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A double heteroatom Mitsunobu coupling with amino hydroxybenzoic acids on solid phase: a novel application of the Mitsunobu reaction to form dendron building blocks

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ABSTRACT

A new highly efficient double heteroatom Mitsunobu coupling with amino hydroxybenzoic acids on solid phase is described. The synthetic routes reported in this work are general and applicable for the preparation of diverse building blocks, controlling protection, arm length, chirality, and peripheral functional groups. These novel units can form unusual dendritic architectures, which could be incorporated into specific complex structures, expanding the scope of dendrimer science.

Dendrimers are polymeric molecules with many arms emanating radially from a central core. High degrees of structural symmetry and a defined number of terminal groups located at the surface are important features of dendritic architectures. Depending on their generation or order, dendrons not only have an impact on the backbone conformation and flexibility, but also introduce a large number of functional groups at the periphery. The combination of these features creates an environment within the dendrimer molecule, which facilitates new discoveries in many important research areas, such as materials and biomedical sciences.[1] However, most dendrimeric polymers known today are constructed from symmetrical dendron building blocks and possess only one kind of functional group (usually either an amine or a hydroxy),[2] which limits the choices for 'surface' engineering. To increase the options for surface chemical derivatization and branching abilities, we decided to develop a short synthesis of novel heteroatom dendron building blocks 'around' a benzoic acid core. Coupling sites other than a typical hydroxy group can provide dendrons with extended tunable physico-chemical properties.

We previously reported the synthesis of two types of bi-functional dendron building blocks (BB) from phenolic templates via double Mitsunobu reactions for convergent dendrimer growth on a solid support.[3] Therein, we concentrated on the 3,5-dihydroxybenzoic acid core and various orthogonal protection strategies of peripheral amines. We found no evidence in the literature of any direct Mitsunobu coupling to an amine, most probably due to its insufficient acidity,[4] although, Iranpoor et al. had reported facile N-alkylation of aromatic amines with 1° and 2° alcohols using triphenylphosphine (PPh_3) and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).[5]

The accepted strategy for derivatization of basic amines through the Mitsunobu reaction employs a three-step approach, involving *N*-nosyl protection, subsequent Mitsunobu coupling, and final deprotection, yielding *N*-alkyl amines.[6] The *N*-nosyl protection is necessary to form a sulfonamide acidic proton that enables the coupling. Therefore, developing a one-step direct heteroatom Mitsunobu reaction can provide a useful method for the synthesis of multi-substituted benzoic acid building blocks for the construction of unusual dendritic structures. Our key hypothesis is based on the amine protons on the aminobenzoic acid core being sufficiently acidic to enable Mitsunobu coupling, due to the presence of an electron-withdrawing (EW) ester group on the benzene ring. Solid phase synthesis was chosen as our synthetic method, being advantageous over solution chemistry, mostly by allowing the use of large excess of reagents and avoiding problems associated with purification.

Herein, we report a novel double heteroatom Mitsunobu coupling on solid phase to prepare diverse dendron building blocks containing an aminohydroxybenzoic acid core. Mitsunobu coupling in the presence of unprotected peripheral secondary amines is also discussed.

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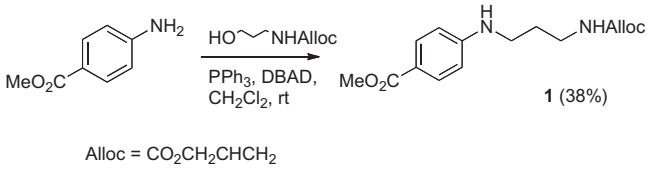


Scheme 1. Mono-Mitsunobu solution phase synthesis of methyl 4-aminobenzoate **1**.

Initially, we reacted Alloc-protected 3-aminopropanol with methyl 4-aminobenzoate (Scheme 1) in solution, to examine whether the corresponding aromatic amine can undergo Mitsunobu reaction. The Mitsunobu product **1** was indeed obtained after flash chromatography purification (SiO_2 gel, chloroform) but in poor yield.

Encouraged by this result, we investigated the mono-Mitsunobu reaction of preloaded 4-aminobenzoic acid on acid-sensitive Cl-Trt resin (Scheme 2). Successful reaction would pave the way to more complex double heteroatom coupling. Thus, after loading 4-aminobenzoic acid on the Cl-Trt resin (0.64 mmol/g) in anhydrous DMF/NMM (*N*-methylmorpholine) followed by capping with methanol, the resulting amine **7** was reacted successfully with representative hydroxy linkers bearing different functional groups under standard Mitsunobu conditions [linker (3 equiv), dibenzyl azodicarboxylate (DBAD) (3 equiv), Ph_3P (3 equiv) in CH_2Cl_2 at room temperature].[7] After cleavage (3% TFA in CH_2Cl_2) and rapid purification by solid phase extraction pack (RP-18, first washed with water and then extracted with acetonitrile) products **2a**–**e** were obtained in good yields. Apparently, classical amine-protecting groups, such as Alloc (**2a** and **2d**) and Boc (**2c**), as well as the thioether functional group (**2b**), tolerated the reaction conditions well, yielding the corresponding alkylated aminobenzoic acids in 84–93% yields. Compounds **2c** and **2d**, which bear alaninol and phenylalaninol optically active moieties, respectively, allow chiral peripheral engineering in dendrimers. Compound **2e**, the result of coupling with 1-phenylpropan-1-ol was also obtained in reasonable yield (78%), demonstrating the ability of aminobenzoic esters to undergo Mitsunobu coupling with secondary alcohols.

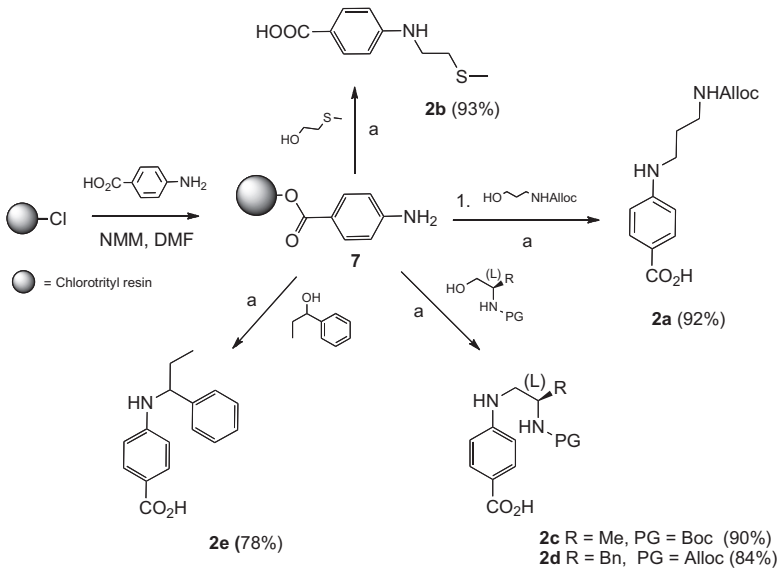
In the next step, we explored the double heteroatom Mitsunobu reaction with a variety of commercially available disubstituted amino- and hydroxybenzoic acids **6a**–**d** (Scheme 3). These benzoic acids were loaded on Cl-Trt resin as usual (NMM, DMF). Subsequently, in the same manner as for **7**, preloaded **8a**–**d** were submitted to heteroatom couplings with functionalized alcohols, yielding a collection of double armed dendron BBs **3a**–**d**, **4** and **5**.[8] These BBs vary in the nature of the alkylated atom (oxygen or amine), arm position on the benzene ring, arm length, peripheral functional groups, protection, and chirality.

In particular, the reaction of **8a**–**d** with AllocNH$(CH_2)_3$OH afforded, after cleavage (3% TFA in CH_2Cl_2) and RP-18 solid phase extraction, the corresponding acids **3a**–**d** in 75–98% yield from **6a**–**d**. Similarly, **8b** was reacted with commercial Boc-L-alaninol to yield **4** in 80% yield. Chiral **4** is of particular interest, demonstrating the extended chiral diversification abilities of diamino and hydroxybenzoic acids from easily accessible protected amino alcohols.

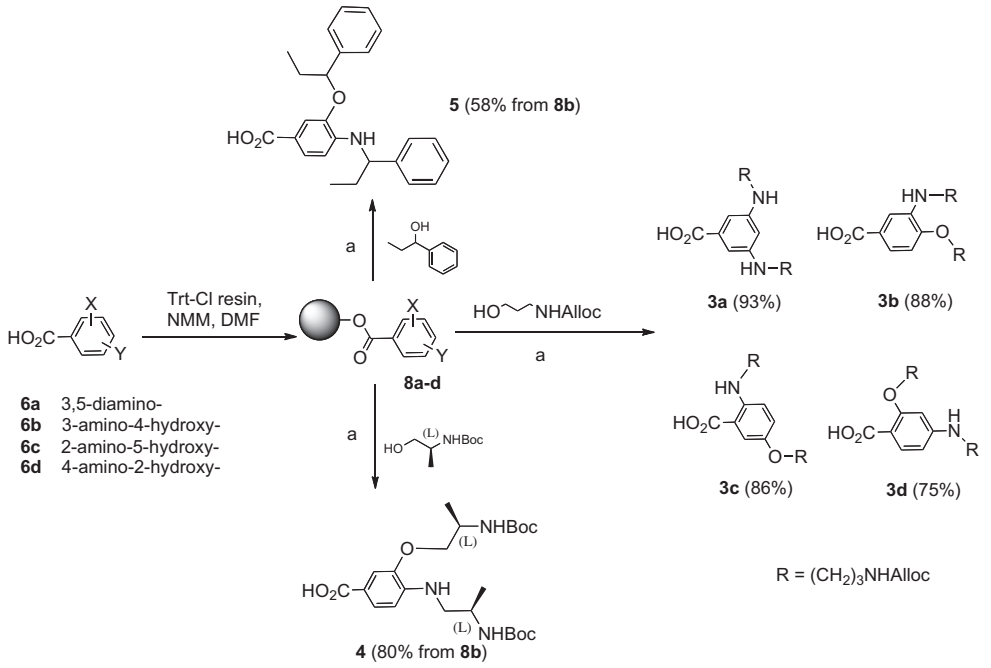
We also applied this method for synthesis of **5** via reaction of **8b** with 1-phenylpropan-1-ol. In this case, product **5** was obtained, after cleavage and RP-18 pack solid phase extraction, in satisfactory overall yield (58%), despite the possible steric hindrance.

We also examined the tolerance of the Mitsunobu coupling reaction of preloaded 3,5-dihydroxybenzoic acid (**6e**) toward unprotected aliphatic primary and secondary amines, located on the alcohol synthons (Scheme 4). Such tolerance would simplify the synthetic process, avoiding additional linker protection and subsequent deprotection steps. Unfortunately, all our attempts to obtain **10** with primary amines at the periphery under standard Mitsunobu reaction conditions failed. On the other hand, unprotected secondary amines were compatible with these conditions. Compound **6e** underwent smooth double coupling with *N*-methylaminoethanol and with allyl 3-(3-hydroxypropylamino)propylcarbamate,[3] to afford, after standard cleavage procedure, unprotected **9a** and partially unprotected **9b** dendrons in satisfactory yields (72% for **9a** and 53% for **9b** from **6e**).

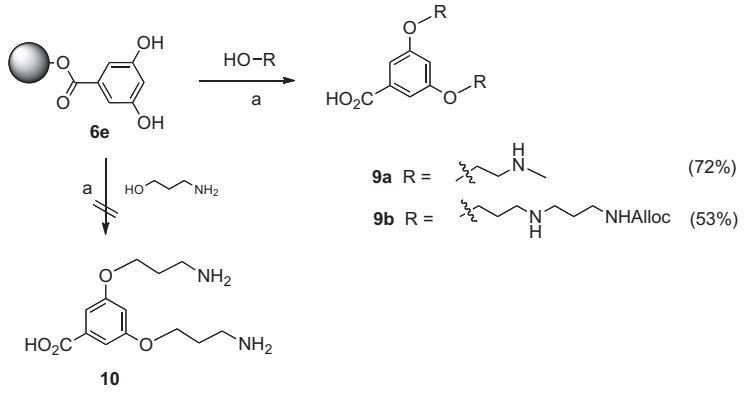
In summary, the fast solid phase heteroatom Mitsunobu reaction described in this Letter yields pure and diverse doublyarmed benzoic acid dendron building blocks for the generation of more complex dendritic architectures by solid phase organic chemistry (SPOC). These building blocks are characterized by well-controlled protection groups, arm length, chirality, and peripheral functional groups. The successful Mitsunobu coupling in the presence of unprotected peripheral secondary amines is also important for



Scheme 2. Mono-Mitsunobu solid phase synthesis of 4-aminobenzoic acids **2a**–**e**. Reagents and condition: a (1) PPh_3, DBAD, CH_2Cl_2, rt; (2) 3% TFA/CH_2Cl_2.



Scheme 3. Double-Mitsunobu solid phase synthesis of amino- and hydroxy benzoic acids **3**–**5**. Reagents and condition: a (1) PPh_3, DBAD, CH_2Cl_2, rt; (2) 3% TFA/CH_2Cl_2.



Scheme 4. Double-Mitsunobu solid phase synthesis of **9a**,**b** using unprotected 2° amine hydroxy linkers. Reagents and condition: a (1) PPh_3, DBAD, CH_2Cl_2, rt; (2) 3% TFA/CH_2Cl_2.

simplifying the synthesis of polyamine dendrimers. Attempts to optimize the reaction conditions, including microwave-assisted chemistry, as well as implementation of our dendron building blocks in convergent dendrimer evolution on a solid support are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.105.

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7. General procedure for the synthesis of mono-Mitsunobu products **2a**–**e**: To 2-chlorotrityl resin (0.2 g, 0.28 mmol loading) was added a solution of 4-aminobenzoic acid (0.034 g, 0.26 mmol) in dry DMF (3.5 mL) and NMM (140 μl, 1.04 mmol). The reaction mixture was shaken for 1.5 h. After completion of the loading, dry MeOH (1.5 mL) was poured into the reactor and shaking was continued for an additional 20 min. The solvent was removed by filtration and the following washings sequentially performed: 2 × CH_2Cl_2/MeOH/DIEA (17:2:1), 2 × CH_2Cl_2, 2 × DMF, 2 × CH_2Cl_2, 2 × CH_2Cl_2/DMF (1:1). To the resin-loaded **7** was added, under N_2 atmosphere, the hydroxy linker

(0.78 mmol) in dry CH_2Cl_2 (5.2 mL), DBAD (0.192 mL, 0.78 mmol) and PPh_3 (0.198 g, 0.78 mmol). After shaking overnight, the solution was filtered and the following washings sequentially performed: 1 × THF, 1 × CH_2Cl_2, 1 × 10% DIEA/DMF, 1 × DMF, 3 × MeOH, 3 × DMF, 3 × CH_2Cl_2. The resin was transferred to a vial and a cooled solution of 3% TFA in CH_2Cl_2 (2 mL) was added. After shaking for 30 min, the solution was collected and the resin was washed several times with CH_2Cl_2. The combined organic solution was evaporated initially under an N_2 stream and then in vacuo to give **2a**–**e**. Data for **2a**: off-white oil (0.062 g, yield 92%). HRMS: found m/z 279.131 (MH^+), calcd: 279.126 for $C_{14}H_{19}N_2O_4$, ν_{max} (KBr): 3310–3070 br s, 1705, 1650, 1340, 1120 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.94 (d, J = 7.5 Hz, 2H), 6.76 (d, J = 7.5 Hz, 2H), 5.93 (ddt, J = 16.7, 10.4, 5.3 Hz, 1H), 5.30 (d, J = 16.7 Hz, 1H), 5.20 (d, J = 10.7, 1H), 4.54 (d, J = 5.3 Hz, 2H), 4.32 (t, J = 5.3 Hz, 2H), 3.37 (t, J = 5.3 Hz, 2H), 1.98 (quint, J = 5.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9 (C), 157.1 (C), 132.8 (C), 131.5 (CH), 117.2 (CH), 116.4 (C), 65.4 (CH_2), 62.2 (CH_2), 37.7 (CH_2), 28.9 (CH_2).

8. Products **3**–**5** were prepared from acids **6a**–**d** (0.26 mmol) in the same manner as for **2**,[7] with 1.33 mmol of the hydroxy linkers, and DBAD and PPh_3. Data for **3a**: off-white oil (0.13 g, yield 93%). HRMS: found m/z 435.049 (MH^+), calcd: 435.224 for $C_{21}H_{31}N_4O_6$, ν_{max} (KBr): 3350–3020 br s, 1700, 1655, 1410, 1070 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.92 (br s, 2H), 6.43 (br s, 1H), 5.92 (ddt, J = 16.7, 10.4, 5.3 Hz, 2H), 5.30 (d, J = 16.7, 2H), 5.20 (d, J = 10.7, 2H), 4.56 (d, J = 5.3 Hz, 4H), 4.34 (t, J = 5.3 Hz, 4H), 3.32 (t, J = 5.3 Hz, 4H), 1.94 (quint, J = 5.3 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.3 (C), 156.6 (C), 133.0 (C), 131.3 (CH), 129.8 (CH), 127.9 (C), 116.6 (CH), 116.0 (C), 64.7 (CH_2), 62.0 (CH_2), 37.3 (CH_2), 29.1 (CH_2).