Removal of Benzyl Protecting Groups from Solid-Supported Compounds by Hydrogenolysis Using Palladium Nanoparticles**

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One of the major problems currently encountered in solid-phase synthesis, especially in the synthesis of oligosaccharides, is the lack of a mild and effective debenzylation reaction on solid supports. The benzyl protecting group has been widely used in organic synthesis as a result of its stability and ease of mild and selective deprotection by catalytic hydrogenolysis.[2] Hydrogenolysis using particle catalysts, however, can not be applied to solid-phase organic synthesis because of steric and mass-transport problems.[3] Although palladium(II) acetate has been successfully used in the hydrogenolysis of benzyl groups in peptide synthesis, the Pd(0) particles formed in situ immediately precipitate in the Merrifield-type resin. In addition, there are no alternative mild methods available for the deprotection of the benzyl group under conditions compatible with acid-sensitive acetal groups and also that are applicable to the changes in the polarity of the substrate in the final stage of the synthesis.[4, 5] Current efforts to address this issue focus on replacing the benzyl group with substituted benzyl ethers, which are removable by relatively mild conditions, such as acid[6] or oxidative[7] hydrolysis, reaction with a Lewis acid,[8] a two-step reduction–oxidation process[9], or treatment with fluoride anions.[7b] However, these new substituted benzyl ethers are unstable under certain reaction conditions, which makes synthetic planning sometimes troublesome.

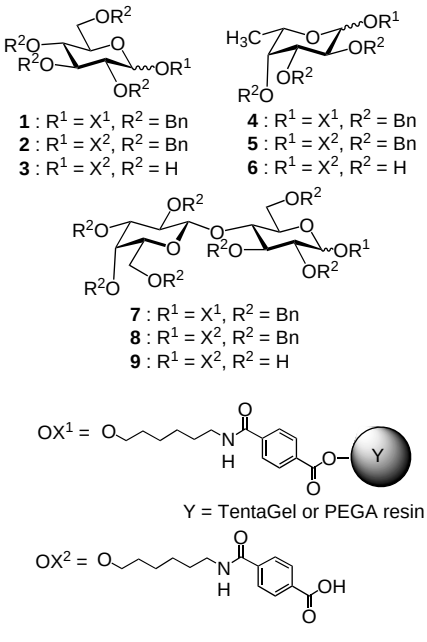
In our endeavor to find a suitably mild benzyl-deprotection method applicable to solid-phase synthesis, we considered Pd nanoparticles with a size equivalent to small organic molecules (10–40 Å diameter) as potential catalysts for the hydrogenolysis reaction. Recent developments in Pd nanoparticles[10] have proven to be successful in making monodispersed Pd nanoparticles with a controlled size that could be used in the hydrogenation of olefins,[10c, 11, 12] although no hydrogenolysis of benzyl groups was reported. One of the problems of using such metal clusters is that the small particles become unstable as they aggregate together. To overcome this problem, polymers, especially poly(*N*-vinyl-2-pyrrolidone) (PVP),[12] are often used to stabilize metal nanoparticles through coordination to the metal cluster and for protection against aggregation.[13] Recently, a fast reduction process was developed, in which a solution of H_2PdCl_4 in ethanol in the presence of PVP was refluxed to produce monodispersed Pd nanoparticles with a mean diameter ranging from 17 to 21 Å and with a narrow distribution ($\sigma <$ 5 Å) [Eq. (1)].[10a]

$$H_2PdCl_4 + EtOH \longrightarrow Pd(0) + CH_3CHO + 4HCl \quad (1)$$

We therefore decided to evaluate the Pd nanoparticles as catalysts for the hydrogenolysis of benzyl ether groups on solid supports.

Before attempting solid-phase hydrogenolysis, we tested a reaction of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose[14] with a colloidal Pd nanoparticle solution and, for comparison, with 10% Pd on charcoal. The colloidal Pd solution was prepared according to the procedure reported previously.[10a, 15] The solution was concentrated and redissolved in EtOH for hydrogenolysis. The reaction with perbenzyl glucose using 0.1 atom equivalent of the nanoparticle solution proceeded much faster (approximately 10 times faster) than the corresponding reaction of Pd on charcoal, and was completed in 2 h to give D-glucose. Having found that the Pd nanoparticles could be used as hydrogenolysis catalysts, we turned our attention to the solid-phase reaction.

The benzyl-protected glycosides of glucose (**1**), fucose (**4**), and lactose (**7**) attached to a solid support were chosen as



representatives for the study. The syntheses of these materials were conducted as follows. Perbenzyl thioglycosides of D-glucose, L-fucose, and lactose[16–18] were coupled with the linker methyl 4-[(6-hydroxyhexyl)amino]carbonyl benzoate

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in a mixture of dichloromethane and diethyl ether in the presence of *N*-iodosuccinimide (NIS) and a catalytic amount of trifluoromethanesulfonic acid (TfOH)[19] at 0 °C. The linker was designed to serve as a chromophore for the HPLC analysis of the reaction after cleavage of the products from the solid support. Anomeric mixtures (ca. 1:1) were used to test if there was, for example, any difference in their reactivity or accessibility to the catalyst particle. After saponification of each methyl ester, the acids (**2**, **5**, and **8**) were converted into the corresponding acid chloride using Vilsmeier's reagent and treated with the OH group of a solid support (Y) to give **1**, **4**, and **7**, respectively. Two types of solid support, TentaGel and PEGA resin, were used to investigate the effect of pore size.

When Pd nanoparticles were used for the reaction with polystyrene beads it was observed that palladium particles were slowly precipitated in the bead. This undesirable precipitation was perhaps a consequence of the steric stabilization of Pd nanoparticles followed by aggregation inside the pore. This problem could, however, be overcome by using an excess amount of PVP (100 monomer equivalents) to further stabilize the nanoparticles.

Thus, the hydrogenolysis of the benzyl protecting groups of solid-supported compounds was examined at 40 °C and was shown to be successful, in all cases, on the basis of HPLC analysis[20] of the materials released from the support. Precipitation of Pd nanoparticles was not observed in the case of the reaction using TentaGel. The HPLC profile of the glucose derivative showed that the peaks corresponding to the partially debenzylated compounds (17 – 30 min) appeared in addition to the starting material **2** (37.8 and 41.1 min) and the fully deprotected compound **3** (11.9 min) was formed gradually. Formation of the product was confirmed by co-injection with the authentic sample in the HPLC and mass spectrometry analyses after isolation of each compound. Although the reaction was not complete after 60 h (85 % yield),[21] peaks of **2** (α, β) were still present, it seems that no further consumption of **2** would occur. Interestingly, very small amounts of partially debenzylated intermediates remained at this stage, probably because of the presence of sites in TentaGel that were inaccessible to the Pd nanoparticles. In addition, it was found from the HPLC profile that compound **3** exists as an anomeric mixture with the same ratio as that of **2**. Furthermore, the color, clarity, and catalytic activity of the Pd nanoparticles remained unchanged.

Since the reaction could not be completed using the Merrifield-type resin, the reactions using a PEGA resin were next examined to see the effect of pore size. Absorption of almost all Pd nanoparticles into the pores of the resin was observed (from the color of the reaction mixture and the resin); however, the hydrogenolysis proceeded smoothly and reached completion within 36 h to give the glucoside **3** and fucoside **6**, respectively. In the case of lactoside **7**, formation of product **9** was confirmed, but the reaction was still incomplete (yield ca. 95 %). The possible reason for the observed adsorption of Pd particles to the support is perhaps because of the presence of amide functions on the solid support; removal of the Pd nanoparticles from the product mixture of solution-phase hydrogenolysis is a difficult problem and these amide functions may be useful.

In conclusion, we have shown that Pd nanoparticles can be used in the hydrogenolysis of benzyl protecting groups on carbohydrates attached to solid supports such as TentaGel and PEGA resins. It was shown for the first time that hydrogenolysis is possible on solid and in solution phase using Pd nanoparticles, although there is still room for improvement. As this method is as mild and effective as the widely accepted solution-phase hydrogenolysis, it may have great potential in solid-phase synthesis, especially when biological assays are to be carried out with compounds on a resin for high-throughput screening. Work is in progress to optimize the reactions and to prepare a carbohydrate library for screening.

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[20] HPLC conditions: column: Millipore NovaPak C18, 4.6 × 150 mm; flow: 1.00 mL min^{-1}; detection: 254 nm; RT; solvents A: 10% CH_3CN in H_2O with 0.1% TFA, B: 10% H_2O in CH_3CN with 0.1% TFA, solvent gradient: 0 min (100% A), 5 min (50:50 A:B), 35 min (30:70 A:B), 45 – 55 min (100% B). Retention time: **2** (37.8 and 41.1 min), **3** (11.9 min), **5** (30.5 and 31.8 min), **6** (16.2 min), **8** (56.3 and 58.1 min), **9** (7.6 min).

[21] The yield was estimated from the peak area of the HPLC chromatogram and the molar absorbance of the benzyl and terephthalate groups.

Tuning the Semiconducting Properties of Sexithiophene by α,ω-Substitution—α,ω-Diperfluorohexylsexithiophene: The First n-Type Sexithiophene for Thin-Film Transistors**

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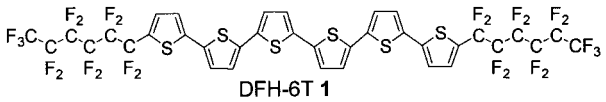
$\alpha\alpha'$-Conjugated thiophene oligomers (nTs) and polymers (PTs) have attracted great interest as semiconducting elements in organic thin-film transistors (TFTs).[1, 2] To be useful

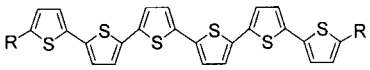
nT, 0 < x < 5 PT

in such structures, the organic material must support a channel of holes or electrons (p- or n-type semiconductor, respectively) created by the gate electrode bias, which switches the device "on". Furthermore, the charge mobility of the material must be sufficiently large to increase the source – drain on-conduction by many orders of magnitude over the "off" state. The most important examples of this family of compounds are unsubstituted, α,ω-, and β,β'-dialkylsubstituted nTs ($x = 1, 2$), and β-alkyl-substituted PTs, where optimized carrier mobilities (0.1 – 0.6 cm^2 V^{-1} s^{-1}) and on/off ratios ($> 10^6$) approach those of amorphous silicon.[1e, 2a,c,e, 3] Without exception, these systems behave as p-type semiconductors, presumably because the electron-richness of the thiophene renders negative carriers susceptible to trapping by more electronegative residual impurities such as oxygen. On the other hand, developing and understanding new n-type materials would enable applications,[4] such as bipolar transistors, p-n junction diodes, and complementary circuits, as well as to afford a better fundamental understanding of charge transport in molecular solids. The major barrier to progress, however, is that most n-type organics are either environmentally sensitive, have relatively low field mobilities, lack volatility for efficient film growth, and/or are difficult to synthesize.[4, 5, 6]

We report here the facile, efficient synthesis of the first n-type sexithiophene conductor, α,ω-diperfluorohexylsexithiophene (DFH-6T; **1**), for TFTs. DFH-6T was synthesized

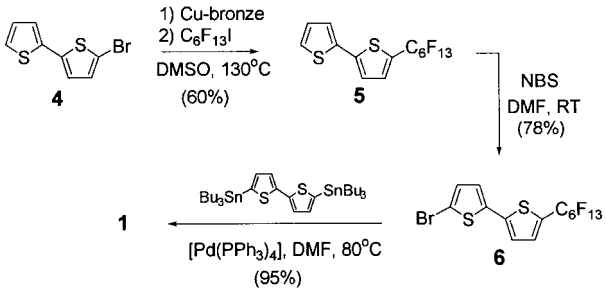


DFH-6T **1**



DH-6T **2**, R = n-C_6H_{13}
6T **3**, R = H

by a Pd^0-catalyzed Stille coupling of 5-bromo-5′-perfluorohexyl-dithiophene (**6**) with 5,5′-di(tributylstannyl)dithiophene (Scheme 1). This route affords DFH-6T (**1**) in high purity and yield after multiple gradient sublimation. Although monosubstituted perfluoroalkyl thiophene oligomers with up to three units have been reported, synthetic yields were typically about 10%.[7]



Scheme 1.

The comparative thermal properties of DFH-6T (**1**) and DH-6T (**2**) were investigated by differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA). The DSC trace of compound **1** exhibits a distinct crystal-to-liquid crystal (LC) transition at 292 °C and a LC-to-isotropic transition at 309 °C, while the crystal-to-LC transition of **2** (300 °C) falls just below the melting point, 308 – 313 °C.[8] These mesophase-formation events are not surprising in view

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