Polar tagging in the synthesis of monodisperse oligo(p-phenyleneethynylene)s and an update on the synthesis of oligoPPEs

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Abstract

One important access to monodisperse (functionalized) oligoPPEs is based on the orthogonality of the alkyne protecting groups triisopropylsilyl and hydroxymethyl (HOM) and on the polar tagging with the hydroxymethyl moiety for an easy chromatographic separation of the products. This paper provides an update of this synthetic route. For the deprotection of HOM protected alkynes, $\gamma$-MnO$_2$ proved to be better than (highly) activated MnO$_2$. The use of HOM as an alkyne protecting group is accompanied by carbometalation as a side reaction in the alkynyl–aryl coupling. The extent of carbometalation can be distinctly reduced through substitution of HOM for 1-hydroxyethyl. The strategy of polar tagging is extended by embedding ether linkages within the solubilising side chains. With building blocks such as 1,4-diiodo-2,5-bis(6-methoxyhexyl) less steps are needed to assemble oligoPPEs with functional end groups and the isolation of pure compounds becomes simple. For the preparation of 1,4-dialkyl-2,5-diiodobenzene a better procedure is presented together with the finding that 1,4-dialkyl-2,3-diiodobenzene, a constitutional isomer of 1,4-dialkyl-2,5-diiodobenzene, is one of the byproducts.

Introduction

Oligo(p-phenyleneethynylene)s (oligoPPEs) have been frequently used as structural units for nanoscopic molecules because of their geometry and their electronic and photophysical properties [1-19]. For their preparation three widely used synthetic routes have emerged:
2. The divergent-convergent Moore–Tour-route (Scheme 2a) [26-29] which employs the diethyltriazenyl group to mask an iodo substituent [30,31]. 1-(Diethyltriazenyl)-4-(2-trimethylsilylethynyl)benzene is the parent compound. Desilylation and exchange of the triazeny substituent for an iodo substituent are the two divergent steps followed by the alkynyl–aryl coupling, the convergent step. The dialkyltriazenyl group decomposes during chromatography on silica gel [28].

3. The divergent-convergent route which makes use of the orthogonality of the two alkyne protecting groups triisopropylsilyl (TIPS) and hydroxymethyl (HOM) (Scheme 2b) [32]. The reaction sequence starts with the HOM and TIPS protected 1,4-diethynylbenzene 1a from which the monoprotected 1,4-diethynylbenzenes 2a and 3a are derived by the removal of either the HOM or the TIPS group. The HOM protected 1,4-diethynylbenzene 3a is coupled with 1,4-diiodobenzene to obtain aryl iodide 4a. This is coupled with the TIPS protected 1,4-diethynylbenzene 2a in the convergent step. It has been shown that HOM can be exchanged for 1-hydroxy-1-methylethyl (2-hydroxyprop-2-yl, HOP) [33-38].

A rather rarely utilized third divergent-convergent approach (Scheme 2c) [39-41] relies on the bromo iodo selectivity of the alkynyl–aryl coupling and bromo iodo exchange via halogen metal exchange.

The principles underlying these methods have been applied to building blocks with additional substituents including func-
tional groups as well as to other aromatic building blocks, such as biphenyl [33], bipyridine [36,42], thiophene [36,43,44], fluorene [45], and triptycene [46], and other shapes, e.g. starlike compounds [2,7,12,34,37].

The divergent-convergent route that employs the two orthogonal alkyne protecting groups TIPS and HOM (Scheme 2b) does not only allow the fast growth of oligomers – only four steps for doubling the number of repeating units with two of the four steps being experimentally extremely simple – but is especially satisfying because of a trouble-free separation of the desired alkylnyl–aryl coupling product and the accompanying oxidative alkyne dimerization product (Glaser coupling product). In our experience, under the standard coupling conditions – i.e. Pd(PPh$_3$)$_2$Cl$_2$, Cul, piperidine, THF, room temperature – Glaser coupling is much faster than the alkylnyl–aryl coupling. Therefore, even traces of oxygen in the reaction vessel will lead to alkyne dimerization. Furthermore, most experimentalists prefer to work up the reaction mixtures under standard conditions which means exposing the reaction mixture to air. Opening the flask will immediately cause any unreacted terminal alkyne to undergo Glaser coupling. This is of no concern provided the alkyne dimer and the alkylnyl–aryl coupling product can be easily separated, and this is what the HOM and related HOP group guarantee since they act as polar tags for the chromatographic separation. Polar tagging with HOM [47-49] or HOP [34,42,45,50-57] has been the key to the successful syntheses of a variety of aryleneethyne building blocks and oligomers [42,45,47-52] and of oligoeneynes [53] including the natural marine compound callyberyne [54].

Since we disclosed this strategy several years have elapsed during which time we have gained more experience with it, became aware of some problems concerning it and improved it. Because the strategy has been adopted in whole or in part by other groups [33,34,47,49,58,59] and oligoPPEs are still a topic of great interest [1-19], we would like to share our results and present an update and an extension of our route in this paper. There are four issues that we want to address: (1) The type of MnO$_2$ used for the removal of the HOM group, (2) carbometalation, a side reaction when using hydroxymethyl as an alkyne protecting group, (3) purity of 1,4-dihexyl-2,5-diiodobenzene, and (4) polar tags in the side chains of building blocks to reduce the number of steps in oligomer synthesis.

**Results and Discussion**

**Type of MnO$_2$ used for alkyne deprotection**

The original paper on the oxidation-decarbonylation of HOM-protected alkynes [60,61] through treatment with MnO$_2$ and powdered KOH does not contain any details about the type of MnO$_2$. We applied this method to the synthesis of oligoPPEs, only exchanging benzene for diethyl ether, and obtained satisfactory results with commercially available active MnO$_2$ (Aldrich) [32]. However, the deprotection of the HOM-protected arylalkynes 1$_{a_1}$ took several hours, especially when the reaction was run on larger scale, i.e. with 500 mg or more of starting material [62]. Even more annoying was that the required reaction time varied drastically from one experiment to another. The best procedure was to add portions of a mixture of MnO$_2$ and KOH in intervals of 15 to 60 minutes until the reaction was complete. The reaction can be easily monitored by thin layer chromatography.

To improve the procedure, we tested the activated MnO$_2$ (purchased; Aldrich), highly activated MnO$_2$ (self-made) [63-65], BaMnO$_4$ (purchased) [66-68], and γ-MnO$_2$ (self-made) [63,64] on 3-(4-bromophenyl)prop-2-ynol in the presence of powdered KOH in diethyl ether at room temperature. The reaction with γ-MnO$_2$ was the fastest. Even more important, γ-MnO$_2$ when applied to the oligomers 1$_{a_1}$ proved to be highly reliable in its oxidizing power making it the reagent of choice for the removal of HOM groups. Some experimental results hint at a reduced activity of γ-MnO$_2$ after it was stored for more than half a year in a closed jar under ambient conditions.

**Carbometalation**

When we published the synthesis of oligoPPEs via the divergent-convergent route which is based on the orthogonality of the alkyne protecting groups TIPS and HOM, we reported the carbometalation product 5a (Scheme 3) which formed as a side product in the coupling of iodo monomer 4$_{a_1}$ with TIPSEthyne [32]. In the original procedure a reaction temperature of 50 °C was employed. Much later we found that the reaction goes to completion even at room temperature. Lowering the temperature reduced the amount of the carbometalation product 5a from 2–16% to 1–5%. Nevertheless, large scale preparative chromatographic separation on silica gel is tedious. Carbometalation product 5a and monomer 1$_{a_1}$ have very similar $R_f$-values and, unfortunately, the byproduct is eluted first.

Luckily, contamination of monomer 1$_{a_1}$ with carbometalation product 5a is of no concern if this material is used to prepare the TIPS protected 1,4-diethylbenzenes 2$_1$ (Scheme 3). Under standard reaction conditions – γ-MnO$_2$, powdered KOH, Et$_2$O, room temperature – the alcohol groups of both compounds 1$_{a_1}$ and 5a are oxidized. Whereas the oxidation product of 1$_{a_1}$, aldehyde 8$_{a_1}$, reacts with KOH to give the ethynyl anion and formic acid which immediately exchange a proton providing deprotected alkyne 2$_1$, the oxidation product of 5a, aldehyde 6a, is inert under the reaction conditions [69,70]. This finding is attributed to the higher energy content and therefore lower nucleofugicity of a vinyl anion as compared to an ethynyl
anion. The products, alkyne 2 and the oxidized carbometalation product 6a, are easily separable by chromatography, which resembles a simple filtration through silica gel because 6a stays anchored on the solid phase through its polar carbonyl group. In this way pure alkyne 2 can be obtained even if carbometalation product 5a is present in the starting material.

The case is quite different when monomer 1a is used as the precursor for the HOM protected 1,4-diethynylbenzene 3a. Treatment of a mixture of 1a and 5a with n-Bu₄NF will not only remove the TIPS group of 1a but also the two TIPS groups of 5a (Scheme 3). The two products are as difficult to separate as the starting compounds. Furthermore, the ethynyl groups of both products are expected to have the same reactivity which can make the isolation of pure compounds of subsequent coupling reactions even more challenging. Finally, we found that carbometalation not only occurs during the preparation of monomer 1a and its trimethylsilyl (TMS)-analogue but also, even though extremely rarely, at later stages of the oligoPPE synthesis. For example, on one occasion we isolated compound 9a (2%, isolated yield) from the reaction between alkyne 2 and iodo monomer 4a which gave dimer 1a as the major product (79%, isolated yield) (Scheme 4).
In other reactions of this type, the carbometalation product may have remained undetected due to the limited sensitivity of $^1$H NMR spectroscopy, which we use as a routine method to assess the composition of the crude product and the chromatographic fractions, although the characteristic triplet at 6.38 ppm ($J = 7$ Hz) [71] arising from the vinyl proton of the carbometalation products is easily observed. If the $^1$H NMR spectrum displays the carbon satellites of an aromatic proton signal from the major product, the threshold for detection the carbometalation product is as low as 0.5%.

While compiling records on carbometalation of hydroxymethyl protected arylalkynes we never found any evidence for carbometalation of TMS or TIPS protected arylalkynes, even when conducting the aryl–alkyne coupling at 50 °C [72-75]. Possibly, the OH-group of the HOM group coordinates to the alkyne loaded Pd(II)-complex and thus acts as a directing and rate increasing group. It may as well be that the bulky trialkylsilyl substituents simply act as steric shields for the arylalkyne. If the latter is true, then the use of 1-hydroxyethyl (HOE) or HOP instead of HOM as polar protecting groups for alkynes could prevent carbometalation. Although HOP is a sterically more demanding group, we decided in favor of HOE because the removal of HOP requires refluxing in toluene for several hours in the presence of sodium hydride or potassium hydroxide [34,36-38,42,50-52,76] whereas we expected that HOE could be detached through treatment with $\gamma$-MnO$_2$ and powdered KOH in diethyl ether at room temperature. This is illustrated for the conversion of hexamer 1b$_6$ and heptamer 1b$_7$ into the alkynes 2$_6$ (98% isolated yield) and 2$_7$ (90% isolated yield), respectively.

Iodination of 1,4-dihexylbenzene

The preparation of 1,4-di-hexyl-2,5-diodobenzene (10a) by the iodination of 1,4-diethylbenzene with a mixture of iodine and potassium iodate in HOAc, H$_2$SO$_4$, and water at 70 °C [32,77,78] gave variable yields and on occasions failed. We obtained 10a much more reliably via iodination with iodine and periodic acid in HOAc, H$_2$SO$_4$, water, and dichloromethane at 70 °C [79,80]. Dichloromethane probably acts as a phase compatibiliser. Nevertheless, the reaction never went to completion: In all cases monooiodination product 11a was found (Scheme 5). Additionally, irrespective of which procedure was followed, the crude product always contained 1,4-diethyl-2,3-diodobenzene (12a) (ca. 3%), a constitutional isomer of 10a. The structure elucidation of these byproducts based on $^1$H NMR spectra is outlined in Supporting Information File 1.

Iodination of 1,4-dihexylbenzene.

Scheme 5: Iodination of 1,4-diethylbenzene.

At least twofold recrystallization is needed to obtain material which contains less than 0.5% of these byproducts (as determined by $^1$H NMR spectroscopy. The $^{13}$C-satellites of the signal of the aromatic protons of 10a were used as the reference). Whereas monooiodination product 11a is of minor concern because it is monofunctional, the constitutional isomer 12a is a severe threat to the structural purity of oligoPPEs and especially polyPPEs. To illustrate this point let us assume that 10a and thereof derived 1,4-diethynyl-2,5-diethylbenzene, both contaminated with only 0.1% of the respective constitutional isomers, are polymerized to give a polymer batch with an average polymerisation degree of 1000. The consequence is that on average each of the polymer chains in this sample will have a kink, i.e. a severe structural defect.
Polar tags in the side chain
In spite of its efficiency, the divergent-convergent synthesis of oligoPPEs involves considerable effort, especially as a result of the chromatography which is required after each alkynyl-aryl coupling. In the case of the synthesis of oligoPPEs with terminal functional groups, it is tempting to reduce the number of steps through the coupling of a diodo compound with oligoPPEs which carry one functional group and have about half of the number of repeating units of the target compound. To give one concrete example (Scheme 6): Starting from $1_{a3}$

![Scheme 6: Different routes to compound 14, a representative of the large group of functionalized oligoPPEs.](image-url)
the synthesis of 14a through the coupling of 13 with diodobenzene 10a (Scheme 6, route A) requires only two alkynyl–aryl couplings (four steps overall), whereas the alternative (Scheme 6, route B) via heptamer 1a7 would take three or four cross coupling reactions (seven or eight steps overall) [81,82].

However, all of these routes will be plagued by the difficulty in separating 14a from the accompanying alkyne dimer (Glaser coupling product). These two products differ only in the number of repeating units. In our experience with functionalized oligoPPEs their chromatographic properties on silica gel are very weakly influenced by the number of the non polar repeating unit, 2,5-dihexyl-1,4-phenyleneethynylene, but dominated by the polar functional groups. Therefore, if the two products differ in the number of polar groups, chromatographic separation can become easy. This idea was put to the test for the shortest route, route A, by employing methoxyhexyl substituted diodobenzene 10b instead of hexyl substituted diodobenzene 10a. The two methoxy groups influence the chromatographic behaviour distinctly ($R_f(14b) = 0.29$, $R_f(15) = 0.71$; silica gel, CH$_2$Cl$_2$/n-pentane 6:4). The oxygen atoms are intentionally inserted remote from the polyconjugated backbone in order not to change the optical properties of the oligomers.

Polar tagging with e.g. the rather inert ether moiety within the side chains at a site distant from the backbone appears to us a generally useful concept for the synthesis of mesoscopic molecules which very often have unbranched or slightly branched alkyI substituents present for solubility reasons.

Supporting Information
Supporting information features the syntheses of compounds used for the discussed experiments, the detailed experimental procedures, and the structure elucidation of the products from the iodination of 1,4-dihexyIbenzene.

Supporting Information File 1
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-57-S1.pdf]

Acknowledgements
Financial support by DFG (GO 555/4-3) is gratefully acknowledged.

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Another stepwise approach consisting of coupling with 4-iodobenzenaldehyde and conversion of the aldehyde group into an ethyne moiety via the Corey-Fuchs reaction.
The use of the triflate group for the alkynyl–aryl coupling and its masking as the precursory OH group offers an alternative that was applied to the synthesis of phenyleneethynylene dendrimers [31], however, not (yet) to the synthesis of oligoPPEs.

We like to call attention to the recent reports that trimethylsil and HOP are orthogonal alkyl protecting groups which make HOP a very interesting protecting group [36,37]. The same is true for tert-butyltrimethylsil and HOP [38].

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69. Experimental proof: Carbometalation product 5a was treated with γ-MnO2 and powdered KOH in diethyl ether at room temperature. The 1H NMR spectrum of the crude product shows unambiguously the signals of the expected aldehyde 6a. There are no signals that fit to the characteristic signals of the unsymmetrically 1,1-disubstituted alkene 7, the product in case 6a had lost the formyl group.

The two sets of 1H NMR signals in an intensity ratio of 22:1 for the aryl protons, the aldehyde proton, and the vinyl proton indicate a mixture of E- and Z-alkene. Alkene isomerization upon oxidation with MnO2 has been reported [70]. The alkene isomerization can also be explained by a reversible addition of hydroxide to the electron acceptor substituted alkene of aldehyde 6a. Characteristic signals of the major isomer: δ = 9.38 (d, J = 8.2 Hz, 1 H, CHO), 7.32 and 7.00 (2 s, 1 H each, ArH), 6.47 (d, J = 8.2 Hz, 1 H, C=CH). Characteristic signals of the minor isomer: δ = 10.28 (d, J = 8.2 Hz, 1 H, CHO), 7.30 and 7.09 (2 s, 1 H each, ArH), 6.31 (d, J = 8.2 Hz, 1 H, C=CH).
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71. Characteristic $^1$H NMR signals of the carbometalation product $9a$ in CDCl$_3$: $\delta = 7.37, 7.31, 7.29, 7.22, 7.17, 6.98$ (6 s, 1 H each, ArH), 6.38 (t, $J = 7$ Hz, 1 H, C=CHCH$_2$OH), 4.06 (t-shaped signal, slightly broadened, $J = 6$ Hz, 2 H, CH$_2$OH).

72. We know of only two publications that report on carbometalation of 1-aryl-2-trialkylsilylethynes [73,74]. The carbometalation reported in [73] is possibly induced by the hydroxy group of the hydroxymethyl substituent in ortho-position to the 2-(trimethylsilyl)ethynyl group. Note also the related Pd-catalyzed addition of TMSethyne onto Z-(2-(2-trimethylsilyl)ethynyl)-3-trimethylsilylprop-2-enol in [75].

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