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The first solid-phase synthesis of oligothiophenes

Patrick R. L. Malenfant and Jean M. J. Fréchet*

Department of Chemistry, University of California, Berkeley, CA 94720-1460, USA.
E-mail: frechet@cchem.berkeley.edu

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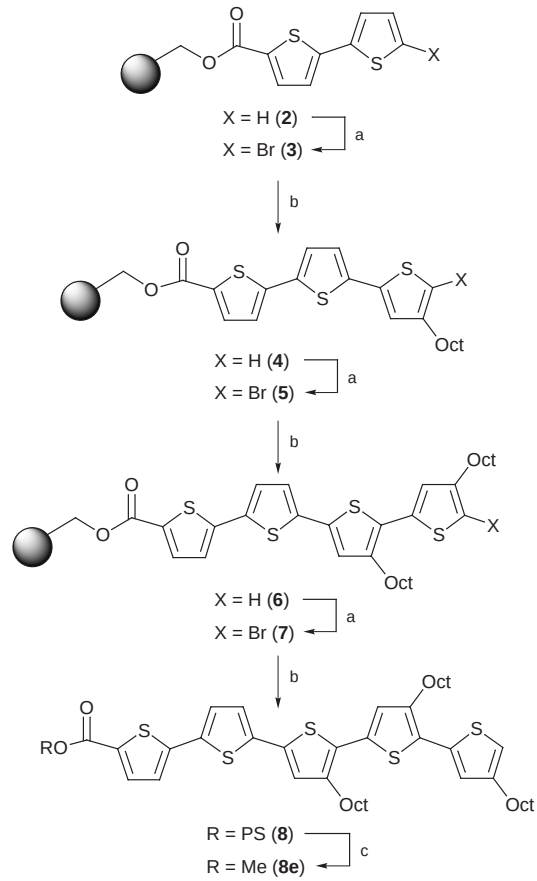
The solid-phase synthesis of asymmetric oligothiophenes on a chloromethylated macroporous resin, using an alternating sequence of bromination and Stille coupling reactions, has been used to afford oligomers up to the pentamer in excellent yield and purity.

Polythiophenes[1] and the related oligothiophenes[2] have received considerable attention due to their interesting optical and electronic properties, as well as their high environmental stability both in the neutral and oxidized state. Unfortunately, the coupling reactions used to prepare oligothiophenes (*i.e.* Kumada, Stille, Suzuki and Negishi)[3] are plagued by undesirable side-reactions such as homocoupling and loss of functionalization, thus making the purification and isolation of pure oligomers in high yield a difficult task. The pioneering work of Merrifield in the area of solid-phase synthesis has provided the synthetic chemist with a powerful tool for the rapid and frequently automated synthesis of oligomeric organic compounds.[4] Solid-phase synthesis is ideal for multi-step syntheses[4–6] since the isolation of intermediates is not required, and rapid purification is easily achieved by simply washing impurities and excess reagents away from the insoluble polymeric support.

Most of the published work employing organometallic cross-coupling reactions on solid supports has focused on one-step syntheses leading to simple bis-aryl or vinyl-aryl compounds.[7] Palladium mediated cross-couplings such as the Heck, Stille and Suzuki reactions have become increasingly important for the solid-phase synthesis of clinically useful compounds.[8] Recently, palladium catalyzed cross-coupling reactions have been employed[9] independently by Moore and Tour to prepare phenylacetylene oligomers on solid support. Herein, we report the first solid phase synthesis of oligothiophenes in which an alternating sequence of bromination and Stille coupling reactions provides an efficient, high-yielding synthesis of oligothiophenes from the dimer to the pentamer with excellent purity.

The solid phase synthesis is depicted in Scheme 1. The 2,2′-bithiophene-5-carboxylic acid moiety **1** was bound to a macroporous Merrifield-type chloromethylated resin using a standard nucleophilic displacement of the resin's benzylic chloride in DMF.[10] While gel resins, in their swollen state, are generally more reactive than their macroporous counterparts, the latter have a more rigid structure with permanent pores that allows their use in almost any solvent and may facilitate reactions involving ionic or sparingly soluble species. Therefore, the high crosslink density/constant-porosity of the macroporous resin is expected to render it less susceptible to both fouling by low solubility by-products and potential side reactions such as homocoupling that may accompany the coupling step. Such side-reactions would increase the cross-linking of a gel resin, limiting both swelling and reaction conversion, while also reducing the ability to wash out any trapped impurities. The use of a macroporous resin also allows relatively high resin loadings while minimizing[10b,11] the potential for the site–site interactions that would lead to attachment to multiple sites.[12] A macroporous resin, Argopore-Cl, with Merrifield-type $ClCH_2$ functionality at a loading level of 1.03 mequiv. Cl g^{-1} met our needs. The extent of loading of **1** determined by cleavage of the dimer from the support using NaOMe in THF was 0.73 mequiv. g^{-1} suggesting that 84% of the sites of the starting resin had been functionalized to **2**. The coupling step itself was readily monitored by FT-IR spectroscopy as the CH_2Cl peak at 1265 cm^{-1} disappeared while a new peak at 1712 cm^{-1} corresponding to the bound bithiophene ester **2** appeared. Bromination of **2** at the terminal α-position using excess NBS in DMF, followed by coupling to 2-(trimethylstannyl)-4-octylthiophene[13] using $Pd(PPh_3)_2Cl_2$ in DMF as the catalyst afforded the resin-bound trimer **4**. A systematic study involving the coupling step followed by cleavage and quantitative analysis of the product showed that a minimum of 4 equiv. of stannane is required to maximize the conversion of the dimer bromide **3** to the trimer. The monobromination of **4** to the trimer bromide **5** using NBS in DMF was only accomplished in high yield when a stoichiometric amount of NBS was used. The use of an excess of NBS leads to a dibromination product, as confirmed by EI-MS and HPLC analysis of the product isolated after cleavage from the resin. ^{1}H NMR analysis of the cleaved product suggests that the second bromine atom is introduced into the thiophene ring and not at the allylic position of the octyl chain. Attempts at monitoring the bromination on solid support by FT-IR proved fruitless as bands characteristic



Scheme 1 *Reagents and conditions*: a, NBS, DMF, room temp.; b, 2-(trimethylstannyl)-4-octylthiophene, $Pd(PPh_3)_2Cl_2$, DMF, 80 °C; c, NaOMe, THF, reflux, 1 h, then MeI, 18-C-6, reflux, 3 h.

Table 1. Purity and yield of methyl ester oligothiophenes cleaved from the resin

Entry	Oligomer	HPLC purity[a] (% yield)
1	Dimer **2e**	98
2	Dimer bromide **3e**	97
3	Trimer **4e**	95
4	Trimer bromide **5e**	95
5	Tetramer **6e**	93
6	Tetramer bromide **7e**	95
7	Pentamer **8e**	89 (90)[b]

[a] Reverse phase HPLC analysis was performed by UV–VIS spectroscopy at 254 nm using THF–ACN as the eluant. [b] The acid/ester cleavage product was converted exclusively to the ester *in situ* by treatment with 18-C-6 and MeI. Loading of the linker was determined by cleavage (0.73 mequiv. g^{-1}). Yield of **8e** (from **2**) is based on the theoretical loading of **8** (0.486 mequiv. g^{-1}) itself calculated assuming quantitative conversion at every step from **2** to **8**.

of the transformations are located in the fingerprint region and thus overlap with strong resin background absorbance. Reaction of trimer bromide **5** with 2-(trimethylstannyl)-4-octylthiophene in DMF using $Pd(PPh_3)_2Cl_2$ as the catalyst afforded the resin-bound tetramer **6**. A final iteration involving successive activation and coupling steps finally afforded the resin bound pentamer **8**. All of the above reactions were performed without stirring since the Argopore macroporous resins are very fragile and are readily ground to a fine powder if magnetic stirring is used. Destruction of the resin beads makes handling difficult and leads to losses since resin fragments can make their way through the filter during work-up.

Cleavage from the resin can be accomplished at any stage in the synthesis, using NaOMe in THF,[10c] to afford the cleaved oligomer as a mixture of the methyl ester and a lesser amount of the sodium carboxylate product. In typical control experiments, 100–200 mg aliquots of the resins were subjected to cleavage and the resulting methyl ester dissolved in CH_2Cl_2 was isolated by filtration through silica prior to analysis by reverse phase HPLC. Entries 1–7 in Table 1 represent a sequence in which the synthesis of the pentamer was monitored at each step through HPLC analysis of the cleaved ester products. Although this HPLC analysis only allows an evaluation of the purity of the cleaved ester product, our findings clearly suggest that all reactions reached a high level of conversion. To accurately measure the yield of pentamer **8e,** the cleaved product mixture (ester and carboxylate) was treated with MeI under phase transfer conditions with 18-crown-6 to ensure conversion of the sodium carboxylate fraction to its methyl ester derivative. This transformation is conveniently accomplished directly as part of the cleavage step even while the resin is still present. After washing the resin with THF, CH_2Cl_2 and MeOH, concentration of the organic phase *in vacuo*, and filtration of the CH_2Cl_2 solution through a short silica plug, pentamer **8e** was isolated in 90% yield and in high purity as assessed by HPLC, ^1H NMR and elemental analysis.[14] This high yield of pentamer is remarkable considering that both the activation and coupling steps are susceptible to side reactions and that no purification, other than a simple filtration, was done after each of the six steps.

Oligothiophene syntheses are notorious for the need of extensive chromatographic purification and the *ease* of purification with the solid-phase protocol is clearly an advantage over the traditional solution phase purification methods. This solid-phase synthesis approach, affording easy access to oligomeric materials, complements our recently demonstrated[13] solution-phase fragment coupling approach in which brominated asymmetric building blocks can be used to prepare longer symmetric oligothiophenes in a single step. Finally, it should be noted that cleavage from the resin affords oligomers with a functional handle that may be exploited later to attach the oligomers to a variety of substrates in order to exploit their intrinsic properties or to impart such properties as enhanced solubility and/or novel optical and electronic properties.[13]

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14 Methyl 4″,4‴,4⁗-trioctyl-2,2′:5′,2″:5″,2‴:5‴,2⁗:5⁗,2⁗′-quinquethiophene-5-carboxylate (**8e**): 0.1903 g of **8** (theory: 0.486 mequiv. g^{-1} or 0.092 mmol) afforded 67.3 mg (0.083 mmol) of **8e** in a yield of 90%. Mp 49 °C (DSC); $\lambda_{max}(CHCl_3)$/nm 422; υ(KBr)/cm^{-1} 3095, 3069, 2953, 2924, 2851, 1710, 957, 934, 847, 822, 805, 786, 745; δ(500 MHz, $CDCl_3$) 7.70 (d, *J* 3.9, 1H), 7.18 (d, *J* 3.8, 1H), 7.12 (d, *J* 3.9, 1H), 7.07 (d, *J* 3.8, 1H), 7.02 (s, 1H), 6.97 (2 d, 2H), 6.90 (s, 1H), 3.89 (s, 3H), 2.75 (2 t, *J* 8.0, 4H), 2.61 (t, *J* 7.7, 2H), 1.66 (m, 6H), 1.49–1.14 (m, 30H), 0.88 (m, *J* 6.8, 9H); δ_C(125 MHz, $CDCl_3$) 162.45, 143.92, 143.69, 140.32, 139.63, 137.97, 135.35, 134.72, 134.33, 133.90, 133.19, 131.29, 131.16, 130.55, 128.66, 127.22, 127.15, 125.98, 124.21, 123.68, 120.10, 52.20, 31.88, 30.57, 30.49, 30.47, 30.43, 29.55, 29.54, 29.45, 29.43, 29.42, 29.40, 29.35, 29.27, 22.67, 14.10; HRMS (FAB) calc. for $C_{46}H_{62}O_2S_5$ 806.3353; found 806.3349 (Calc. for $C_{46}H_{62}O_2S_5$: C, 68.44; H, 7.74; S, 19.86. Found: C, 68.60; H, 8.00; S, 19.63%).

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