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Facilitated synthesis of functional oligothiophenes for application in thin film devices and live cell imaging[†]

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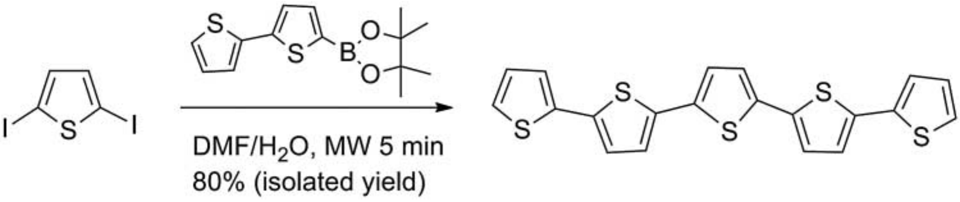
This paper describes recent developments in the synthesis of ultrapure functional oligothiophene-based materials taking advantage of enabling techniques such as microwave/ultrasound irradiation and chitosan-supported palladium catalysts. Examples showing how ultrapure oligothiophenes self-organize in order to optimize charge transport in thin film devices and fluorescence emission inside living cells are reported.



Keywords: oligothiophenes; synthesis; purity; fluorescence; charge transport

1. Introduction

Nanoscience and nanotechnologies rely on the synthesis of innovative materials. Among the new materials successfully developed in the last few decades are thiophene-based oligomers and polymers, which are still of great current interest from a scientific and technological point of view.[1] Thiophene-based materials have numerous useful properties: they are electroactive and fluorescent; are chemically stable and allow a great diversity in molecular structures and functional properties; display ‘plasticity’ in adapting their geometry to the environment in the solid state and in creating supramolecular self-assemblies; and have the capability to finely interact with biologically relevant molecules such as intracellular proteins. They have been extensively investigated for application in organic electronics and more recently in photovoltaics.[1, 2] Much less attention has been devoted so far to the various possible biological applications of these materials such as monitoring protein aggregates at the origin of severe diseases [3] or acting as fluorophores for live cell imaging.[4] Their application in materials science requires that thiophene

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[†] Article for the Special Issue in memory of Professor Alessandro Degl’Innocenti.

derivatives are prepared in a reproducible way in very pure form and in sufficient amount, that they are synthesized in an environmentally safe way, and that their toxicity is accurately monitored.

Over the past few years the most investigated reactions for the preparation of thiophene materials have been the catalyzed cross-couplings between halogenated and metalated thienyls, which allow the regioselective construction of the aromatic backbone starting from functionalized thiophene monomers. The most exploited cross-coupling reactions are palladium-catalyzed Stille [5] and Suzuki–Miyaura [6] reactions. The Stille reaction consists in the coupling of weakly nucleophilic thienyl stannanes with thienyl halogenides (Br, I), generally in the presence of palladium(0) complexes. For the formation of the thienyl–thienyl linkage, the palladium-catalyzed Suzuki–Miyaura reaction uses thienyl boronic acids or esters as nucleophiles in the presence of electrophilic thienyl halides. The boron derivatives are less toxic than the tin derivatives and the reaction is compatible with a great variety of functional groups and reaction conditions. Both reactions are greatly dependent on the steric and electronic characteristics of reagents and catalysts and require careful adjustment of experimental conditions. Alternative methods for thienyl–thienyl bond formation have also been proposed [7] but they often do not posses the versatility of the Stille and Suzuki–Miyaura reactions, which allow the preparation of highly regioregular compounds of the most various sizes and functionalization types via stepwise addition of functionalized units.

In this paper, we describe how the combination of different enabling techniques [8] in the Suzuki–Miyaura reaction in aqueous solvents leads to the expedient, rapid, cost-effective, and environment friendly synthesis of ultrapure oligothiophenes from dimers to hexadecamers useful for applications in supramolecular chemistry and chemical biology.

2. Enabling techniques

Among the various enabling techniques which have been described to speed up synthetic reactions and ease workup and products separation,[8] we have employed microwave and ultrasound irradiation and supported palladium catalysts.

2.1. *Microwave and ultrasound irradiation*

Replacing conventional heating with microwave heating leads to more homogeneous and higher temperatures, faster reaction rates, higher yields, use of aqueous solvents, easy workup, and sometimes regio- and stereoselectivity of reactions.[9, 10] The last decade has witnessed an increasing interest of organic chemists in microwave-assisted reactions, in both research laboratories and industry, which has led to major improvements in equipment quality and parameters control, in particular temperature and pressure. Microwave assistance has been explored in the synthesis of thiophene oligomers in the solid state as well as in solution.[11, 12] Generally, in the presence of microwaves, the formation of the thienyl–thienyl linkage takes place in a very short time, sometimes minutes, and in high yields. The rate of the cross-coupling reaction is accelerated with respect to that of halogen–metal exchange and, in consequence, much less undesired products are formed. The yield of the Suzuki–Miyaura reaction depends on many tunable parameters related to the electronic and steric characteristics of reagents and catalyst, solvent, base, and temperature which are difficult to optimize. Increase of the reaction rate impressed by microwaves irradiation allows a rapid screening of a wide range of conditions to identify the best combination of experimental parameters. Once this is established, thiophene oligomers are rapidly obtained in high yields and in mixtures that can easily be purified.

Ultrasound irradiation enhances the rate of chemical reactions and shortens the reaction times via the process of acoustic cavitation.[13] When ultrasound irradiation is applied during a reaction, pressure and temperature changes displace the system from equilibrium, van der Waals forces are unable to maintain intermolecular cohesion, and small cavities, that is, micro-bubbles, are formed. Formation and collapse of these micrometer-scale bubbles constitute the phenomenon of cavitation. Molecules inside the micro-bubbles experience high temperatures and pressures which can lead to the breaking of the chemical bonds and the consequent return of short-living species to the bulk liquid at room temperature favoring the reactivity. Recently, ultrasound irradiation has been demonstrated to be very effective in the bromination of thiophene oligomers.[14]

2.2. *Chitosan-supported Pd catalysts*

The use of palladium catalysts supported by silicon or chitosan (a water-tolerant polysaccharide) leads to the synthesis of highly pure thiophene oligomers, which are not contaminated by traces of metals that can alter charge conduction and other functional properties.[15] Combining the use of supported catalysts with microwave assistance in the Suzuki–Miyaura reaction resulted in a marked acceleration of the cross-coupling reaction when using iodinated thienyls. [15] We have now implemented the synthesis of a new chitosan-supported catalyst, named CHITCAT-Me, that is characterized by the presence of an additional methyl group compared to the previously described one. The combination of the new catalyst and microwave acceleration in aqueous solvents allows a further reduction of the reaction times – from 1 h or more to few minutes – even when brominated thienyls are used (Table 1). Moreover, as its unmethylated counterpart, this catalyst can be easily removed from the reaction mixture by filtration and reused in consecutive reactions – up to 4 times – without substantial yield variations.

The molecular structure and the synthetic pattern for the preparation of CHICAT-Me using the synthetic modalities already described for its unmethylated counterpart [15] is shown in Scheme 1.

All thiophene oligomers, from bi- to quinquethiophene, are obtained in high yield from iodinated as well as brominated precursors in few minutes in aqueous EtOH or DMF. The conditions employed also favor the rapid and high-yield formation of oligomers bearing a thiophene-*S*,*S*-dioxide unit.

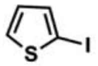
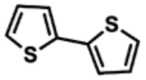
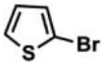
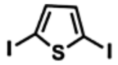
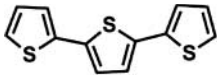
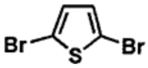
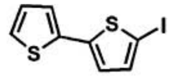
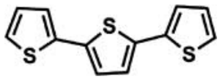
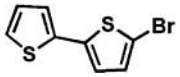
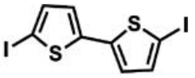
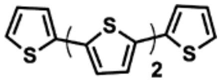
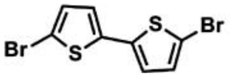
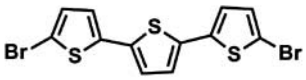
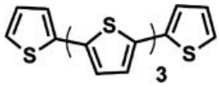
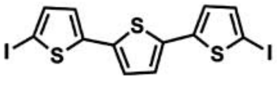
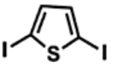
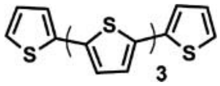
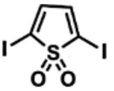
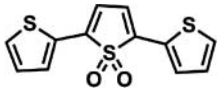
3. Synthesis of ultrapure thiophene oligomers

3.1. *α, ω-Dialkylquaterthiophenes*

Electronics based on organic materials as an alternative to the classical silicon technology has rapidly progressed in the last few years and, owing to synthetic efforts, several polymers and small molecules have been discovered displaying charge mobilities exceeding that of amorphous silicon.[16] The main advantage in using electroactive organic materials is the compatibility with solution processing and low-temperature vacuum evaporation techniques which are much less expensive than the lithographic processes required by silicon technology.

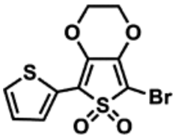
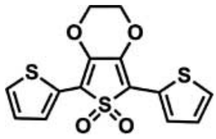
Much interest has been devoted to thiophene oligomers for application in devices such as thin film field-effect transistors (FETs), light-emitting diodes, light-emitting transistors, and photovoltaic devices.[1] They have also been investigated as useful materials for understanding the relationship between the molecular structure and the functional properties and elucidating the fundamental processes underlying charge transport and light emission in organic materials.[17] Among the most investigated thiophene oligomers as active components in thin film FETs are quaterthiophenes, which are excellent semiconducting materials.[18, 19] In particular, it has been demonstrated that the purity of the materials employed is a stringent prerequisite to obtain significantly good charge transport performance.

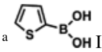
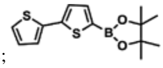
Table 1. Products, reagents and experimental conditions[a] of the reaction of thienyl halogenides boronic acid/ester in the presence of CHITCAT-Me.

Entry	Starting material	Product	Solvent 1:1(v/v)	Microwave[b] irradiation (%) time (min)	Yield[c] (%)
1			$\mathrm{EtOH/H_2O}$	2	100
			$\mathrm{DMF/H_2O}$	2	100
			$\mathrm{EtOH/H_2O}$	6	23
			$\mathrm{DMF/H_2O}$	6	30
2			$\mathrm{EtOH/H_2O}$	3	100
			$\mathrm{DMF/H_2O}$	3	100
			$\mathrm{EtOH/H_2O}$	6	23
			$\mathrm{DMF/H_2O}$	6	22
3			$\mathrm{EtOH/H_2O}$	3	80
			$\mathrm{DMF/H_2O}$	3	90
			$\mathrm{EtOH/H_2O}$	6	68
			$\mathrm{DMF/H_2O}$	6	88
4			$\mathrm{EtOH/H_2O}$	3	78
			$\mathrm{DMF/H_2O}$	3	85
			$\mathrm{EtOH/H_2O}$	2	30
			$\mathrm{DMF/H_2O}$	2	35
5			$\mathrm{EtOH/H_2O}$	12	24
			$\mathrm{DMF/H_2O}$	8	72
			$\mathrm{EtOH/H_2O}$	8	72
			$\mathrm{DMF/H_2O}$	3	86
6			$\mathrm{EtOH/H_2O}$	5	22
			$\mathrm{DMF/H_2O}$	5	80
7			$\mathrm{EtOH/H_2O}$	4	71
			$\mathrm{DMF/H_2O}$	4	81

(*Continued*)

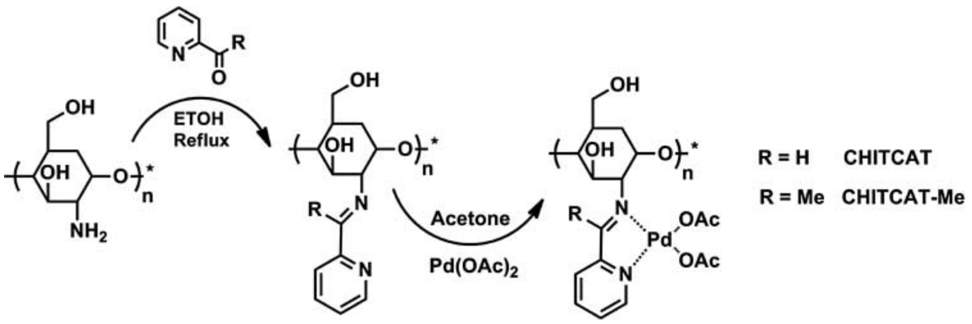
Table 1. Continued.

Entry	Starting material	Product	Solvent 1:1(v/v)	Microwave[b] irradiation (%) time (min)	Yield[c] (%)
8			EtOH/H_2O	4	60
			DMF/H_2O	4	80

[a]  Items 1-5, 7-8;  item 6; halide 1.0 equiv. boronic acid/ester 3 equiv. for monohalide, 4 equiv. for dihalide, 3.5 mol%, CHITCAT-Me, KF 3 equiv. per halide.

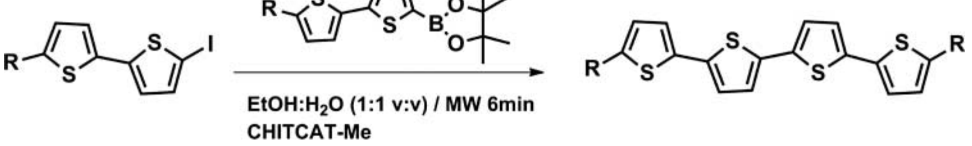
[b] Fixed $T = 140°C$ (power 300 W).

[c] GC conversion with respect to *n*-dodecane as internal standard.



Scheme 1. Molecular structure and synthetic pattern for the preparation of chitosan-supported catalysts CHICAT-Me and CHITCAT.

The title compounds with R $= CH_3, C_4H_9, C_6H_{13}$ – prepared according to the pattern reported in Scheme 2, in highly pure form, metal free, and in yields varying from 75% to 87% – were tested in thin film FETs prepared by vacuum sublimation on a poly(methylmethacrylate), transparent support as gate dielectric. The FETs employed were bottom-gate top-contact devices with gold contacts acting as source and drain electrodes. The active layer – made of ultrapure quaterthiophene – was 10 nm thick. A comparative study of charge transport properties, film morphology, and crystallinity as a function of the alkyl substituents was carried out. It was found that the length of the terminal alkyl chains has a deep impact on the self-assembly process of thin films, hence on charge transport properties.[20]



Scheme 2. Synthetic pattern for the preparation of α,ω-dimethyl; α,ω-di-*n*-butyl and α,ω-di-*n*-hexyl quaterthiophenes using microwave irradiation and chitosan-supported CHITCAT-Me catalyst as enabling techniques.

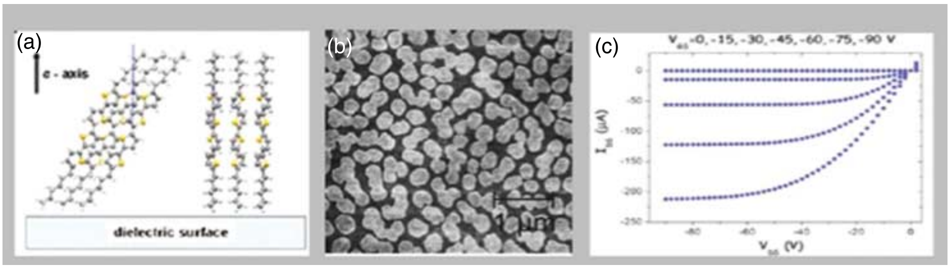


Figure 1. (a) Supramolecular self-assembly as determined from low-angle thin-film X-ray diffraction, (b) film morphology obtained by atomic force microscopy for a film thickness value of 1 nm, and (c) current/voltage output of a thin-film FET having α, ω-di-*n*-hexyl quaterthiophene as the active material.

The di-*n*-hexyl quaterthiophene displays the best charge mobility ($0.09\,\mathrm{cm}^2\,\mathrm{V}^{-1}\,\mathrm{s}^{-1}$) as a result of the interplay of superior supramolecular organization and film morphology (Figure 1).

However, the charge transport properties do not systematically improve by increasing the alkyl chain length. Indeed, di-*n*-butyl-quaterthiophene, having an intermediate chain length of the terminal groups, displays the lowest charge mobility. Also in this case the supramolecular arrangement plays a key role. Indeed, while X-ray thin film diffraction of di-*n*-hexyl- and dimethyl quaterthiophenes shows reflection peaks typical of well-organized and crystalline materials with the molecules aligned with their long axis perpendicular to the substrate, for di-*n*-butyl quaterthiophene no diffraction peaks were observed indicating the lack of crystalline order, an arrangement disfavoring charge transport.

3.2. *Sulfur overrich octa- and hexadecathiophenes*

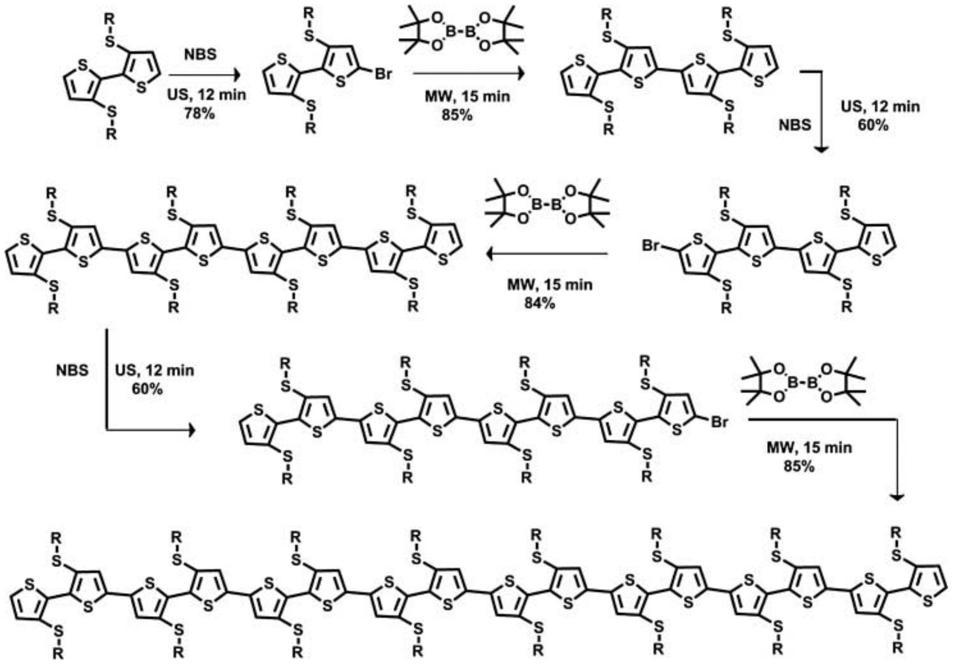
With the aid of microwave and ultrasound irradiation in the Suzuki–Miyaura reaction, we have synthesized thiophene octamer and hexadecamer characterized by the repetition of the 3,3′-bis(hexylthio)-2,2′-bithiophene.[21, 22]

In addition to the fact that long alkyl chains favor solubility and processability, the rationale behind the choice of these oligomers – that we named ‘sulfur-overrich’ because of the presence of one extra sulfur per ring attached to one β carbon – was to understand the effect of intra- and intermolecular S$\cdots$S interactions on the aggregation modalities and the functional properties. The regiochemistry of substitution was of the type called ‘head–head’, a substitution pattern generally avoided since it induces backbone distortions causing a loss of π–π overlap and the formation of amorphous films. In our case, however, the loss of π conjugation is compensated by the donating effect of the β-sulfurs and the aggregation properties into crystalline structures are favored by intra- and intermolecular S$\cdots$S interactions.

The synthesis was carried out by doubling the oligomer size via sequential selective monobrominations using *N*-bromosuccinimide (NBS) and one-pot borylation/cross-coupling reactions using 4,4,5,5-tetramethyl-1,3,2-dioxaborolane in the presence of a palladium catalyst, Pd(dppf)$_2$, according to the pattern described in Scheme 3.

The octamer had the right balance of shape, size, and conformation and the appropriate S$\cdots$S intra- and intermolecular interactions to self-assemble on surfaces in the form of crystalline microfibers that were conductive and electroactive.[21] Most of the fibers were helical in shape as shown in Figure 2. The figure also displays the intense circular dichroism (CD) signal of the film where helical fibers were spontaneously formed on glass.

Since the octamer does not contain chiral centers, no CD signal is observed in solution. Thus, the CD signal observed in film is the result of molecular and supramolecular chirality in the solid state. In other words, it is the result of two contributions: one, due to molecular chirality



Scheme 3. Microwave (MW)- and ultrasound (US)-assisted synthesis of sulfur overrich octamer and hexadecamer. Solvent: THF/water (1:1 v/v); R = C_6H_{13}; isolated yields.

induced by the freezing of the molecule on the surface, and the other, due to the supramolecular organization achieved in the film. The presence of the CD signal and its inversion from one film to the other is probably due to the restrictions to rotation around the thienyl–thienyl interring bond which causes the molecule to loose all symmetry elements (atropisomerism). Once the first molecule is deposited on the surface in the form of one or the other enantiomer, the remaining molecules deposit in the same way causing chiral amplification.

The two different CD signals displayed in Figure 2, reversed in sign, come from two different samples deposited on glass. In agreement with the interpretation given above, the helicity handedness is random. The thickness of the films does not exceed 2 μm, hence the intensity of the CD signal is remarkable.

The thiophene fibers described above are the first examples of conjugate functional fibers displaying the same supramolecular arrangement no matter what the nature of the support on which they were deposited was. Their remarkable thermodynamic stability was ascribed to the S···S intra- and intermolecular interactions related to the regiochemistry of substitution and defining a novel 'recognition algorithm'.[21]

Finally, it must be noted that micrometer-sized fibers, bridging the gap between the microscopic and macroscoping world, are the necessary step toward a bottom-up self-organizing organic electronics.

The hexadecamer was one of the longest thiophene oligomers ever prepared and was characterized by the largest molar absorption coefficient reported so far for thiophene oligomers (95.069 $\mathrm{cm^{-1}\,mol^{-1}}$). Its UV–VIS spectrum and redox potentials were very similar to those of poly(3-hexylthiophene), P3HT. However, contrary to P3HT, the sulfur overrich hexadecamer was very soluble and, being a monodisperse compound, much easier to re-prepare with exactly the same characteristics, including material's purity.

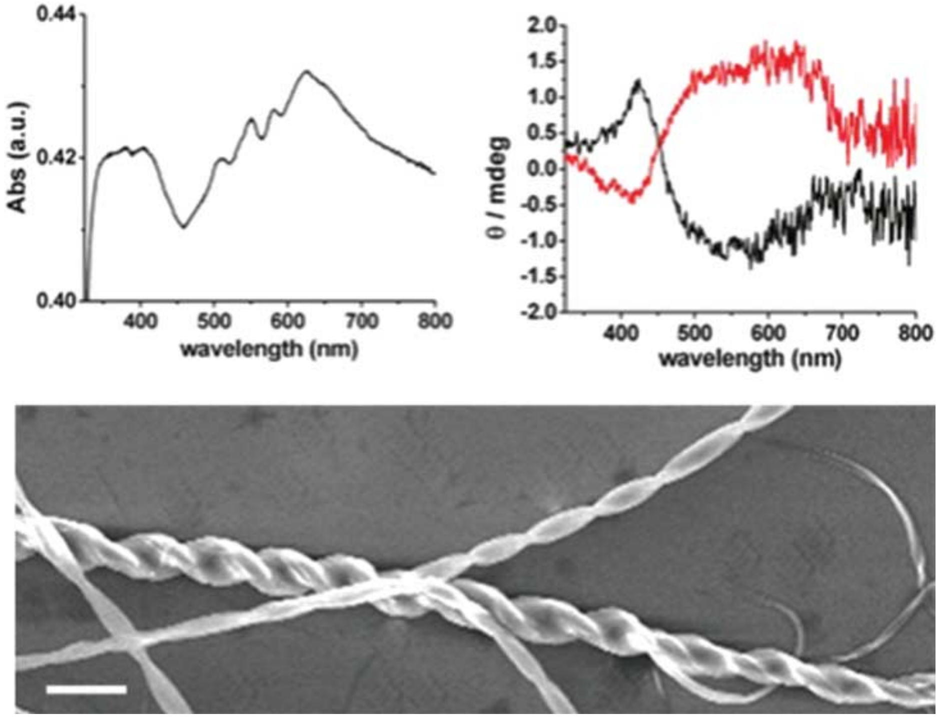


Figure 2. Bottom: Scanning electron microscopy image of helical microfibers spontaneously formed on glass by sulfur overrich octathiophene. Top: Absorption and CD spectra of two different films of the same compound on glass showing CD signals of opposite sign. Scale bar: 25 μm.

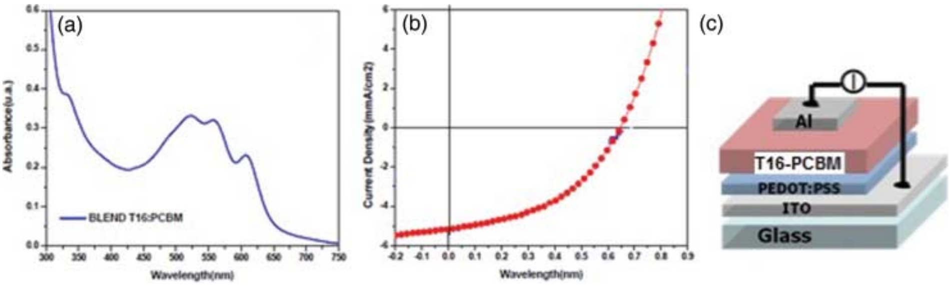


Figure 3. (a) Absorption spectrum and (b) current density/wavelength output of the bulk heterojunction photovoltaic cell with a blend of hexadecamer:PCBM as the active element. The efficiency of light–current conversion of the blend was 1.49%. (c) Sketch of the solar cell embodying the blend of hexadecamer and PCBM as the active element.

The hexadecamer was also an electroactive compound and a charge mobility value of $10^{-5}/10^{-4}\ \mathrm{cm^2\,V^{-1}s^{-1}}$ was reproducibly measured in FET devices.[22]

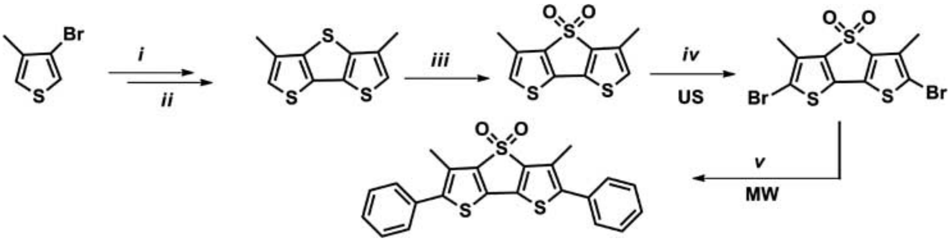
Owing to the HOMO and LUMO energy values similar to those of P3HT, the hexadecamer could be employed in a solar cell (Figure 3).

A bulk heterojunction solar cell with the hexadecamer as electron donor and a fullerene derivative, namely 1-(3-methoxycarbonyl)propyl-1-phenyl[6,6]-methanofullerene (PCBM), as electron acceptor afforded a reproducible light-energy conversion efficiency of 1.49% without any attempt to optimize device fabrication or processing conditions. Figure 3 shows a sketch of the solar cell, the absorption spectrum of a 1:1 (w:w) blend of the hexadecamer and PCBM, and the current density of the device as a function of the wavelength.

3.3. *Dithienothiophene-S,S-dioxide fluorophores*

Currently, fluorescence microscopy is rapidly developing in the field of chemical biology owing to the discovery of innovative classes of fluorescent probes (fluorophores) such as green fluorescent proteins [23] or quantum dots.[24] Several classes of small molecule organic fluorophores have also been developed, among them thiophene-based fluorophores.[4, 25] Since even tiny amounts of undesired contaminants may lead to a drop of the quantum yield – namely the number of photons emitted per photons adsorbed – the fluorophores prepared via organic synthesis must be obtained with the maximum degree of purity.

With the assistance of ultrasounds and microwaves, we have synthesized a few classes of efficient thiophene-based fluorophores.[25] Recently, we have focused our interest on thiophene-based fluorophores capable of spontaneously crossing the membrane of live cells and reveal cellular processes detectable via fluorescence techniques.[4] Scheme 4 reports the synthesis of the most intriguing thiophene-based fluorophore that we have been able to engineer so far, namely 2,6-diphenyl-3,5-dimethyl-dithieno[3,2-b:2′,3′-d]thiophene-4,4-dioxide (DTTO). When obtained in very pure form, the green fluorescent DTTO displays a quantum efficiency on the order of 90%.



Scheme 4. Microwave (MW)- and ultrasound (US)-assisted synthesis of DTTO: (i) bis(tri-*n*-butyltin) sulfide, $Pd(PPh_3)_4$, toluene, 130°C, 90%; (ii) *n*-BuLi, $CuCl_2$, ethyl ether, 0°C, 50%; (iii) 3-chloroperbenzoic acid, CH_2Cl_2, 70%; (iv) 2 equiv. of NBS, CH_3COOH/CH_2Cl_2, US, 80%; (v) tributyl(phenyl)stannane, 5% Pd(PPh3)4, toluene, MW, 80°C, 95%. Isolated yields.

Treatment of living NIH 3T3 mouse embryonic fibroblast cells with DTTO dissolved in physiological solution led first to rapid and uniform fluorescent staining of the cytoplasm of the cells, without low or undetectable labeling of the nucleus. Then bundles of green fluorescent fibrils of micrometer length and sub-micrometric diameter started to be formed and be progressively accumulated into the cell-conditioned medium (Figure 4). Finally, the fluorescent fibers were extruded into the extracellular matrix.[4]

During the entire process, cell viability and proliferation activity remained unaltered while fluorescence was transmitted from mother to daughter cell. Persistence of fluorescence up to 10 days was observed.

Laser scanning confocal microscopy images of independent cell cultures examined at different times revealed that the fluorescent fibrils were synthesized inside the cells and then released as unique supramolecular assemblies through the cell plasma membrane. By means of various experimental data supported by theoretical calculations, it was found that collagen type-I was a structural component of the backbone of the fluorescent fibrils.[4] The protein, which is the main product of the functional activity of fibroblasts, was able to incorporate the dye via molecular recognition between DTTO and the hydroxyproline component of procollagen polypeptide chains and formation of multiple hydrogen bondings. It is known that the structural hallmark of collagen is a rod-like triple helix with a core domain involving the repeating amino acid triplet Gly-X-Y, where Gly is the smallest amino acid glycine and X and Y are most frequently an L-proline and

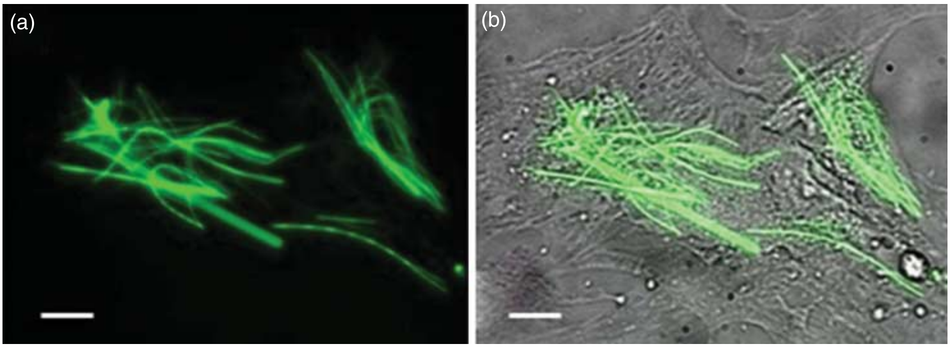


Figure 4. Green fluorescent micrometer-sized fibers formed inside living mouse fibroblasts upon treatment with DTTO in physiological solution and extruded into the extracellular matrix. (a) Laser scanning confocal microscopy image, (b) overlay of image A with that obtained by light transmission optical microscopy showing the underlying cells. Images obtained after 24 h of treatment of the fibroblasts with DTTO and extensive washing to eliminate the free fluorophore. Scale bar: 10 μm.

a 4(R)-hydroxy-L-proline residue, respectively. It has been reported that each glycine amide-NH forms a hydrogen bond with the X-position amide carbonyl on an adjacent strand, whereas the X- and Y-positions stabilize the triple helix by stereoelectronic effects and water-bridged hydrogen bonds. Therefore, it was conceivable that for its peculiar properties, such as the presence of oxygen atoms in the central position and its molecular symmetry, DTTO could have some affinity for interacting with collagen, characterized by a quaternary structure and inherently folded via self-assembly.

4. Conclusions

Preparing functional oligothiophenes in very pure form by means of rapid and environmentally friendly procedures is crucial for the application of these compounds in materials chemistry as semiconductor and fluorescent compounds for electronic and optoelectronic devices as well as for application in cell imaging and monitoring of intracellular processes. The presence of by-products originated by demetalation or dehalogenation of the starting materials or by homo-coupling or boron–halogen exchange side reactions or by the presence of catalyst residues is highly detrimental for their performance in the different fields, altering charge conduction and fluorescence efficiency.

We have demonstrated that the combination of microwave and ultrasound irradiation and/or the use of chitosan-supported catalysts in Suzuki–Miyaura coupling reactions allows the rapid and high-yield preparation of ultrapure oligothiophenes at the best of their functional properties, that is, displaying excellent charge transport mobility and fluorescence efficiency.

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