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Synthesis of *S*-Acetyl Oligoarylenedithiols via Suzuki−Miyaura Cross-Coupling

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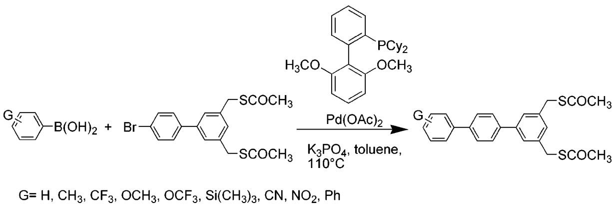

Oligoarylenes with three or four aromatic rings, bearing two *S*-acetylated mercaptomethyl groups in 1,3 position on one end of the polyaromatic system and presenting various functionalities on the other terminal ring, have been synthesized by the Suzuki−Miyaura cross-coupling reaction. The use of palladium complexes with a Buchwald's phosphine as ligand allowed us to perform this coupling reaction also in the presence of benzylic *S*-acetyl-protected functionalities on the aromatic halide. The obtained oligoarylenes are potential novel candidates for the generation of self-assembling monolayers on metal substrates.

Self-assembled monolayers (SAMs)[1] derived from alkanethiols on noble metal surfaces and, in particular, on Au(111) have been extensively studied,[2] owing to their very easy formation and the possibility of patterning the monolayer with potential applications in the study of interfacial phenomena, corrosion protection, and electrode modification. SAMs of conjugated oligomers, such as oligoarylenes[3] or oligoaryleneethynylenes,[4] with the sulfur atom either directly connected to the conjugated backbone or separated by a methylene bridge,[5] have attracted special interest as nanoscale electrical conductors (nanowires) in molecular electronics applications.[4b,6] The major drawback connected with organic thiols for SAM preparation is their easy oxidation in air. Therefore, these compounds are mainly handled as *S*-acetyl derivatives, owing to the possibility of a straightforward removal of the protecting group, which can be performed in situ during their deposition on gold from solution by adding a few drops of aqueous ammonia.[4a]

Conjugated thiols used in self-assembling experiments are generally provided with a single junction on the metal surface, that is, one thiol group at the end of the molecular structure. An interesting aspect to study should be the behavior of self-assembling molecules bearing two sulfur functionalities in a suitable relative position to enable a rigid two-point anchorage on the metal layer, which in principle would originate very stable and ordered monolayers. In this framework, the coordination of simple *ortho*, *meta* and *para* isomers of xylene-α,α'-dithiols on silver and gold surfaces has been investigated, showing different binding geometries, depending also on the metal.[7] This type of investigation, however, has been restricted only to one aromatic ring system and has not been widened to include materials with a more extended π-conjugation. In this context, oligophenylenes **3** (Scheme 1) appear to be potential candidates as a new molecular architecture able to generate SAMs characterized by a high stability and high order degree. To the best of our knowledge, oligophenylene derivatives incorporating two *meta*-methylmercapto functionalities have never been reported and, consequently, never tested in self-assembly experiments.

In the framework of our extensive work devoted to the development of methodologies leading to the synthesis of conjugated oligomers and polymers for electronic applications,[8] in this paper, we wish to report our synthetic approach to oligophenylenes **3** (Scheme 1).

Our target was the elaboration of a strategy which would allow us to obtain a series of derivatives with a wide range of functionalizations at the end of the polyaromatic system, thus making possible a study of the self-assembling properties of these compounds and of the characteristics of the films in relation to the nature of the substituents onto the conjugated backbone.

The key step in our synthetic strategy to oligophenylenes **3** is based on the Suzuki−Miyaura[9] cross-coupling between aryl halide **2** (see Scheme 1) and aryl boronic acids **1**.

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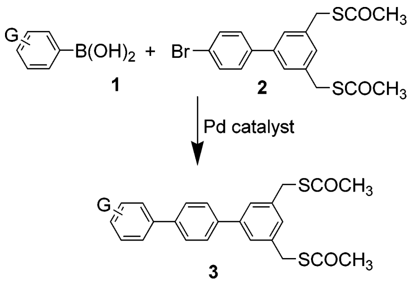
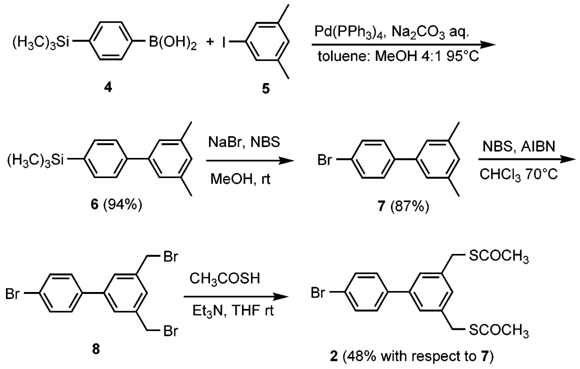
10.1021/jo701918z CCC: $37.00

SCHEME 1. Synthesis of Oligoarylenes 3



SCHEME 2. Synthesis of the Intermediate 2



Substrate **2** was easily prepared according to the four-step strategy described in Scheme 2.

The palladium-catalyzed coupling between the commercially available 5-iodo-1,3-dimethylbenzene **5** and *p*-trimethylsilylbenzeneboronic acid **4** was followed by an *ipso*-bromodesilylation reaction to give **7**.

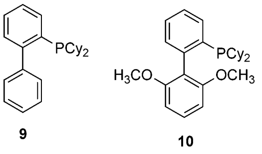
We found that the most convenient way to convert the bromide **7** in the *S*-acetylthio derivative **2** is represented by the benzylic bromination with NBS to give the tribromide **8**,[10] followed by nucleophilic substitution with thioacetic acid/triethylamine to isolate the desired product **2**.

TABLE 1. Coupling Reactions of 2 with *p*-Methoxyphenylboronic Acid 1a[a]

entry	catalyst	solvent/base	*T* (°C)	time (h)	yield[b] (conv), %
1[c]	5% Pd(PPh$_3$)$_4$	dioxane/Na$_2$CO$_3$/Ag$_2$O	80	24	8 (20)
2[d]	5% Pd$_2$(dba)$_3$/6% P(*t*-Bu)$_3$	THF/KF	rt	24	44 (60)
3[e]	2% Pd(OAc)$_2$/3% **9**	dioxane/CsF	80	24	57 (60)
4[f]	5% Pd(OAc)$_2$/12.5% **10**	toluene/K$_3$PO$_4$	110	3	74 (98)

[a] All reactions were performed under a nitrogen atmosphere. [b] Isolated overall yields and conversions after silica gel chromatography. [c] With 1 equiv of **2**, 1.2 equiv of **1a**, 3.3 equiv of anhydrous base, 2 equiv of Ag$_2$O. [d] With 1 equiv of **2**, 1.2 equiv of **1a**, 3.3 equiv of KF. [e] With 1 equiv of **2**, 1.5 equiv of **1a**, 3.3 equiv of CsF. [f] With 1 equiv of **2**, 1.5 equiv of **1a**, 2 equiv of K$_3$PO$_4$.

CHART 1. Buchwald's Ligands



The success of the Suzuki–Miyaura coupling reaction in the presence of the *S*-acetyl functionalities onto the halide partner could not be taken for granted. Indeed, although some palladium-catalyzed reactions, such as the Cassar–Heck–Sonogashira coupling, tolerate the presence of acetylthio groups,[11] it has been reported that the cross-coupling of arylboron derivatives with 1-bromo-4-thioacetylbenzene gives very poor results (0.7% yield) due to an unexpected but interesting parallel reaction.[12] The 2-methoxybutyryl group[12] or thiol surrogates[13] were proposed as a solution to the problem, but the unique feature, mentioned above (a very easy in situ deprotection during deposition), of the acetylthio group for SAM preparation purpose has stimulated our efforts toward the feasibility of the Suzuki–Miyaura coupling in the presence of such a functionality.

For this purpose, the coupling of **2** with *p*-methoxyphenylboronic acid **1a** was selected as a model reaction, and different catalytic systems and experimental conditions were applied. Assuming that aqueous conditions would promote the deprotection of the thioacetyl groups, we decided to consider only anhydrous heterogeneous protocols.

The results reported in Table 1 are representative of this investigation (a more detailed description is reported in the Supporting Information) and show clearly that anhydrous conditions using the standard Pd(PPh$_3$)$_4$ catalyst[14] (entry 1) are quite unsatisfactory. The poor reactivity of **2** is probably connected with a slow oxidative addition step of the C–Br bond to the catalyst. Better results were obtained when Pd$_2$(dba)$_3$/P(*t*-Bu)$_3$[15] was employed in THF and KF was used as base. These conditions are able to promote the coupling of unreactive aryl chlorides or electron-rich aryl bromides and iodides at room temperature.

However, the use of Pd(OAc)$_2$ in the presence of bulky, electron-rich biaryl phosphines **9** and **10** (Chart 1),[16] known as Buchwald's ligands, recently addressed as the most effective ligands in the Suzuki–Miyaura reaction, allowed us to obtain very satisfactory results.

In particular, the highest yield in the coupling product, together with a near quantitative conversion, was obtained at short reaction time when 2′,6′-dimethoxy-2-(biscyclohexylphosphino)biphenyl[17] **10** was employed as palladium ligand.

The versatility of this synthetic tool was tested in other cross-coupling reactions involving **2** and a wide series of aryl boronic acids. The results of this screening are reported in Table 2.

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(10) Actually, benzylic bromination of **7** afforded an unseparable mixture of tribromide **8** (74%) together with the 4′-bromo-3-dibromomethyl-5-bromomethyldiphenyl **8a** (26%). However, this mixture was used in the subsequent step, and the product **2** could be easily separated from the product **2a** derived from the substitution on the bromomethyl group in **8a**. The dibromomethyl group is unreactive in the substitution reaction. See Supporting Information and: Rukavishnikov, A. V.; Phadke, A.; Lee, M. D.; LaMuyon, D. H.; Pethukov, P. A.; Keana, J. F. W. *Tetrahedron Lett.* **1999**, *40*, 6353.

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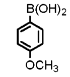
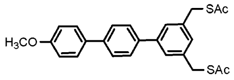
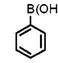
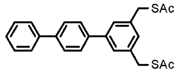
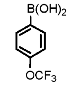
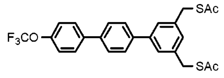
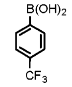
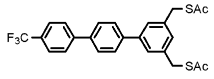
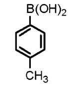
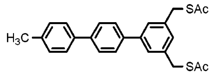
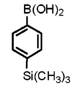
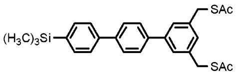
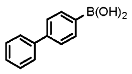
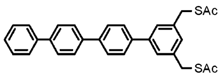
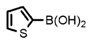
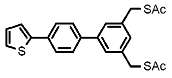
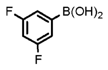
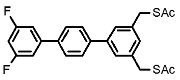
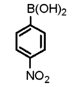
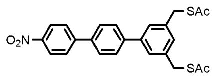
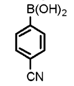
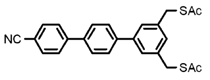
TABLE 2. Coupling Reactions of 2 with Boronic Acids 1a−k[a]

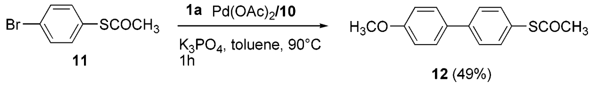
entry	boronic acid	coupling product	reaction time (h)	yield[b] (conv[c]) (%)
1	 **1a**	 **3a**	3	74(98)
2	 **1b**	 **3b**	3	100
3	 **1c**	 **3c**	3	100
4	 **1d**	 **3d**	3	100
5	 **1e**	 **3e**	3	76
6	 **1f**	 **3f**	3	88
7	 **1g**	 **3g**	3	88
8	 **1h**	 **3h**	3	73
9	 **1i**	 **3i**	12	77(98)
10	 **1j**	 **3j**	24	51(51)
11	 **1k**	 **3k**	24	56(98)

[a] All reactions were performed under a nitrogen atmosphere. [b] Overall isolated yields after silica gel chromatography. [c] When conversion is not specified, its value is 100%.

Boronic acids from **1b** to **1k**, although having substituents with different electronic effect, showed very high reactivity, affording substituted terarylenes with good to excellent yields and moderate to high conversion of the starting halide.

It is worth noting that this protocol could be also applied to the coupling of boronic acids with strong electron-withdrawing substituents, such as nitro (**1j**) and cyano (**1k**) groups. Indeed, it is known that the presence of a strongly electron-withdrawing group on the reactant slows markedly the transmetalation step and increases the formation of homocoupling products.[18] In our case, we obtained terphenyls **3j** and **3k** in fair yields with minor amounts of the biaryls derived from the homocoupling of **1j** and **1k**.

SCHEME 3. Synthesis of an Aromatic Thiol



Furthermore, fluorinated functionalities could be introduced, as in the case of terphenyl derivatives **1c**, **1d**, and **1i**, in good to excellent yields.

Finally, this methodology allowed us to obtain a quaterphenylene derivative in high yield when the biaryl boronic acid **1g** was used.

Taking into account the poor results reported for the Suzuki−Miyaura coupling reaction in the synthesis of aromatic *S*-acetyl thiols,[12] we have also applied this protocol to the coupling of the *S*-acetyl *p*-bromothiophenol **11** with boronic acid **1a** as a representative example of the synthesis of protected aromatic thiols such as **12** (Scheme 3).

The moderate yield appears as a promising result with respect to the much lower values obtained in different conditions and with other palladium ligands, demonstrating the efficiency of the phosphine **10** for the synthesis of functionalized aromatic thiols.

In conclusion, using the Suzuki−Miyaura cross-coupling conditions, with the aid of the biphenyl phosphine **10** as ligand, we were able to perform for the first time the synthesis of different oligoarylene derivatives bearing two acetylthiomethyl functionalities on a terminal phenyl ring in good to excellent yields. Furthermore, this versatile protocol allowed the introduction of a wide range of functional groups with different electronic effects on the other end of the conjugated backbone. These materials are potentially able to self-assemble on gold, and the electrical and optical characteristics of the resulting SAMs may be now investigated with relation to the effect of the substituent on the polyaromatic system. These studies are in progress, and the results will be reported in due course.

Experimental Section

Representative Procedure for the Synthesis of Oligoarylenes 3. Thioacetic Acid *S*-(5″-Acetylsulfanylmethyl-4-methoxy-[1,1′;4′,1″]terphenyl-3″-ylmethyl) Ester (3a). An oven-dried Schlenk tube containing a magnetic stirrer was evacuated and backfilled with nitrogen (3 times). Then it was charged with Pd(OAc)$_2$ (5.0 mg, 0.024 mmol, 5 mol %), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (0.210 g, 0.05 mmol, 12.5 mol %), arylboronic acid **1a** (0.091 g, 0.6 mmol, 1.5 equiv), powdered anhydrous K$_3$PO$_4$ (0.170 g, 0.8 mmol, 2.0 equiv), and thioacetic acid *S*-(5-acetylsulfanylmethyl-4′-bromobiphenyl-3-ylmethyl) ester (0.164 mg, 0.4 mmol) **2**, and the mixture was stirred while the tube was evacuated and backfilled with nitrogen (3 times). Dry toluene (3 mL), degassed by vigorously flushing nitrogen for 30 min, was added to the mixture that was stirred for a few minutes at room temperature and then heated to 110 °C. The reaction was monitored by TLC or GC−MS analysis until the disappearance of **2**. The reaction mixture was then cooled to room temperature, filtered through a thin pad of silica gel (eluting with ethyl acetate or dichloromethane), and concentrated under reduced pressure. The

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[18] Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087.

crude material obtained was purified by preparative chromatography on silica gel: white solid; mp 141−143 °C (dichloromethane/hexane); (0.129 g, 74% yield); $R_f = 0.23$ (SiO_2, petroleum ether/ethyl acetate 85:15); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 4H), 7.52 (d like, $J = 9$ Hz, 2H), 7.43 (br d, $J = 1.6$ Hz, 2H), 7.17−7.20 (m, 1H), 7.00 (d like, $J = 9$ Hz, 2H), 4.16 (s, 4H), 3.86 (s, 3H), 2.37 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 159.2, 141.6, 140.0, 138.6, 133.0, 128.0, 127.4, 127.0, 126.4, 114.2, 55.3, 33.3, 30.3 ppm; IR (KBr) ν 2929, 1690, 1498, 1253, 1126, 821 cm^{-1}; UV−vis, $\lambda = 293.0$ nm ($CHCl_3$); photoluminescence, $\lambda = 367.8$ nm ($CHCl_3$). Anal. Calcd for $C_{25}H_{24}O_3S_2$: C, 68.78; H, 5.54; S, 14.69. Found: C, 68.58; H, 5.63; S, 14.89.

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Supporting Information Available: General experimental, details for the synthesis of compounds **2** and **6**−**8**, characterization data for compounds **3b**−**k** and **12**, and copies of NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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