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Fast and Scalable Route to Aryl Polyallyl Dendrons and Dendrimers

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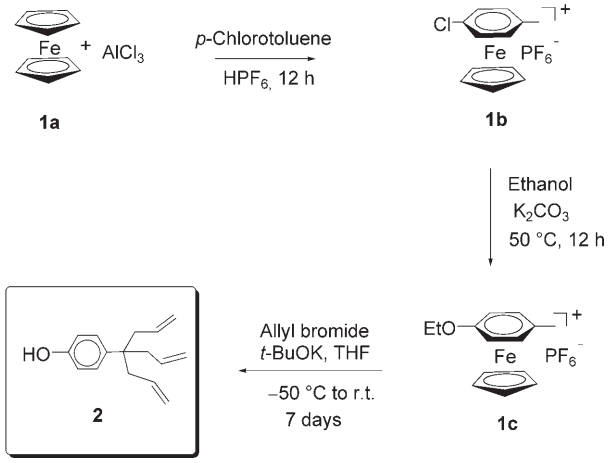
Abstract: In the quest for general and efficient synthetic procedures for dendrons and dendrimers, allylphenol, allylnaphthol and 6-bromonaphthalene AB_3 dendrons have been successfully prepared on a large-scale by a rapid and clean route starting from commercially available esters and allyl bromide. In contrast to the known organoiron strategy, the above-mentioned methodology enables the large-scale synthesis of AB_3 dendrons in only two days.

Keywords: AB_3 dendrons; allylcarbinol; aryl polyallyl dendrons/dendrimers; dendrimers

Introduction

The construction of organic, inorganic and organometallic dendrimers is now a well-established field of research.[1] Publications from the last few years demonstrate a continuing interest in the development of new and ever more efficient synthetic methodologies,[2] and a considerable number of dendritic compounds have been prepared for industrial applications[3] as well as academic studies[4]. Because of their controlled molecular architectures, dendrimers have found use in various areas such as catalysis,[5] supramolecular chemistry,[6] biomimetics,[7] surface chemistry,[8] light-harvesting materials,[9] and medicine.[10] A number of useful methods for the synthesis of dendrimers have been reported. Among these, the temporary complexation of aromatics by 12-electron organotransition metal units provides a powerful means to activate aromatics towards nucleophilic and deprotonation reactions.[11] In this context, Astruc et al., have developed an original way to prepare dendrimers and dendrons, using a synergy between two modes of aromatic activation by the electron-withdrawing cation $CpFe^+$: the enhanced acidity of the benzylic protons and the nucleophilic cleavage of the O-alkyl bond of phenyl ether complexes. Thus, they have shown that the perfunctionalization and heterolytic cleavage of the O-alkyl bond of phenyl ether complex **1c** in a one-pot reaction, nine sequence, directly lead to a dendron.[11] The 4-triallylmethylphenol dendron **2** has been synthesized following this route, from the ferrocene complex **1a**, in 10 days, with an overall yield of 25%, as outlined in Scheme 1.



Scheme 1. Organometallic one-pot route to 4-triallylmethylphenol dendron (**2**).[11]

In spite of the difficulty to prepare the AB_3 dendron **2**, the latter remains an interesting starting material for the fast synthesis of dendrimers. Indeed, this dendron has several advantages: (i) it can be functionalized at both the phenolic and allylic positions;[12] (ii) it allows a rapid dendritic growth for the construction of giant dendrimers[13] with a very high number of branches, since the number of branches is multiplied

by three for each new generation of dendrimer; (iii) it can be bound, after suitable elaboration of functionalities, to nanoparticles,[14] surfaces and polymers[8] (convergent synthesis), as well as star and dendritic cores (divergent method). For example, the use of this tripodal dendron in our laboratory has shown its broad synthetic potential for the fast divergent and convergent synthesis of polyallyl dendrons, dendrimers and metallodendrimers.[11,12] However, the only procedure reported so far for the synthesis of the phenol dendron **2** is the above-mentioned organoiron method. In spite of remarkable improvements of the organoiron procedure in recent years, its use was still compromised by several restrictions, especially the modest yield (25%) and the length of the overall synthetic procedure. On the other hand, AB_3 dendrons are very attractive for industrial and academic chemists as they allow a rapid dendritic structure growth and are often used to functionalize molecular and nanoscale materials.[15] Thus, a concise and clean route for the large-scale synthesis of such dendrons is necessary. Ideally, the syntheses would require only very few steps, use precursors that are inexpensive, and be amenable to application on a large scale. Furthermore, it would be advantageous if the method could be applied to the synthesis of new aromatic AB_3 dendrons.

Herein, we describe a fast and efficient protocol for a large-scale synthesis of 4-triallylmethylphenol dendron **2** starting from the commercially available methyl 4-methoxybenzoate **2a** (Scheme 2). In order to generalize the usefulness of this procedure to aryl derivatives, naphthalene AB_3 dendrons – 6-triallylmethyl-2-naphthol (**3**) and 6-bromo-2-triallylmethylnaphthalene (**4**) have also been prepared, starting from readily available ethyl 4-methoxynaphthoate (**3a**), and methyl 6-bromo-2-naphthoate (**4a**) respectively (Scheme 3 and Scheme 4). Compared to the organoiron procedure outlined in Scheme 1 for the synthesis of 4-triallylmethylphenol (**2**), our synthetic route, which consists of a three-step sequence, brings significant improvements, such as lower cost, lower overall reaction time (2 *vs.* 10 days) and better overall yield (87 *vs.* 25%).

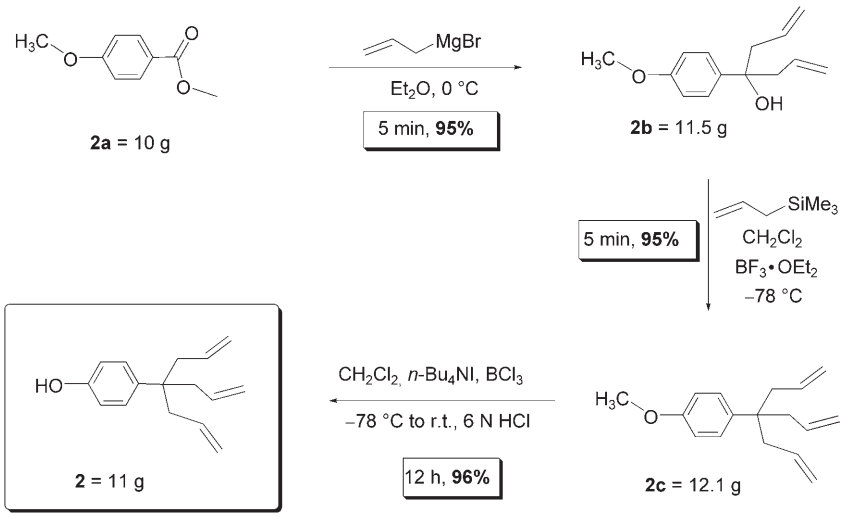
Results and Discussion

The organic approach to the large-scale synthesis of 4-triallylmethylphenol dendron (**2**) starting from the commercially available methyl 4-methoxybenzoate (**2a**) is summarized in Scheme 2.

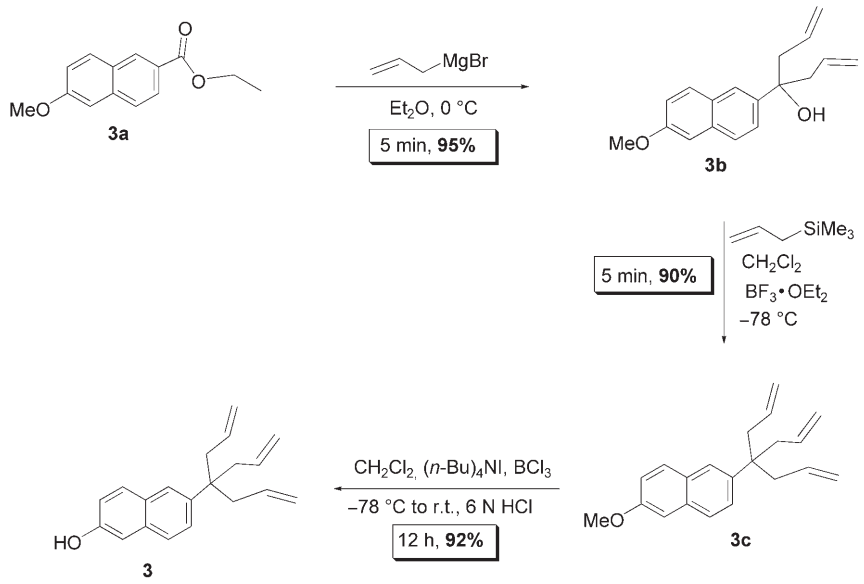
The first step involved the synthesis of diallylated carbinol 4-(4-methoxyphenyl)-hepta-1,6-dien-4-ol (**2b**), prepared from methyl 4-methoxybenzoate (**2a**) and allylmagnesium bromide at 0 °C.[16] The mixture of both reagents in diethyl ether showed a rapid colour change from green to white, yielding the diallyl 4-(4-methoxyphenyl)-hepta-1,6-dien-4-ol (**2b**) as a colourless oil in 95% yield after column chromatography purification.

In the second step, the allylation by allyltrimethylsilane of the carbenium ion generated in the ionization process of diallylcarbinol **2b** with boron trifluoride at −78 °C,[17] leads to 4-methoxytriallylmethylbenzene in 95% yield. Our experiments to find the optimal conditions have shown that the success of this reaction is highly temperature dependent. While only 26% of **2c** was isolated at 20 °C, decreasing the reaction temperature to −78 °C led to 95% of the triallylated product.

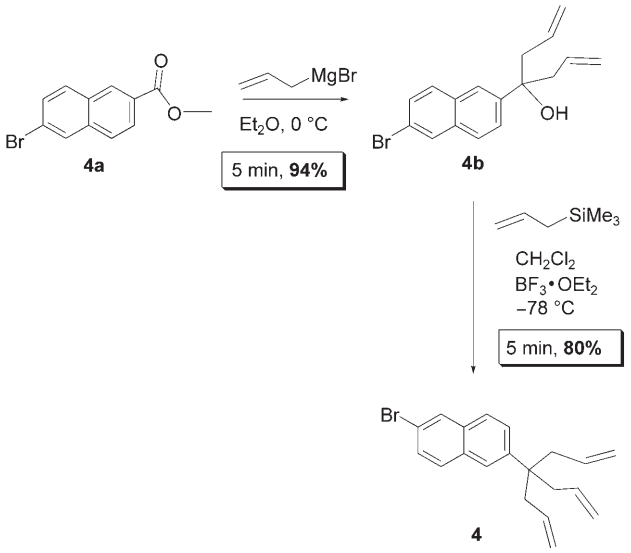
The last step consists of the deprotection of the phenol group in **2c** using the reported $(n\text{-Bu})_4NI/BCl_3$ system.[18] When the protected 4-methoxytriallylmethylbenzene (**2c**) was treated with tetrabutylammonium iodide and boron trichloride from −78 °C to room



Scheme 2. Organic approach to 4-triallylmethylphenol dendron (2).



Scheme 3. Synthesis of dendron 6-triallylmethyl-2-naphthol (3).



Scheme 4. Synthesis of 6-bromo-2-triallylmethylnaphthalene dendron (**4**).

temperature, the 4-triallylmethylphenol dendron **2** was obtained as a colourless oil in 96% yield after column chromatographic purification. The reaction is followed by the complete disappearance of the ^{1}H NMR signal (3.80 ppm) indicative of the methoxy group of **2c**. Initial attempts to prepare **2** on a large scale (using up to 40 g of **2a**) led to comparable yields.

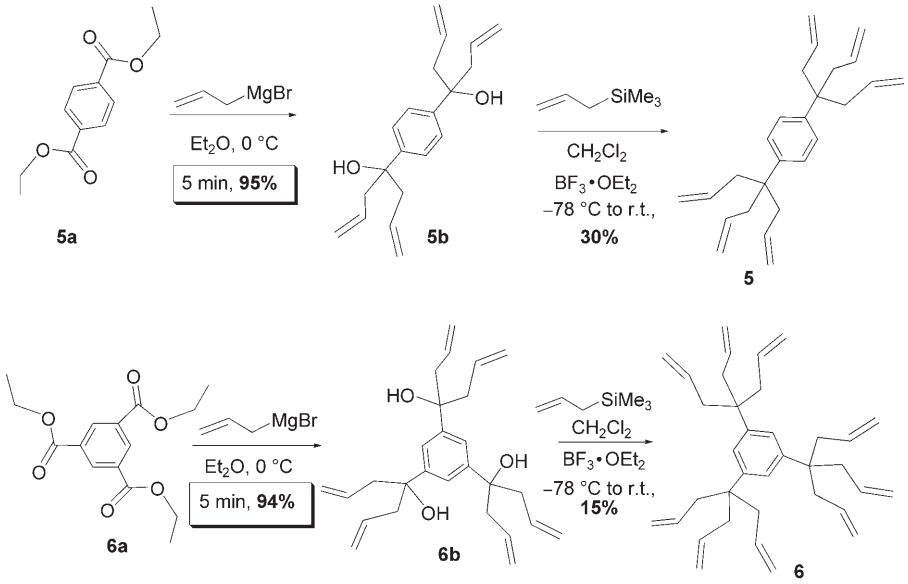
In order to evaluate the efficiency of this procedure and to generalize its usefulness to aromatic compounds, naphthalene AB_3 dendrons have been prepared. Thus, following the same protocol, the dendron 6-triallylmethyl-2-naphthol (**3**) has been successfully obtained in three steps, starting from the ethyl 6-methoxy-2-naphthoate (**3a**) and allylmagnesium bromide (Scheme 3).

In analogy to **2b**, the first step involved the synthesis of diallylcarbinols – 4-(6-methoxynaphthyl)-hepta-1,6-dien-4-ol (**3b**) obtained in 95% from the corresponding naphthoate and allylmagnesium bromide. The allylation of the readily ionizable **3b** with allyltrimethylsilane in a solution of BF_3 in dichloromethane gave the naphthol protected 6-methoxy-2-triallylmethylnaphthalene **3c** in 90% yield. The deprotection of the phenol group in **3c** in the presence of (*n*-Bu)$_4$NI/BCl_3[18] led to the 6-triallylmethyl-2-naphthol dendron (**3**) in 92% yield.

This procedure was also applied to the direct synthesis of the aryl halide AB_3 dendron in two steps, as outlined in Scheme 4. Thus, the allylation of methyl 6-bromo-2-naphthoate **4a** with allylmagnesium bromide, as described for **2a**, gives the double allylated compound 4-(6-bromonaphthyl)-hepta-1,6-dien-4-ol (**4b**) in 94% yield. The latter in the presence of allyltrimethylsilane and the BF_3/CH_2Cl_2 system, leads to the formation of 6-bromo-2-triallylmethylnaphthalene dendron **4** in 80% yield.

The evaluation of the synthetic performance of halide substituted AB_3 arene dendrons such as **4** in C–C coupling reactions is being investigated in our group. Indeed, their use in C–C bond coupling reactions constitutes a challenging approach for the direct functionalization of functional molecules and dendrimers with dendrons.

The above-mentioned synthetic approach was also applied to the direct synthesis of dendritic cores. Thus, hexa- and nonaallyl dendritic cores **5** and **6**[19]



Scheme 5. Organic approach to the hexaallyl **5** and nonaallyl **6** dendritic cores.[19]

were synthesized in two steps from the corresponding aryl di- and triesters (Scheme 5).

In the first step, allylmagnesium bromide reacts with commercially available diethyl terephthalate (**5a)** and triethyl 1,3,5-benzenetricarboxylate (**6a**) affording the desired tetraallyl dicarbinol **5b** and hexaallyltricarbinol **6b** in 95 and 94% yields, respectively. The allylation of carbinols **5b** and **6b** with allyltrimethylsilane in the presence of BF_3, from −78 °C to room temperature afforded the hexaallyl **5** and nonaallyl dendrimers **6** in 30 and 15%, respectively. In this case, the rapid colour change of the mixture to orange observed with **2**, **3** and **4**, indicative of reaction efficiency at −78 °C, was not observed. However, the orange colour slowly appeared with the increase of the reaction temperature. These low yields in the allylation of di- and tricarbinol might be assigned to the competing processes arising from the carbenium ion-mediated dimerization or polymerization.[17] Analytical data of **5** and **6** are consistent with the proposed structures, and are similar to those reported when using the organoiron protocol.[19] It is interesting to note that, in spite of the modest yields for the second step of this novel procedure, substantial quantities of up to 5.5 g and 3.7 g have been obtained respectively for **5** and **6**. Overall, the strategy reported in this manuscript represents a rapid, efficient and inexpensive procedure for the large scale preparation of **5** and **6**.

Conclusions

We have shown that allylic AB_3 phenyl or naphthyl dendrons can be obtained in large-scale reactions in good to excellent yields, *via* a new procedure using commercially or readily available starting materials. This protocol has been successfully applied to the direct synthesis of allylic dendritic cores, and appears as a significantly more efficient, less expensive and time-consuming alternative to the organoiron route used previously to access such compounds. We believe that this method should be valuable for the rapid synthesis of new functionalized dendrons, and consequently, for the rapid growth of various higher generation dendrimers. The evaluation of the synthetic performance of this strategy with respect to more sophisticated dendrons and dendrimers is being investigated in our group.

Experimental Section

General Procedure for the Synthesis of Allylcarbinol Compounds

Under an inert atmosphere, a solution of aryl ester (55.5 mmol) in 20 mL diethyl ether cooled at 0 °C, was added to a Schlenk tube with 1 M allylmagnesium bromide solution in diethyl ether (138 mmol, 138 mL) at 0 °C. The green colour of the reaction mixture changed immediately and a white precipitate was formed. After 5 min stirring, a solution of 6 M NH_4Cl (100 mL) was added to the reaction mixture, and the product was extracted with diethyl ether (3×40 mL), and dried over Na_2SO_4. The solvent was removed under vacuum and the product purified by chromatography on a silica gel column.

General Procedure for the Allylation of Allylcarbinol Compounds

In a Schlenk tube, to a solution of allyltrimethylsilane (250 mmol, 39.5.4 mL) in 40 mL CH_2Cl_2, cooled to −78 °C,

was added a solution of 1 M BF_3 in Et_2O (250 mmol, 250 mL). Then, a CH_2Cl_2 (40 mL) solution of allylcarbinol (50 mmol) also cooled to −78 °C was added to the reaction mixture. The colourless mixture changed immediately to orange. After 5 min stirring, the cooling bath was removed and the solvent evaporated under vacuum. Then, 50 mL of Et_2O and 50 mL of H_2O were added. The product was extracted with Et_2O (40 mL × 2) and dried over Na_2SO_4. The solvent was removed under vacuum and the product purified by chromatography on a silica gel column with a pentane/diethyl ether eluent mixture. The rapid orange colour change of the mixture that expressed the reaction efficiency at −78 °C for monocarbinol compounds, was not observed in the case of tetraallyl dicarbinol **5b** and hexaallyl tricarbinol **6b**. Therefore, the reaction time was lengthened to 30 min for **5b** and to 1 hour for **6b**.

General Procedure for the Synthesis of AB_3 Arenol Triallyl Dendrons from the Corresponding Methoxy Derivatives

A mixture of **2c** or **3c** (45 mmol) and $(n\text{-Bu})_4NI$ (54 mmol, 19.9 g) in 30 mL of CH_2Cl_2, was cooled to −78 °C. Then, a solution of 1 M BCl_3 in hexane (56 mmol, 56 mL) was slowly added to the reaction mixture. After 12 h stirring, 49 mL of H_2O was added to the mixture followed by 118 mL of 6 N HCl. The product was extracted with Et_2O (30 mL × 3) and the organic layer washed with a solution (20 mL) of $Na_2S_2O_3$ and dried over Na_2SO_4. The solvent was removed under vacuum and the product purified by chromatography on a silica gel column with a petroleum ether/diethyl ether eluent mixture.

Supporting Information

Full characterization of all new compounds and experimental procedures are given in the Supporting Information section.

Acknowledgements

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