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A Practical and Efficient Synthesis of Uniform Conjugated Rod-Like Oligomers

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Herein, a more practical and efficient synthesis protocol for the preparation of uniform rod-like oligo(1,4-phenylene ethynylene)s (OPE)s is presented. Applying an iterative reaction cycle consisting of a decarboxylative coupling reaction and a saponification of an alkynyl carboxylic ester, a uniform pentamer is obtained in ten steps with 14% overall yield. The copper-free conditions prevent homocoupling until the trimer stage, resulting in a significantly easier work-up of the products. Homocoupling is observed from the tetramer stage on, but a simple variation of the work-up procedure also yields the uniform tetramer and pentamer. A thorough comparison with the commonly used and described Sonogashira approach reveals that with the new presented strategy, OPEs can be built in similar overall yield, but easier purification and in a quarter of the time. All oligomers are fully characterized by proton and carbon nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), size-exclusion chromatography (SEC), and infrared spectroscopy (IR).

1. Introduction

Recently, the synthesis of uniform macromolecules with defined monomer sequences has gained interest in polymer science.[1] With commonly used polymerization methods, such as for instance controlled radical polymerization, a control over the polymer sequence, but not monodisperse and sequence-defined macromolecules, can be achieved.[2] Hence, recent approaches, based on stepwise iterative synthesis strategies, have been developed and the obtained uniform oligomers serve as model systems for potential applications.[3] For instance, uniform conjugated rod-like oligomers, such as oligo (1,4-phenylene ethynylene)s (OPE)s with their extended pi-conjugation, exhibit interesting properties for optical and electronic applications including biosensors,[4] organic solar cells,[5] light-emitting diods,[6] or molecular wires.[7,8] To achieve the desired function, the precise positioning of building blocks within the oligomer and a thorough investigation of structure property relationships is essential. Several routes for the synthesis of monodisperse OPEs are reported and comprise iterative linear,[9,10] bidirectional,[8,11] or divergent/convergent[12] approaches. Although the molecular weight build-up of the oligomers per iterative cycle in bidirectional and divergent/convergent approaches is faster compared to the linear elongation, these strategies do not provide full control over each repeating unit. The most common approach toward monodisperse OPEs consists an iterative cycle of Sonogashira cross-coupling, followed by deprotection of a trimethyl silyl (TMS) protected triple bond. Using this synthesis method, Tour and co-workers reported different examples, including a linear approach up to a trimer[10] and a bidirectional approach up to a hexamer,[13] using the same building block for every coupling step. In 2018, sequence-definition was introduced by our group, whereby a uniform pentamer with five different side chains was obtained after ten steps in an overall yield of 3.2%.[14] The major limitation was the homocoupling of two terminal alkynes (Glaser reaction), decreasing the yield and complicating purification via silica column chromatography due to almost similar physical and chemical properties of the product mixture. Linear and iterative synthesis procedures are necessary to achieve gradual changes in the electronic level of the OPE via sequence-definition. In this context, we herein developed a new copper-free synthesis strategy to avoid homocoupling, based on a decarboxylative coupling reaction,[15,16] followed by a saponification of an ester protected alkynyl carboxylic acid. The availability of such an alternative system allows a significantly faster synthesis of OPEs with similar yields and purity.

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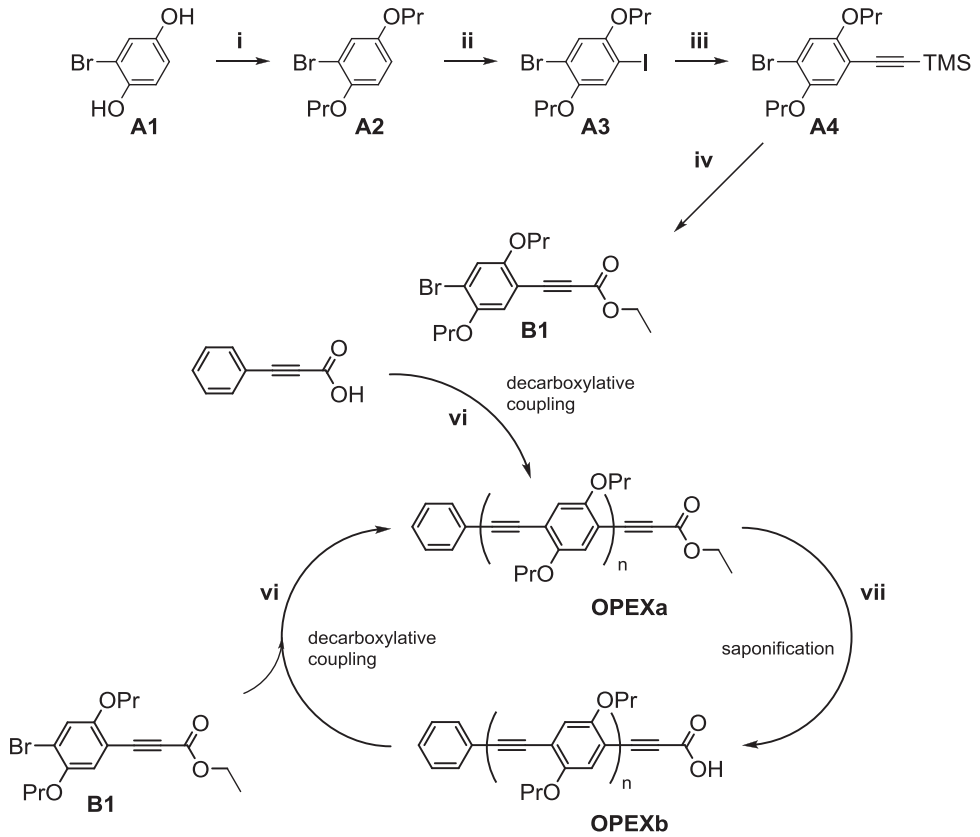

Figure 1. Synthesis procedure toward uniform OPEs. Building block B1 is prepared in a four-step procedure from bromo hydroquinone A1: i) KOH, C3H7Br, EtOH, 80 °C, 2 h; ii) H5IO6, I2, MeOH, 70 °C, 4 h; iii) CuI, Pd(PPh3)2Cl2, C6H15N, 0 °C, 1.5 h; iv) 1) CsF, CO2, DMSO, 3 h; 2) C2H5I, overnight. The respective oligomer esters OPE1a-OPE5a (n = X) and oligomer acids OPE1b-OPE5b (n = X) are synthesized by decarboxylative coupling reaction: vi) SPhos, Pd(dppf)Cl2·CH2Cl2, Cs2CO3, toluene/THF (7:3), 65 °C, overnight; and saponification of the corresponding ethyl esters, respectively: vii) NaOH, THF/MeOH/H2O (3:1:1).

2. Results and Discussion

2.1. Building Block Synthesis

For the synthesis of uniform rod-like molecules, via the strategy outlined in **Figure 1**, a new building block **B1** was synthesized in four steps. Instead of a TMS protected building unit, commonly used for the above mentioned Sonogashira approach, an ester protected alkynyl carboxylic acid was necessary. Starting from bromo hydroquinone **A1**, a Williamson ether synthesis with 1-bromopropane yielded 2-bromo-1,4-dipropoxybenzene **A2**. By treatment with iodine and periodic acid, 1-bromo-4-iodo-2,5-dipropoxybenze **A3** was obtained, which was reacted with trimethylsilyl acetylene in a Sonogashira mono-coupling to the respective bifunctional building block **A4**. In the last step, the TMS protecting group was converted to an ethyl ester via a carboxylation with carbon dioxide, mediated by cesium fluoride in dimethyl sulfoxide and subsequent alkylation with ethyl iodide.[17] Thus, after four synthesis steps, the building block **B1** was obtained in 54% overall yield. Building block **B1**, as well as all intermediates, were characterized by proton and carbon nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR) and mass spectrometry (MS) (Supporting Information).

2.2. Oligomer Synthesis Strategy

The new synthesis concept is outlined in Figure 1. Phenylpropiolic acid was used in the first decarboxylative cross-coupling reaction together with the building block **B1** yielding monomer **OPE1a**. Subsequently, the ethyl ester group was saponified with sodium hydroxide. The resulting alkynyl carboxylic acid **OPE1b** was then reacted in another decarboxylative cross-coupling reaction with **B1**. Repetition of this two-step iterative cycle conjugated rod-like molecules were built up in a linear fashion.

2.3. Oligomer Synthesis

Oligomers (**OPE1a-OPE5b**) were prepared according to the developed synthesis protocol described in Figure 1. The reaction conditions for the decarboxylative cross-coupling were adapted from Li and co-workers.[16] Phenylpropiolic acid was used as starting material in small excess (1.25 eq.) in the first decarboxylative cross-coupling reaction to assure full conversion of the building block **B1**. Similarly, in later coupling reactions, **B1** was used in small excess (1.10 eq.) to guarantee full conversion of the growing oligomer chain. The reactants were placed in a sealed vial and stirred at 65 °C for 20 h under argon

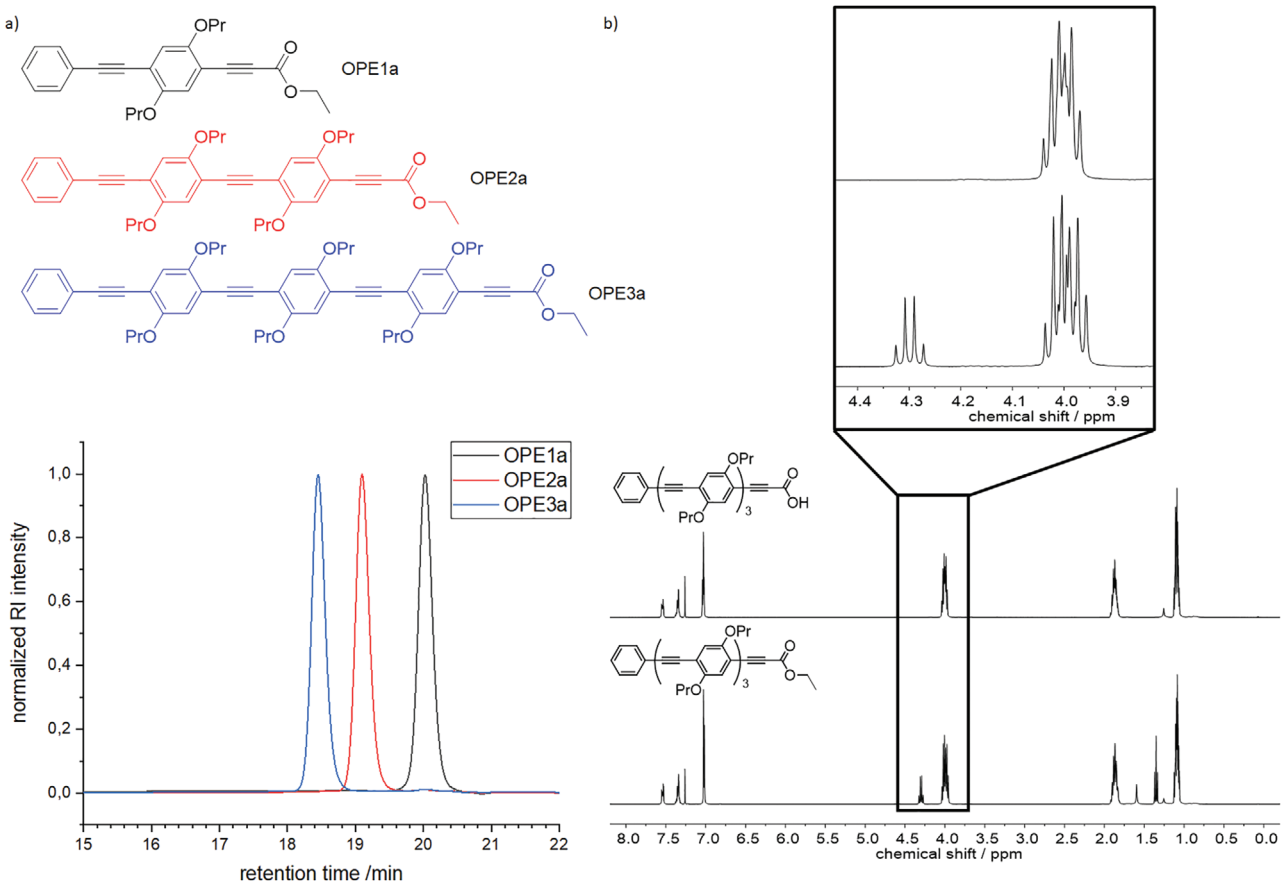

Figure 2. a) Structure of **OPE1a-OPE3a** and their corresponding SEC traces. All oligomers show very high purity; b) ^{1}H spectra of **OPE3a** (bottom) and **OPE3b** (top). The signal of the CH_2 group of the ethyl ester at 4.3 ppm disappears and pure **OPE3b** is obtained after saponification.

atmosphere. The reactions were monitored by thin layer chromatography (TLC). By iteration of the reaction cycle, a uniform trimer was obtained after six steps in an overall yield of 48% in a scale of 386 mg. The oligomers **OPE1a-OPE3a** (**Figure 2**a) were obtained after purification via column chromatography in yields ranging from 68% to 80%. Analysis by proton and carbon NMR, IR, MS, and size exclusion chromatography (SEC) were performed to confirm the respective structures. Monomodal and narrow peaks were observed by SEC analysis, indicating a high purity and uniformity (Figure 2a). After each coupling step, saponifications were performed with sodium hydroxide in a mixture of THF/methanol/water (3:1:1) and the alkynyl carboxylic acids (**OPE1b-OPE3b**) were obtained in quantitative yields. Full conversion was ensured by TLC monitoring and the cleavage of the ethyl ester was observed in the proton NMR spectrum (Figure 2b). The alkynyl carboxylic acids were sufficiently pure after acidification with hydrochloric acid and simple extraction with dichloromethane and were used without further purification for further cross-coupling reactions.

For the synthesis of tetramer **OPE4a**, an additional peak at lower retention times and thus a higher hydrodynamic radius was observed by SEC (**Figure 3**a, blue curve), which could not be separated via column chromatography due to almost similar retention factors. Since no additional signals were observed in the ^{1}H NMR spectrum of **OPE4a**, the formation of a homocoupling product seems to have occurred. The respective mass of the homocoupling product of **OPE3b** was indeed found by electrospray ionization mass spectrometry (ESI-MS), confirming this assumption (see Figure S14, Supporting Information). The reason could be that with growing oligomer length, conjugation is increased, deactivating the acid, and thus leading to a homocoupling process. However, the cross-coupling process was still largely favored and yielded the desired oligomer (Figure 3a). Due to the purification problems, the synthesis strategy had to be adapted and we thus proceeded with the saponification of **OPE4a** to **OPE4b**. While the oligomeric ester **OPE4a** was saponified, the homocoupling product was not affected. The pure alkynyl carboxylic acid **OPE4b** was then obtained after a simple silica filtration column, as the free carboxylic acid moiety resulted in a significantly different retention factor of **OPE4b** in comparison to the homocoupling product. Thus, first the homocoupling product was eluted with pure dichloromethane, and subsequently the eluent was switched to a mixture of acetone and methanol with 1% acetic acid to elute pure **OPE4b** (Figure 3a, green curve). The additional peak of the homocoupled by-product in SEC was observed for the pentamer **OPE5a** as well (see Figure S17, Supporting Information), and the synthesis and purification were performed as described above for **OPE4b**. Thus, **OPE5b** was obtained after ten steps in an overall yield of 14%. In Figure 3b, the SEC traces of all pure

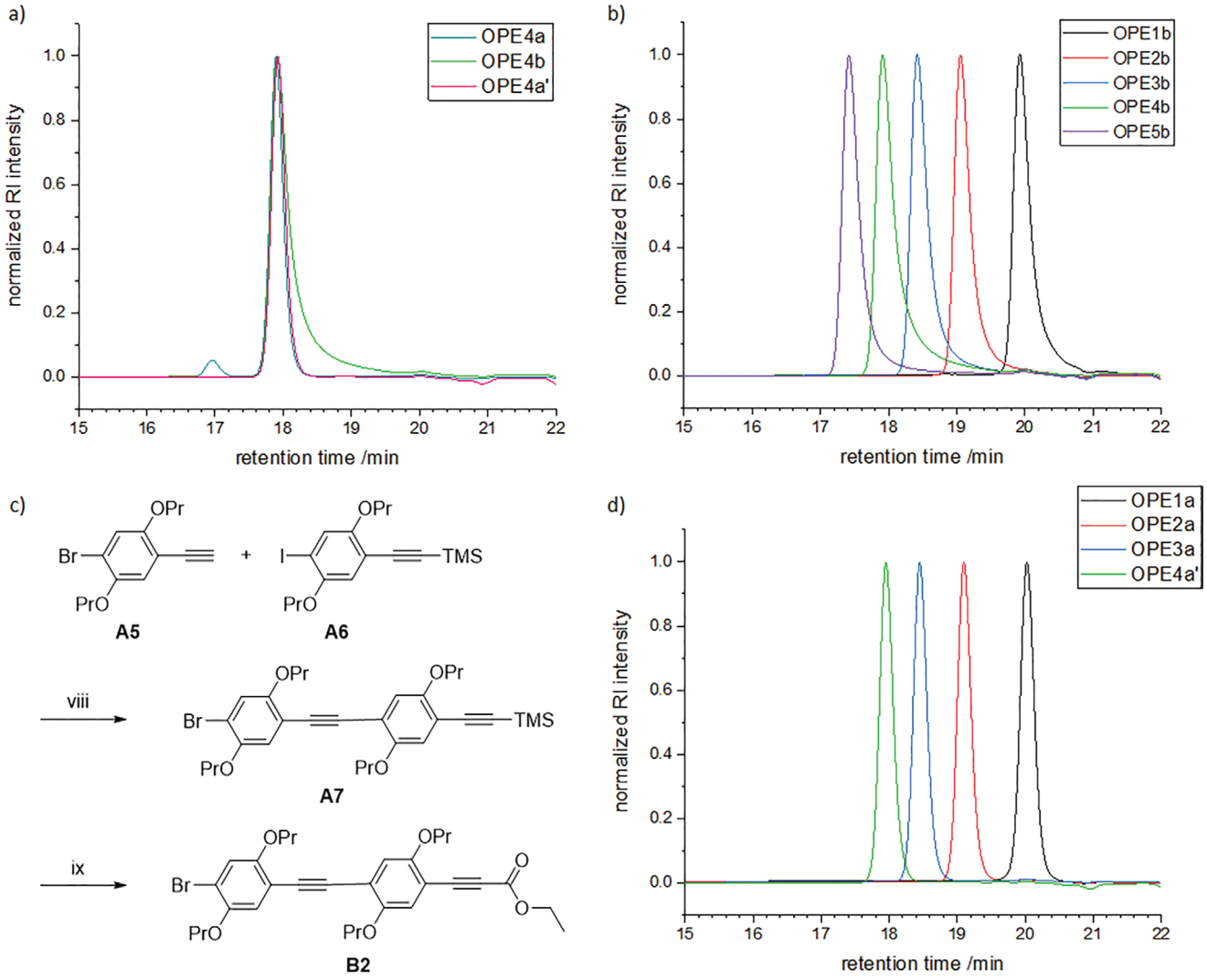

Figure 3. a) SEC trace of the tetramer stage. **OPE4a** (blue curve) shows a peak toward lower retention times (17 min), indicating formation of homocoupling product. After saponification pure **OPE4b** (green curve) was obtained; b) SEC traces of **OPE1b-OPE5b**; c) Synthesis of building block **B2**: (viii) CuI, $Pd(PPh_3)_2Cl$, NEt_3, 0 °C, 1h; (ix) 1) CsF, CO_2, DMSO, 3h; 2) EtI, overnight; d) SEC traces of **OPE1a-OPE3a** and **OPE4a′**; the narrow distribution confirms the high purity.

alkynyl carboxylic acids (**OPE1b-OPE5b**) are displayed. These SECs show tailing toward smaller hydrodynamic radii, which is a result of the free carboxylic acids possibly interacting with the column material. Indeed, the esterified products (**OPE1a-OPE5a**) did not show such a tailing. Thus, also considering NMR as well as MS data, it is reasonable to assume that both the series of esterified oligomers and carboxylic acid terminated oligomers are monodisperse.

To confirm that homocoupling starts at the trimer stage, an alternative synthesis pathway was investigated. Therefore, a building block **B2** introducing two repeat units at once was synthesized (Figure 3c). Then, **OPE2b** was reacted with **B2** and after column chromatography pure **OPE4a'** could be obtained. SEC traces (Figure 3d, green curve) showed no additional peak at lower retention times, indeed confirming that homocoupling starts from the trimer stage on. Advantageously, the oligomers grow faster using **B2**, however, the yield in the decarboxylative coupling reaction decreased to 56%. Generally, homocoupling is a major limitation in the synthesis of monodisperse OPEs, but can now be bypassed by saponification and a simple silica filtration column at any stage.

To clearly demonstrate the advantage of the herein described new synthesis protocol, a thorough comparison in terms of efficiency and working time to our reported Sonogashira approach from 2018 is shown in **Table 1**.[14] A uniform pentamer and a sequence-defined pentamer were synthesized with an overall yield of 18% and 3.2%, respectively. However, the major drawback of this well-established procedure is the formation of homocoupling product via Glaser coupling, which complicates the purification. Separation of the OPE from the Glaser side product via silica column chromatography required up to 2 weeks in the Sonogashira approach and is highly solvent consuming. In Table 1, the results from the Sonogashira coupling approach and the herein presented decarboxylative coupling

Table 1. Comparison of the developed decarboxylative coupling approach and the Sonogashira approach.

	Decarboxylative coupling[a)]	Sonogashira[a)]
Reaction time	160 h	348 h
Purification	7 × column chromatography	12 × column chromatography
Time for purification	68 h	256 h
Overall yield	14%	18%

[a)]Combined numbers over ten reaction steps. For the numbers of each single reaction, see the Supporting Information.

approach are compared regarding time, purification, and overall yield for the uniform pentamer.

The reaction setup for both approaches were very similar. All reactants and solvents were added to a Schlenk flask under an argon atmosphere and stirred for the indicated time. For the decarboxylative coupling approach, a reaction time of 16 h over night was sufficient for any step to reach full conversion of the reactants (TLC). In the Sonogashira approach, a reaction time of 48 or 72 h was needed for the coupling and 16 h for the deprotection step. All ten reaction steps combined resulted in a reaction time of 160 h for the decarboxylative coupling approach compared to 348 h for the Sonogashira approach.

To obtain uniform oligomers, careful purification is essential after each synthetic step. Oligomers obtained from the decarboxylative coupling approach could be eluted significantly faster, since no homocoupling was observed until the trimer stage. After saponification, the alkynyl carboxylic acids were sufficiently pure and were used without further purification. From the tetramer stage on, the alkynyl carboxylic acids were purified via a short and fast to perform silica filtration column, compared to the Sonogashira approach, in which column chromatography is necessary after each coupling and deprotection step. This saves time as well as large amounts of solvents and less waste is produced as a positive side effect. Previously, the oligomers had to be eluted very slowly to assure good separation from the homocoupling product, which is present from the first stage on. Often a second column was necessary to obtain the uniform oligomers. The deprotected oligomers were obtained after column chromatography as well. In total, 12 steps required purification with column chromatography in the Sonogashira approach. In contrast, in the decarboxylative coupling approach, only seven purification steps with faster column chromatography were necessary to obtain the final product.

Hand in hand with the amount of column chromatography is the factor of active working time, which decreases significantly for the decarboxylative coupling approach. Column chromatography in the Sonogashira approach could take up to ten days for one oligomer and purification for all ten steps took around 256 h in total. Since less purification steps via column chromatography were performed and the oligomers can be eluted much faster in the decarboxylative coupling approach, the time for purification decreases to around 68 h, which is approximately a quarter of the time and makes the newly developed approach much more time efficient.

Regarding the yield, the decarboxylative coupling approach shows yields ranging 68–85% for all coupling steps. The length of the OPE chain does not seem to have a significant influence on the coupling reaction until the trimer stage. However, starting with the tetramer, the formation of the homocoupling product decreases the yield of the desired OPEs marginally. The Sonogashira coupling shows a continuously decreasing yield with a growing OPE chain, since the oligomers are more prone to undergo homocoupling. After 10 steps, a uniform pentamer is obtained with an overall yield of 14% for the decarboxylative coupling approach and 18% for the Sonogashira approach.

Conclusion

In summary, we developed a new linear synthesis strategy consisting a decarboxylative cross-coupling and a saponification for the synthesis of OPEs. The obtained oligomers show high purity as evidenced by proton and carbon NMR, MS, IR, and SEC. Homocoupling was avoided until the trimer stage. In case of homocoupling, observed from the tetramer synthesis stage onwards, two possible alternative pathways were presented. A uniform pentamer was thus obtained after 10 steps with an overall yield of 14%. Furthermore, the results are compared to the commonly used Sonogashira approach. With the new approach, OPEs can be obtained in a similar overall yield, with less purification and within a quarter of the time. Since the oligomers are built up linearly by adding one building block at a time, the approach can be extended to sequence-defined oligomers in the future for tailoring characteristic properties for possible optical and electronic applications.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Data Availability

Data available in article supplementary material.

Conflict of Interest

The authors declare no conflict of interest.

Keywords

oligo(1,4-phenylene ethynylene)s, decarboxylative coupling, oligomers, sequence-definition

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