ORGANIC LETTERS

2013
Vol. 15, No. 2
374–377

Repetitive Synthetic Method for *o,o,p*-Oligophenylenes Using C−H Arylation

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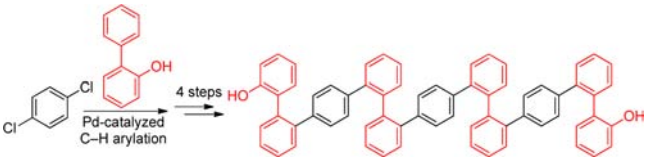
Received December 5, 2012

ABSTRACT



A synthetic method for the preparation of *o,o,p*-oligophenylenes has been developed. It involves Miura's C−H arylation of 2-biphenols with aryl nonaflates as the key step. Oligophenylenes with defined lengths are successfully synthesized using this method.

Oligophenylenes, which are composed of benzene rings connected through a single bond, constitute an important class of oligomers[1] and are widely used architectures in electronic devices[2] and as self-assembling molecules,[3] biologically active compounds,[4] and catalytic molecules.[5] However, the ability to design and synthesize oligophenylenes with well-defined secondary structures, except for helix-forming *o*-[6] and *m*-oligophenylenes,[3d] in which benzene rings are connected only at the *ortho*- and *meta*-positions, respectively, is still in a primitive state. We seek to construct a new type of secondary structure using the proper combinations of the possible connectivities (*o*-, *m*-, and *p*-). Preliminary investigations of the combinations by the Merck Molecular Force Field (MMFF) molecular mechanics method[7] revealed that *o,o,p*-oligophenylenes, unknown in the literature,[8] adopt a helical conformation with six benzene units per helical turn (Figure 1; the structure was optimized using density functional theory (DFT) calculations[7,9] after a conformational search at the MMFF level).[10] This folding structure maximizes stacking and T-shape contacts among benzene rings and provides novel scaffolds for the development of functional molecules. To explore the chemistry of this oligomer, it is necessary to develop a method that enables the efficient synthesis of oligomers with a specific chain length and substituents at the desired positions.[11] Herein, we describe a versatile method of *o,o,p*-oligophenylene

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10.1021/ol303327k
Published on Web 01/04/2013

synthesis for preparing a variety of oligomers for further research.

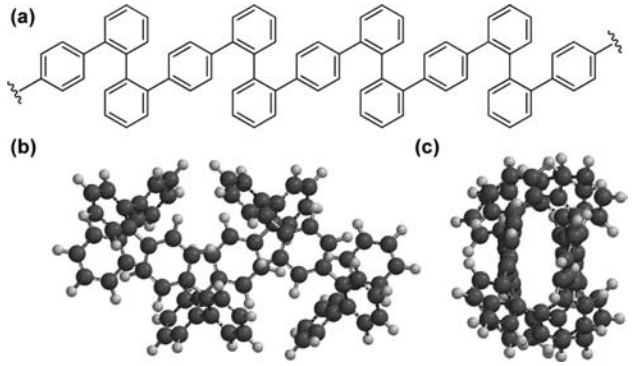
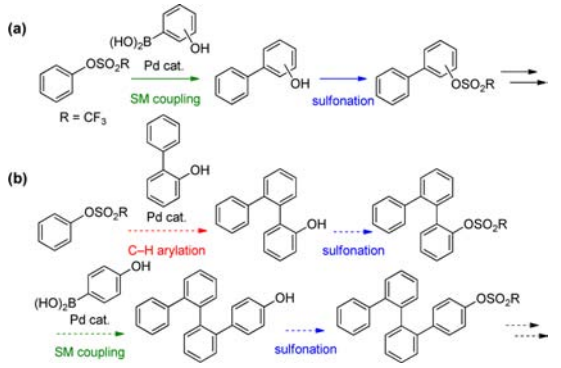


Figure 1. (a) *o,o,p*-Oligophenylene. (b) Side view of the DFT (B3LYP/6-31(d))-optimized structure of a 13-mer. (c) Top view.

Previously, we developed a synthetic method for the preparation of oligophenylenes via repetitive Suzuki–Miyaura (SM) coupling[12] of hydroxyphenylboronic acids and sebsequent triflation of the hydroxy group to afford oligophenylenes with a specific chain length and substituents at the desired positions (Scheme 1a).[13] On this basis, we designed a new synthetic route to *o,o,p*-oligophenylenes. It involves C–H arylation of 2-biphenols, developed by Miura et al.,[14] as the key step in the construction of an *o,o*-connected moiety. Repetition of C–H arylation and the subsequent sulfonation/SM coupling (with a *p*-hydroxyphenylboronic acid)/sulfonation procedure gives *o,o,p*-oligophenylenes (Scheme 1b). Since using biphenols instead of boronic acids is a more atom-economical approach, this method is superior to the previous one.

Scheme 1. Repetitive Synthetic Methods of Oligophenylenes



(a) Our previous method for oligoarene synthesis. (b) Method involving C–H arylation of 2-biphenol as a key step.

Miura et al. reported arylation at the 2′-position of 2-biphenol with aryl iodides or bromides in the presence of a Pd catalyst and a base.[14] To apply this reaction to our synthetic scheme, it was much more beneficial to use aryl sulfonates such as triflates, as the arylating agents, instead of aryl iodides or bromides, because the former can be easily prepared from the corresponding phenols, the key synthetic intermediates in our route. However, the instability of aryl triflates under basic reaction conditions at high temperature was a severe drawback in this strategy. Triflyl migration to the hydroxy group of 2-biphenol occurred, together with hydrolysis of the triflates by adventitious moisture, resulting in low yields of the desired arylated products and the substantial production of byproducts. Therefore, we tested arylating agents other than aryl triflates and found that aryl nonafluorobutanesulfonates (nonaflates)[15] were better. Aryl nonaflates are less prone to O–SO_2 cleavage than triflates.[16] In addition, they are easily prepared from phenols and nonafluorobutanesulfonyl fluoride, which is usually less expensive than the commonly used triflating agent, triflic anhydride. Thus, we decided to use aryl nonaflates in our synthesis.

Next, we screened various ligands to Pd in the reaction of nonaflate **1** with 2-biphenol in refluxing mesitylene (Table 1), determined to be the best solvent in our preliminary studies. When PPh_3 was used, the desired product (**2**) was obtained in an unsatisfactory yield (entry 1), along with a small amount of [1,1′:2′,1″-terphenyl]-2-ol, which was probably formed because PPh_3 acted as the phenylating agent.[14] We further tested various phosphines, including monodentate and bidentate phosphines with different steric and electronic properties, and found that PCy_3 in a Pd/P ratio of 1:2 gave the best result (entry 10). Bisarylation at the 2′- and 6′-position of the biphenols, which is known to occur in the presence of excess arylating agent,[14] was not observed when using 1.5 equiv of biphenol, as shown in Table 1. A methoxy-substituted biphenol was also arylated in good yield (entry 11).

With the optimized C–H arylation conditions in hand, we explored the feasibility of the synthetic strategy shown in Scheme 1b, starting with nonaflate **4** (Scheme 2). The

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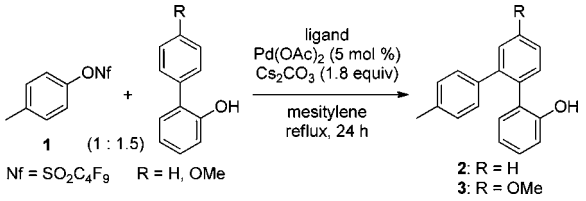
Table 1. Effect of Ligands in C−H Arylation of Biphenols with Nonaflate **1**



entry	R	ligand (mol %)	yield (%)
1	H	PPh_3 (20)	35
2	H	$P(C_6H_4\text{-}4\text{-}CF_3)_3$ (20)	5
3	H	DPPF (20)	36
4	H	Xantphos (10)	44
5	H	$P(t\text{-}Bu)_3 \cdot HBF_4$ (10)	13
6	H	(2-biphenyl)PCy_2 (10)	30
7	H	XPhos (10)	33
8	H	SPhos (10)	36
9	H	PCy_3 (20)	68
10	H	PCy_3 (10)	76
11	OMe	PCy_3 (10)	78

C−H arylated product **5** was obtained in 64% yield. Nonaflation of the hydroxy group of **5** gave nonaflate **6**, which was then converted to **7** in high yield by SM coupling with *p*-hydroxyphenylboronic acid in the presence of the Pd−SPhos catalyst.[17] Nonaflation of **7** afforded the substrate for the next C−H arylation step, which proceeded well to give **9** in reasonable yield. Subsequent nonaflation, SM coupling, nonaflation, and C−H arylation afforded *o,o,p*-oligophenylene 9-mer **13**. Thus, repeated use of C−H arylation, nonaflation, and SM coupling in the appropriate sequence allowed for the facile synthesis of *o,o,p*-oligophenylenes. While only unsubstituted biphenol was used in the C−H arylation steps, substituted biphenols should also be tolerated under the present reaction conditions, considering that methoxybiphenol underwent C−H arylation with a similar yield (Table 1, entry 11). To the best of our knowledge, this is the first example of the use of repeated C−H arylation to synthesize oligophenylenes with a defined chain length.[18]

The synthetic strategy shown in Scheme 2 was also applicable to the elongation of both ends of the symmetric oligomers, as shown in Scheme 3. *p*-Dichlorobenzene reacted with 2-biphenol to give symmetric 5-mer **14**. While the yield of **14** was modest, to the best of our knowledge, this is the first example of C−H arylation of 2-biphenol with chlorobenzenes, demonstrating the versatility of our C−H arylation conditions. Repetition of the elongation process including nonaflation, SM coupling, and C−H arylation afforded symmetric 11-mer **18** from *p*-dichlorobenzene in five steps. This synthesis further

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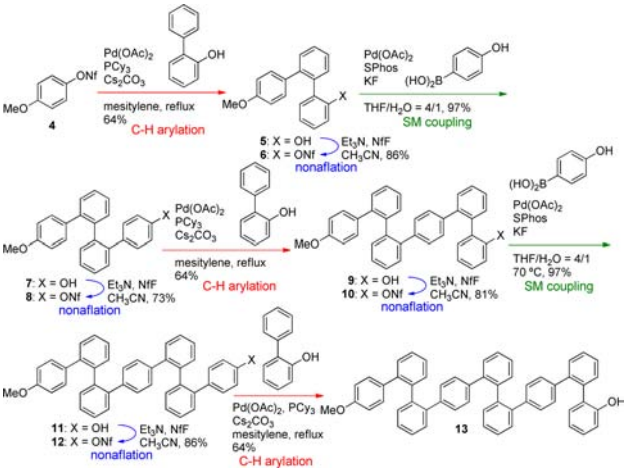
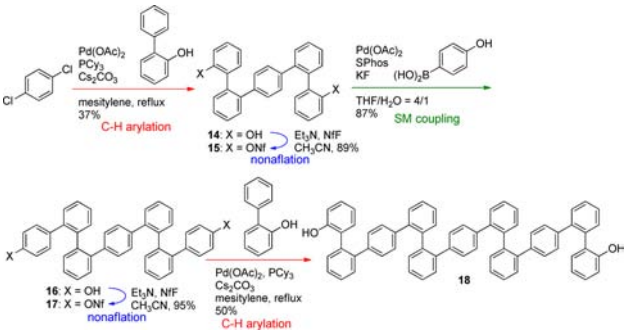
Scheme 2. Synthesis of *o,o,p*-Oligophenylene 9-Mer **13**



demonstrated the feasibility of the strategy shown in Scheme 1b.

Scheme 3. Synthesis of *o,o,p*-Oligophenylene 11-Mer **18**



^{1}H and ^{13}C NMR spectra of *o,o,p*-oligophenylenes longer than 6-mers were complicated, suggesting the existence of rotamers that slowly interconverted at rt on the NMR time scale. Although detailed conformational studies of the *o,o,p*-oligophenylenes have not been conducted, preliminary variable-temperature-NMR studies of 7-mer **11** were conducted (Figure 2). Since the predicted structure of *o,o,p*-oligophenylene (Figure 1) has a helical conformation with six benzene units per helical turn, 7-mers are the shortest possible oligomers having a complete helical turn. The ^{1}H NMR spectrum of **11** at 25 °C in DMSO-d_6 exhibited two singlets corresponding to the methoxy protons, at ~3.6−3.7 ppm (Figure 2a). These two sets of signals coalesced at high temperatures. For example, increasing the temperature from 25 to 100 °C in DMSO-d_6 resulted in coalescence of the methoxy signals into a single peak (Figure 2d), with a coalescence temperature of ~70 °C (Figure 2c). The signals in the aromatic region (6.2−7.4 ppm) also coalesced to some extent at high temperatures.

While complete assignment of the species observed in the NMR spectra is yet to be achieved, DFT-optimized

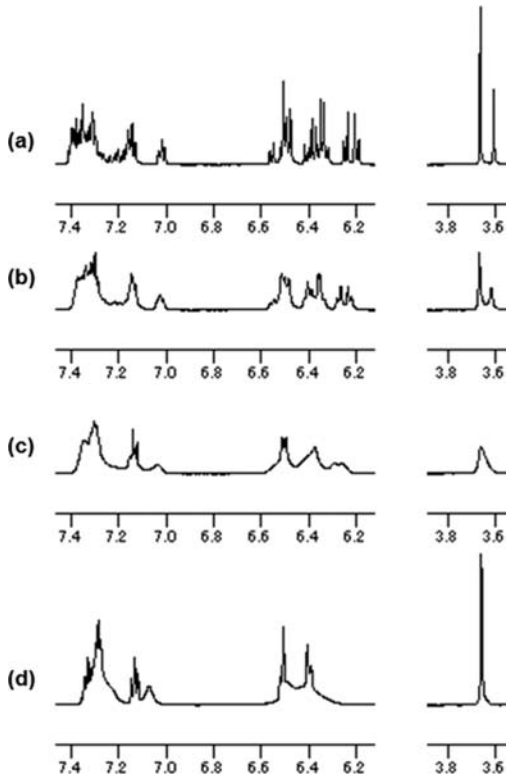


Figure 2. ^{1}H NMR spectra of **11** in DMSO-d_6 at (a) 25, (b) 50, (c) 70, and (d) 100 °C.

structures[7] found in the conformation search of unsubstituted 7-mer **19** shed light on the conformational behavior of 7-mer **11**. Eight conformers were found (Figure 3), which can be categorized into four groups that differ in the helicity of the *o,o*-connected quaterphenyl units (defined as *P* and *M*) and in the positions of the terminal benzene rings **A** and **G** relative to the central benzene ring **D** (defined as cisoid and transoid). In each group, there are two conformers that differ mainly in the dihedral angle between rings **D** and **E**. The enantiomers of these conformers also exist, although they are omitted for clarity. Interconversion among **19a**, **19b**, **19c**, and **19d** or among **19e**, **19f**, **19g**, and **19h** should occur rapidly because of the possible fast rotation of a single bond connected at the *p*-disubstituted ring **D**. On the other hand, interconversion among **19a,b** and **19e,f** or among **19c,d** and **19g,h** occurs through changes in the helicity of the *o,o*-connected quaterphenyl units, a process that is expected to be slower.[19] Therefore, we assume that the two sets of signals observed in the NMR spectra at 25 °C correspond to the averaged signals of (*M*,*M*)-cisoid-1,2 and (*M*,*M*)-transoid-1,2 and those of (*M*,*P*)-cisoid-1,2 and (*M*,*P*)-transoid-1,2 (as well as those of the enantiomer series). From the coalescence behavior shown in Figure 2, the energy barrier of the interconversion was calculated to be 72 kJ mol^{-1} at 70 °C.

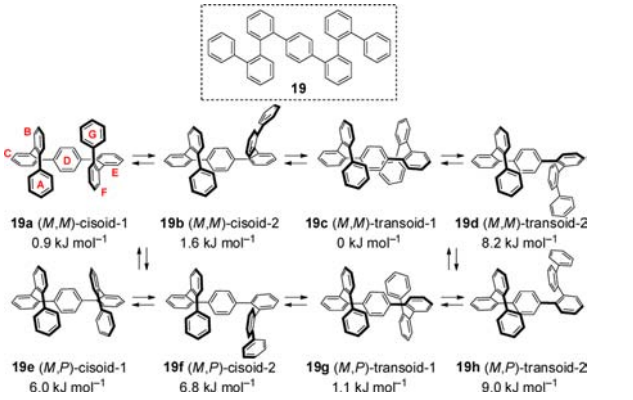


Figure 3. Eight conformers of **19** and their relative energies calculated by the DFT method (B3LYP/6-31G(d)).

Conformer **19a** is very similar to the substructure of the helix shown in Figure 1. Figure 3 indicates that **19b**,**c**,**g** are as stable as **19a**, suggesting that conformers other than the helix should also exist for *o,o,p*-oligophenylenes. In fact, oligomers with more than six benzene units yielded complicated NMR spectra at rt, indicating that the oligomers existed as mixtures of several conformers that interconvert slowly on the NMR time scale. While it may be necessary to introduce appropriate substituents that stabilize the helix more effectively,[20] our synthetic strategy seems applicable to oligomers with various substituents and hence may allow for the efficient preparation of a new helical motif.

In conclusion, a new synthetic route to *o,o,p*-oligophenylenes involving Pd-catalyzed C−H arylation of aryl nonaflates with 2-biphenols has been developed. The proposed synthetic strategy is suitable for obtaining oligomers with substituents. Further studies to develop oligophenylenes with well-defined secondary structures are currently underway.

Acknowledgment. We thank Keisuke Mori (University of Shizuoka) for his assistance in computational studies.

Supporting Information Available. Experimental and computational procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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