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Efficient and accelerated growth of multifunctional dendrimers using orthogonal thiol–ene and S_N2 reactions†

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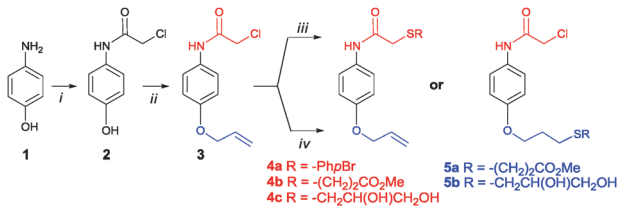
An orthogonal coupling strategy was developed by combining thiol–ene and S_N2 reactions, which was subsequently applied to the accelerated synthesis of multifunctional dendrimers using carbohydrate building blocks. In surface plasmon resonance (SPR) studies, the β-D-galacto-pyranoside-coated dendrimer exhibited nM binding affinity with the bacterial LecA lectin extracted from *Pseudomonas aeruginosa*.

Dendrimers are hyperbranched globular shape macromolecules, with significant applications in fields ranging from nanomaterials to biology.[1] The syntheses of dendrimers *via* classical convergent and divergent approaches generally require deprotection or activation steps between each generation, leading to a large number for synthetic manipulations. Various methods have been developed for the rapid and accelerated synthesis of these fascinating dendritic macromolecules in fewer steps, out of which, the efficient orthogonal coupling strategy[2] disclosed by Zimmerman stands out.[2a] The concept of orthogonality has been extensively applied in the synthesis of complex organic molecules and biomolecules.[3,4] The orthogonal chemical coupling strategy consists of using bifunctional monomers containing complementary functional groups (A_xB_y) with the ability to undergo selective group manipulations without the necessity for deprotection or activation steps, which will in turn dramatically reduce the number of required synthetic steps.

We describe herein an under exploited combination of orthogonal coupling reactions based on thiol functionality; namely thiol–ene (radical mediated addition of thiol across double bonds) and nucleophilic substitution (S_N2) reactions toward the rapid assembly of dendrimers. The thiol–ene reaction shares the many attributes of click chemistry that has been copiously employed for the synthesis of polymers, dendrimers, and other macromolecules.[5] We have designed the monomers with the mutually tolerable *N*-chloroacetamide and allyl functionalities (**3** and **8**) and optimized the conditions for the chemoselective thiol–ene or S_N2 reactions. By using the orthogonality of a sugar-based AB_4 monomer **8**, a new family of multifunctionalized G(1) and G(2) dendrimers has been synthesized. The details of the synthesis are presented herein. In order to optimize the orthogonality of the thiol–ene *vs.* S_N2 reactions, a bifunctional monomer model **3** decorated with allyl and chloroacetyl groups was prepared from *p*-aminophenol **1** according to Scheme 1.



Scheme 1 Orthogonal thiol–ene and S_N2 reactions of bifunctional monomer **3** with various thiols. *Reagents and conditions*: (i) K_2CO_3, $ClCH_2COCl$, acetone–H_2O, rt, 1 h, 70%; (ii) K_2CO_3, AllBr, DMF, 50 °C, 3 h, 71%; (iii) RSH, K_2CO_3, THF, rt, 12 h; (iv) DMPAP, 365 nm, MeOH, rt, 2 h (see ESI† for details).

The coupling of **1** with chloroacetyl chloride led to the formation of intermediate **2**,[6] which upon subsequent allylation with excess allyl bromide and K_2CO_3 afforded bifunctional compound **3**. The exclusive reactivity of **3** towards the thiol–ene *vs.* the S_N2 reaction conditions was first demonstrated using common thiols and the optimized conditions (see ESI† for yields and details). The nucleophilic substitutions of the *N*-chloroacetamide group of **3** using a variety of thiols were accomplished (**4**) in the presence of K_2CO_3–THF, keeping the allyl group entirely intact. Alternatively, the chemoselective photolytic addition of thiols to the allyl group of **3** was achieved in the presence of a radical initiator α,α-dimethoxy-α-phenylacetophenone (DMPAP, 10 mol%) under UV irradiation at 365 nm and room temperature (**5**). All products were unambiguously characterized by ^{1}H- and ^{13}C-NMR spectroscopy and MS. Conspicuously, the ^{1}H-NMR spectrum of the crude products clearly showed complete disappearance of olefinic protons that have undergone the thiol–ene reactions while the up-field shift of the chloroacetyl protons remained entirely intact. Conversely, the latter protons unambiguously moved from δ 4.18 ppm ($COCH_2Cl$) to δ 3.30–3.70 ppm ($COCH_2S$) in the S_N2 reactions, thus confirming the perfect orthogonality of the system.

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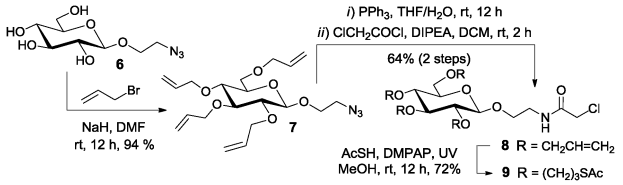
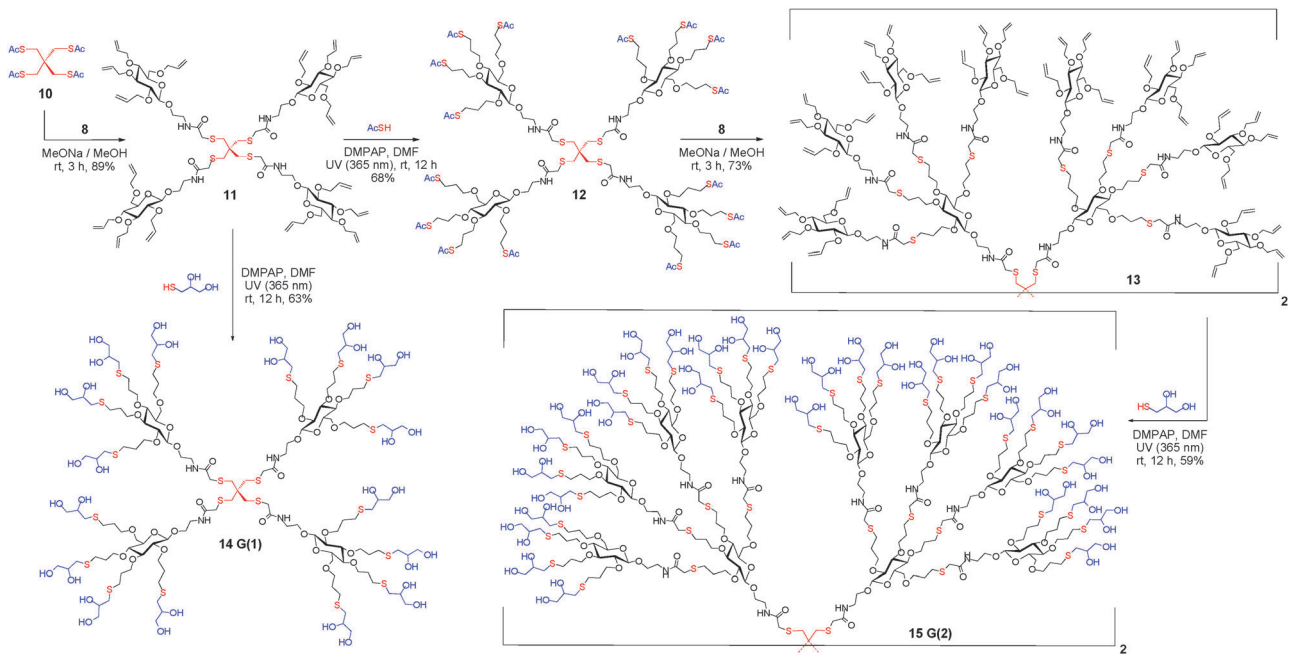


Scheme 2 Synthesis of AB_4-type building block **8** from glucose.

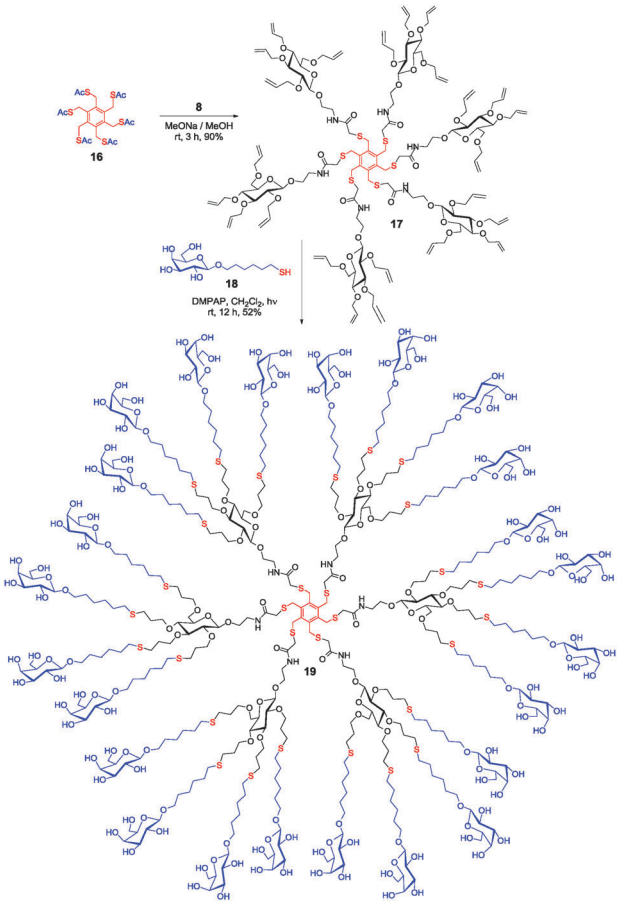
Having established the complete orthogonality of the thiol–ene *vs.* S_N2 reactivity of model derivative **3**, a glucose based AB_4 monomer (**8**), possessing four allyl appendages and a *N*-(2-(glucosyloxy)ethyl)-2-chloroacetamide group as the aglycon, was synthesized (Scheme 2).

The synthesis was initiated using the known 2-azidoethyl β-D-glucopyranoside **6**.[7] Direct allylation of **6** with allyl bromide (NaH, DMF, rt, 12 h) afforded derivative **7**. Staudinger reduction of azide **7** with PPh_3 (aq. THF, rt, 12 h) and *in situ* treatment with chloroacetyl chloride in the presence of Hunig's base led to the formation of the desired AB_4 monomer **8**, in a 64% overall yield. Thiol–ene reaction of monomer **8** with thioacetic acid under the conditions described above led to the formation of **9**, thus confirming the complete orthogonality of the strategy towards multifunctional monomers.

This approach was next extended to the accelerated synthesis of polyallylated dendrimers **11**, **13** and **17** to demonstrate its efficiency in the construction of complex architectures (Schemes 3 and 4). To this end, the previously reported A_4 and A_6 thioacetylated monomers **10** and **16**[8] have been used as precursors for the S_N2 reaction with monomer **8**. Hence, S-alkylation of **8** with thioacetates **10** and **16** in the presence of a slight excess of 1 M MeONa–MeOH solution (see ESI†) led to the formation of 16-, 64- and 24-allyl functionalized dendrimers **11**, **13** and **17** in excellent yields, regardless of aliphatic or aromatic thioacetylated precursors. Completion and chemoselectivity of the reactions were unambiguously supported by ^{1}H-NMR analysis of **11**, which showed the disappearance of a singlet at δ 4.01 ppm corresponding to the –COCH_2Cl group together with the appearance of the signal at δ 3.20 ppm of the newly formed –COCH_2S– linkages, while the characteristic allylic patterns at δ 5.20 and 5.90 ppm showed the expected integration. In addition, the presence of only one signal in the ^{13}C-NMR spectrum for **17** at δ 136.3 ppm, corresponding to central C_{ar}, indicated full hexakis substitution. The full chemical integrity of **11** and **17** was further confirmed by HRMS analysis, which displayed the expected molecular ion adducts. Subsequently, the thiol–ene reaction of **11** with thioacetic acid in the presence of DMPAP under UV radiation at 365 nm led to the formation of intermediate **12** en route to the next dendrimer generation and having sixteen thioacetyl termini. As expected and besides satisfactory HRMS data, the complete disappearance of allylic signals in the ^{1}H-NMR spectra supported the complete thiol–ene coupling reactions, together with the desired integration for the methyl protons of the SAc groups (48H) compared with those of amides (4H, δ 7.20 ppm), anomeric (4H, δ 4.20 ppm) and C_qCH_2S internal (8H, δ 2.75 ppm) protons. Our optimized S_N2 conditions between **8** (2.5 eq. per site) and **12** (G1) subsequently afforded G(2) dendrimer **13** harbouring 64-allyl functions in 73% yield (Scheme 3). Once again, the total absence of SAc signals in the ^{1}H-NMR spectra conjugated with the presence of the newly formed allylic signals confirmed the complete transformation of peracetylated G(1) dendrimer **12**. Moreover, the precise integration of the allylic protons compared nicely with those of the methylene linker at δ 1.90 ppm (OCH$_2$CH_2CH$_2$S) further confirming complete conversion which also discarded the possibility of thiol oxidation to cross-linked materials. Another strong evidence of the structure's uniformity was provided by Gel Permeation Chromatography (GPC) that clearly showed a symmetrical Gaussian pattern with a low PDI of 1.064 (see ESI†).



Scheme 3 Synthesis of polyol-terminated dendrimers **14** (G(1)) and **15** (G(2)) harbouring 32- and 128-OH groups.



Scheme 4 Synthesis of dendrimer **19** with 24-galactosides.

Finally, the photocapping of both G(1) (**11**) and G(2) (**13**) dendrimers with thioglycerol under standard conditions followed by dialysis (1.0 kDa cut-off) afforded the desired polyhydroxylated dendrimers **14** and **15**. Once again, ^{1}H- and ^{13}C-NMR spectra clearly indicated the absence of the olefinic protons, highlighting completion of the final multiple thiol–ene process in an excellent yield (>99% per addition). In parallel, the thiol–ene reaction between **17** and thiogalactoside **18**[9] provided glycodendrimer **19** having 24-appended sugar residues in a single step. The glycodendrimer was purified from excess thiol or disulphide through dialysis with a 2.5 kDa cutoff membrane. Notably, during the synthesis of dendrimers **14**, **15** and **19**, a carbohydrate (**8**) has been used as a highly functionalizable intermediate building block (AB_4), a situation not frequently encountered in the literature. Moreover, varying the type of building block between each generation of dendrimers has not been sufficiently exploited yet and we wish to coin this strategy as "an onion peel approach".

Following our synthesis, the improved protein binding properties of galactodendrimer **19** were evaluated using a galactoside specific bacterial lectin, LecA extracted from *P. aeruginosa*,[10] by surface plasmon resonance (SPR). For the interaction studies, the lectin was immobilized onto the surface of a CM5 sensor chip through usual amine coupling (see ESI†) and the corresponding sensorgrams for the specific interactions are shown in Fig. S1 (ESI†). The K_D value derived from the fitting of sensorgrams in a 1 : 1 Langmuir model was found to be 230 nM, which is significantly higher in comparison with monovalent galactosides (in the order of 10^{-4} M)[11] that can be explained on the basis of the "multivalency effect".

In conclusion, we developed an efficient orthogonal coupling strategy based on the combination of thiol–ene and S_N2 reactions. By using an orthogonal approach, multifunctional dendrimers were synthesized without the necessity for carrying out protection–deprotection steps and hence the approach is applicable to the construction of complex organic molecules. For the synthesis of dendrimers **14**, **15** and **19**, unexplored carbohydrate AB_4 building blocks were used. Interestingly, glycodendrimer **19** exhibited high affinity with the LecA lectin, highlighting the fact that globular dendritic systems with a low number of generations could efficiently serve as potent anti-adhesive agents against bacterial infections and biofilm formation. The strategy clearly pinpoints the high efficiency of sugars for the accelerated growth of multifunctional dendrimers within limited generation.

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