, 0.25 mol) was added portionwise at −20°C to a solution of bithiophene (41.5 g, 0.25 mol) in DMF (150 mL), and stirred for 4 h, poured onto ice, and extracted several times with CH₂Cl₂. The organic phases were combined, washed with water, and dried (Na₂SO₄). Evaporation of the solvent and fractionated distillation under reduced pressure yielded the yellow solid; yield: 42.8 g (70%); mp 33–34°C [Lit. mp 30–33°C; GC > 97%]. Subsequent recrystallization from MeOH gave 2b in pure form; yield: 33.7 g (55%); mp 34°C (GC > 99%).

1H NMR (300 MHz): δ = 6.91 (1 H, d, 3J₆₋₅ = 3.9 Hz, 3-H), 6.96 (1 H, d, 3J₅₋₄ = 3.9 Hz, 4-H), 6.70 (1 H, dd, 3J₆₋₅ = 5.2 Hz, 3J₅₋₄ = 3.6 Hz, 4-H), 7.10 (1 H, dd, 3J₆₋₅ = 1.1 Hz, 3J₅₋₄ = 3.6 Hz, 3'-H), 7.22 (1 H, dd, 3J₆₋₅ = 5.1 Hz, 4J₅₋₄ = 1.1 Hz, 5'-H).

5-Bromo-2,2':5',2″-terthiophene (2c):
In the absence of light, NBS (3.2 g, 18 mmol) was added portionwise over a period of 2 to 3 d at −20°C to a stirred solution of terthiophene 1c (5.0 g, 20 mmol) in DMF (45 mL). Compound 2c started to precipitate from the reaction mixture after the addition of about 10% NBS. After the last portion of NBS had been added, the suspension was stirred for additional 20 h, poured onto ice, and extracted several times with CH₂Cl₂. The organic phases were combined, washed with water, and dried (Na₂SO₄). Evaporation of the solvent and recrystallization from hexane afforded pure 2c as yellow solid; yield: 5.06 g (86%); mp 141–142°C [Lit. mp 136–137.5°C; (HPLC > 96%).

1H NMR (300 MHz): δ = 6.90 (1 H, d, 3J₆₋₅ = 3.9 Hz, 3-H), 6.97 (1 H, d, 3J₅₋₄ = 3.8 Hz, 4-H), 7.00 (1 H, d, 3J₆₋₅ = 3.8 Hz, 3'-H), 7.02 (1 H, dd, 3J₆₋₅ = 5.1 Hz, 3J₅₋₄ = 3.6 Hz, 4'-H), 7.06 (1 H, d, 3J₆₋₅ = 3.8 Hz, 3'-H), 7.17 (1 H, dd, 3J₆₋₅ = 3.6 Hz, 4J₅₋₄ = 1.1 Hz, 3'-H), 7.23 (1 H, dd, 3J₆₋₅ = 5.1 Hz, 4J₅₋₄ = 1.1 Hz, 5'-H).

5,5'-Dibromo-2,2'-bithiophene (3b):
In the absence of light, NBS (26.6 g, 0.15 mol) was added portionwise at −20°C to a solution of bithiophene (12.3 g, 0.044 mol) in DMF (100 mL), stirred for 3 h, poured onto ice, and the white precipitate was filtered and washed several times with water. Drying over P₂O₅ and recrystallization from abs. EtOAc afforded 3b as white solid; yield: 21.2 g (88%); mp 146°C [Lit. mp 145°C; GC > 99%].

1H NMR (300 MHz): δ = 6.84 (2 H, d, 3J₆₋₅ = 3.9 Hz, 3(3')-H), 6.98 (2 H, d, 3J₆₋₅ = 3.8 Hz, 4(4')-H).

5,5'-Dibromo-2,2':5,2″-terthiophene (3c):
NBS (3.74 g, 21 mmol) was added to terthiophene (2.48 g, 10 mmol) dissolved in DMF (130 mL) and reacted under the conditions given for the synthesis of 3b. After the usual workup 3.96 g (98%, GC > 98%) and subsequent recrystallization from tolune/hexane 3c was isolated; yield: 3.42 g (84%); mp 159–160°C [Lit. mp 156–157°C; GC > 99%].

1H NMR (300 MHz): δ = 6.91 (2 H, d, 3J₆₋₅ = 3.9 Hz, 3(3')-H), 6.98 (2 H, d, 3J₆₋₅ = 3.9 Hz, 4(4')-H), 6.99 (2 H, s, 3(3')-H).

5,5'-Dibromo-2,2':5,2″-quaterthiophene (3d):
NBS (0.356 g, 2 mmol) dissolved in DMF (10 mL) was rapidly dropped to a stirred solution of quaterthiophene (0.330 g, 1 mmol) in DMF (80 mL) at 60°C. After 2 h the solution was cooled to r.t. and poured onto ice. Workup gave 3d as orange solid; yield: 0.37 g (76%); mp 263–264°C (toluene) [Lit. mp 255–256°C].
5-Dodecyl-2,2'-bithiophene (4b):
From 2-bromothiophene (2.61 g, 16 mmol) and Mg turnings (0.41 g, 17 mmol) in EtO (25 mL), the corresponding Grignard reagent was prepared and coupled with bromide 5 (3.31 g, 10 mmol) and Ni(dpppc)Cl₂ (55 mg, 0.1 mmol)²⁴ in EtO (25 mL) and the reaction mixture was refluxed for 6 h. After cooling to r.t., the solution was hydrolyzed with cold 0.5 N HCl and extracted several times with EtO. The organic phases were combined, washed successively with NaHCO₃ solution and water, and dried (Na₂SO₄). Evaporation of the solvent, chromatography (silica gel, 2:1 hexane/CH₂Cl₂), and recrystallization from MeOH/ET₂O afforded pure 4b as bright yellow solid; yield: 0.90 g (87%); mp 38-38.5°C (HPLC > 99%).

5-Dodecyl-2,2':5',2'-terthiophene (6c):
The corresponding Grignard reagent prepared from bromide 5 (8.78 g, 26.5 mmol) and Mg turnings (0.73 g, 30 mmol) in EtO (30 mL), was coupled with 2,5-dibromothiophene 1b (1.94 g, 8 mmol) and Ni(dpppc)Cl₂ (22.3 mg, 0.04 mmol) according to the procedure described for 4c. The reaction time was extended to 64 h in this case. After workup and recrystallization from hexane/toluene (1:2) 6d was isolated as bright yellow solid; yield: 3.87 g (81%); mp 97–98°C (HPLC > 99%).

5-Dodecyl-2,2':5',2'-terthiophene (6d):
From bromide 5 (7.29 g, 22 mmol) and Mg turnings (0.56 g, 23 mmol) in EtO (30 mL), the corresponding Grignard reagent was prepared under heating to reflux for 2 h, and with the aid of an ultrasonic bath and a few drops of dibromoethane as entrainer. The Grignard solution was transferred to the dropping funnel of a second apparatus via cannula and was added dropwise, through a frit, to an ice-cooled suspension of bromobithiophene 2b (4.90 g, 20 mmol) and Ni(dpppc)Cl₂ (110 mg, 0.2 mmol) in EtO (30 mL). The mixture was refluxed for 24 h, cooled to r.t., and hydrolyzed with 1N HCl. The Et₂O phases were separated, neutralized, washed with water, dried over Na₂SO₄, and evaporated. The residue was recrystallized from hexane and was subjected to MPLC (silica gel, hexane). The first fraction afforded pure 5,5'-didecyl-2,2'-bithiophene (6b) as colorless solid; yield: 0.5 g (6%); mp 64–65°C (HPLC > 99%).

5-Dodecyl-2,2':5',2'-quaterthiophene (4d):
Following the conditions given for 4c, the Grignard reagent of 5 (2.83 g, 8.6 mmol) and magnesium turnings (0.22 g, 9 mmol) in EtO (15 mL) was coupled with bromothiophene 2c (1.0 g, 3.1 mmol) and Ni(dpppc)Cl₂ (16.6 mg, 0.03 mmol) in EtO benzene (2:1, 25 mL). After refluxing for 64 h, workup was performed. Chromatography (silica gel, hexane) of the remaining material gave unreacted 2c as the first fraction; by further elution with CH₂Cl₂, the orange-red product was obtained which was recrystallized from benzene to give 4d; yield: 0.91 g (59%); mp 156–158°C (HPLC > 99%).

2-Bromo-5-dodecylthiophene (5):
In the absence of light, a solution of NBS (8.9 g, 50 mmol) in DMF (30 mL) was slowly added dropwise to an ice-cooled solution of 2-dodecylthiophene 4a (12.6 g, 50 mmol) in DMF (30 mL), and the mixture was stirred for 4 h at r.t. Workup and fractionated distillation gave 5 as yellowish solid; yield: 14.5 g (87%); bp 120–125°C/0.01 Torr; (GC > 98%).

1H NMR (250 MHz): δ = 0.88 (3 H, t, J = 6.8 Hz, CH₃), 1.26 (36 H, m, alkyl-CH₂), 1.67 (4 H, m, β-CH₂), 2.78 (2 H, t, J = 7.5 Hz, α-CH₂), 6.67 (2 H, d, J = 3.6 Hz, 4-H), 6.98 (1 H, d, J = 3.7 Hz, J₈₋₉ = 3.6 Hz, 4-H), 7.00 (1 H, d, J = 3.7 Hz, J₈₋₉ = 3.6 Hz, 4-H), 7.03 (1 H, dd, J = 3.6 Hz, J₈₋₉ = 3.6 Hz, 4-H), 7.17 (1 H, dd, J = 3.6 Hz, J₈₋₉ = 1.2 Hz, 3-H), 7.22 (1 H, dd, J = 5.1 Hz, J₈₋₉ = 1.2 Hz, 3-H).

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