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Copper-catalyzed alkyne-azide cycloaddition for the functionalization of fullerene building blocks*

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Abstract: In this paper, we report our ongoing progress in the preparation of fullerene-azide or fullerene-alkyne building blocks, allowing their further chemical transformation under the copper-catalyzed alkyne-azide cycloaddition (CuAAC) reaction conditions.

Keywords: alkynes; azides; cycloadditions; fullerene chemistry; triazole.

INTRODUCTION

Carbon-rich nanostructures have been a major hot topic in chemical research over the past two decades [1]. In particular, fullerenes combining three-dimensionality with unique electronic properties are extremely promising nanostructures for the preparation of new advanced materials [2] or biologically active molecules [3]. The chemical reactivity of C_{60} is now well established, and a large number of fullerene derivatives have been prepared [4]. Whereas most of the fullerene derivatives reported to date have been prepared by the direct functionalization of C_{60} in the final step, the use of fullerene building blocks in multistep synthesis has not been often reported. This is mainly associated with the chemical reactivity of the fullerene moiety. Effectively, C_{60} derivatives react readily with radicals, various nucleophiles, and carbenes, and participate as reactive 2π components in a variety of cycloaddition reactions [4]. In this respect, the range of reactions that can be used for the further transformations of fullerene derivatives appears to be quite limited. Nonetheless, an increasing number of reactions involving fullerene building blocks have been reported in recent years. Examples are activation of fullerene-carboxylic acid derivatives for subsequent esterification or preparation of amides [5], condensation reactions [6], and construction of porphyrins from fullerene-benzaldehydes [7]. Recently, our group has started a research program on the preparation of fullerene-azide or fullerene-alkyne building blocks, allowing their further chemical transformation under the copper-catalyzed alkyne-azide cycloaddition (CuAAC) reaction conditions. In this paper, our ongoing progress in this particular field is summarized.

CLICK CHEMISTRY WITH FULLERENE MONO- AND BIS-ADDUCTS

Click chemistry is an attractive tool for fullerene chemistry as click reactions are modular, tolerant to a wide range of functional groups, and high yielding [8]. The copper-mediated Huisgen 1,3-dipolar cycloaddition of organic azides and alkynes [9] to give 1,2,3-triazoles is without any doubt the most

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useful member of this family of reactions. However, whereas this click reaction has proven to be powerful for a large variety of building blocks [10], its compatibility with fullerene derivatives was not obvious, as organic azides may also undergo [3 + 2]cycloadditions to the [6,6]double bonds of fullerenes [11]. Recently, the potential of the CuAAC reaction to functionalize fullerene derivatives has been systematically evaluated in our group [12–14]. The first series of click reactions was performed from fullerene derivatives functionalized with terminal alkyne groups (Fig. 1) [12]. Treatment of **1** (1 equiv) with benzyl azide (3 equiv), $CuSO_4 \cdot 5H_2O$ (0.1 equiv), and sodium ascorbate (0.3 equiv) in CH_2Cl_2/H_2O under vigorous stirring at room temperature for 96 h gave the cycloaddition product **2** in a moderate yield (48 %). The solubility of compound **1** is quite low, and all the starting material was not dissolved under the copper-mediated Huisgen reaction conditions. Thus, the reaction was slow, and side reactions, most probably cycloaddition of benzyl azides to the fullerene core, were observed. To solve this problem, it was decided to prepare a more soluble methanofullerene-alkyne derivative bearing a 3,5-didodecyloxybenzyl group (**3**). The reaction of this compound with benzyl azide in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate in CH_2Cl_2/H_2O could be achieved under optimized concentration conditions. Compound **4** was thus obtained in a good yield (80 %), thus showing that the reactivity of the fullerene moiety with organic azides plays only a minor role under copper-mediated Huisgen 1,3-dipolar cycloaddition conditions. To further decrease the reactivity of the C_{60} moiety toward the azide reagents in the click reactions, a fullerene bis-adduct bearing two terminal alkyne groups was prepared. It is well known that the reactivity of the fullerene unit is decreased by increasing the number of substituents on the carbon cage [15]. Reaction of **5** with benzyl azide under the conditions optimized for the preparation of compound **2** gave bis-1,2,3-triazole **6** in 70 % yield. When compared to the preparation of compound **2** from methanofullerene **1**, the increased yield can be explained by both the higher solubility of the starting terminal alkyne and the decreased reactivity of the bis-substituted fullerene group.

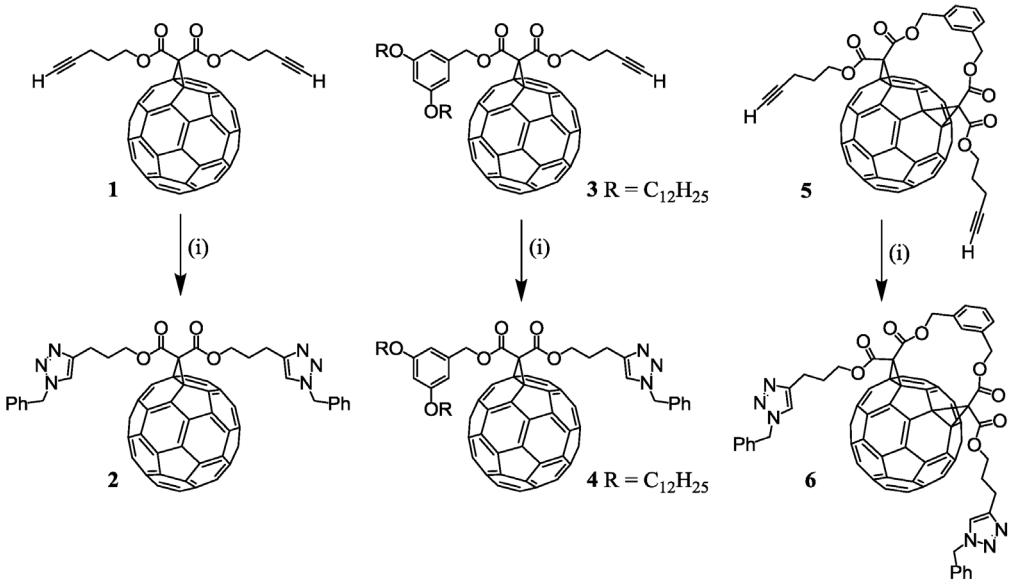

Fig. 1 CuAAC reactions with fullerene-alkyne building blocks. *Reagents and conditions*: (i) benzyl azide, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, CH_2Cl_2/H_2O, rt.

In a second series of CuAAC reactions, the use of fullerene building blocks functionalized with azide groups was evaluated [13]. To this end, the synthesis of methanofullerene derivatives substituted

with one or two azide groups was attempted. Unfortunately, these compounds were found to be very unstable in the solid state although reasonably stable in solution. Most probably, intermolecular cycloaddition reactions between the C_{60} and the azide groups led to complex mixtures of polymeric compounds. Actually, only fullerene bis-adducts were sufficiently stable to be used as synthetic intermediates in click reactions. This observation confirms the decreased reactivity of the fullerene moiety by increasing the number of substituents on the carbon cage. Bis-adduct **8** was obtained in 16 % yield by reaction of **7** with C_{60}, I_2, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at room temperature (Fig. 2).

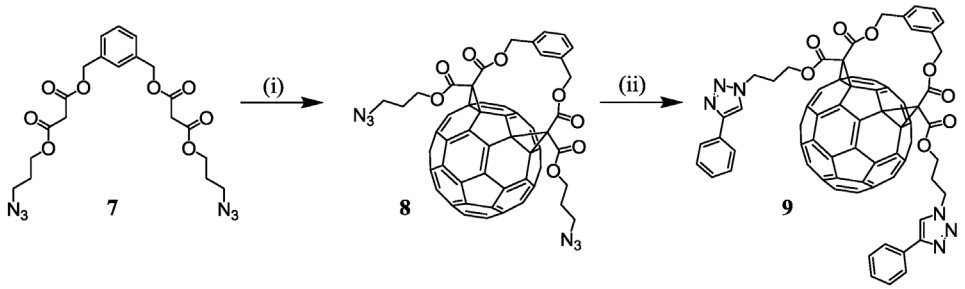

Fig. 2 Preparation of building block **8** and its subsequent reaction with phenylacetylene under CuAAC conditions. *Reagents and conditions*: (i) C_{60}, DBU, I_2, PhMe, rt (16 %); (ii) phenylacetylene, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, CH_2Cl_2/H_2O, rt (78 %).

Reaction of **8** with phenylacetylene under optimized conditions afforded bis-1,2,3-triazole **9** in 78 % yield. Indeed, upon preparation and purification, compound **8** must be used for the click reactions within the next couple of hours to obtain good yields. Therefore, the availability of this synthetic intermediate is quite limited. In order to obtain a stable fullerene azide derivative, it was decided to take advantage of the encapsulation of the fullerene sphere in a cyclic addend surrounded by two 3,5-didodecylbenzyl ester moieties [16]; the azide function being attached onto the bridging subunit. In this way, steric hindrance should prevent the reaction of the azide group with the C_{60} core and, thus, provide a stable compound [17]. The synthesis of building block **11** is depicted in Fig. 3.

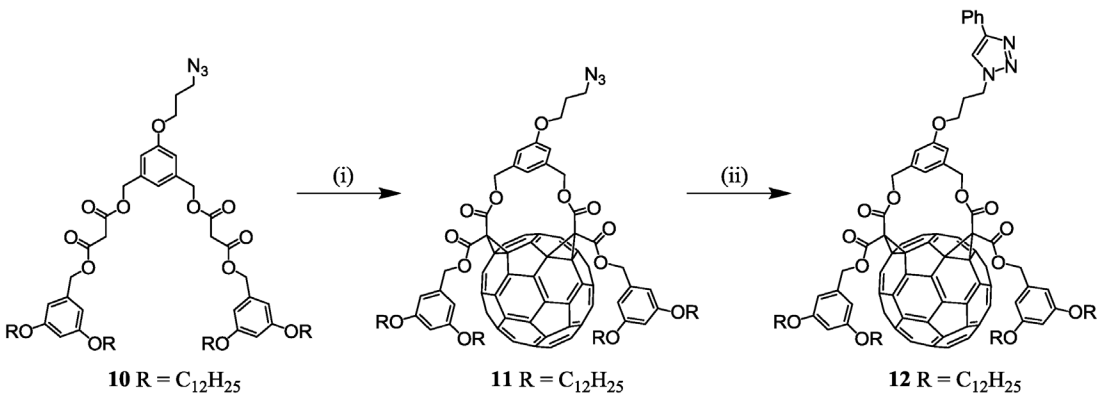

Fig. 3 Preparation of building block **11** and its subsequent reaction with phenylacetylene under CuAAC conditions. *Reagents and conditions*: (i) C_{60}, DBU, I_2, PhMe, rt (56 %); (ii) phenylacetylene, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, CH_2Cl_2/H_2O, rt (73 %).

Reaction of **10** with C_{60}, I_2, and DBU in toluene at room temperature afforded the cyclization product **11** in 56 % yield. Importantly, fullerene azide derivative **11** was found to be a stable compound under normal laboratory conditions. A sample was stored in the fridge for several months without any detectable decomposition. The reaction conditions for the 1,3-dipolar cycloaddition of compound **11** with terminal alkynes were adjusted with phenylacetylene. Under optimized conditions, a mixture of **11** (1 equiv), phenylacetylene (2 equiv), $CuSO_4 \cdot 5H_2O$ (0.1 equiv), and sodium ascorbate (0.3 equiv) in CH_2Cl_2/H_2O was vigorously stirred at room temperature for 12 h. After work-up and purification, compound **12** was thus obtained in 73 % yield.

Having developed a stable fullerene azide building block, allowing its further transformation under the CuAAC conditions, we have decided to use it for the preparation of a porphyrin-fullerene conjugate [18]. Indeed, porphyrins and fullerenes are interesting complementary building blocks for the preparation of artificial photosynthetic systems as photoinduced electron transfer is usually evidenced in fullerene-porphyrin conjugates [19]. As shown in Fig. 4, treatment of **13** with fullerene azide **11** in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate gave compound **14** in 64 % yield.

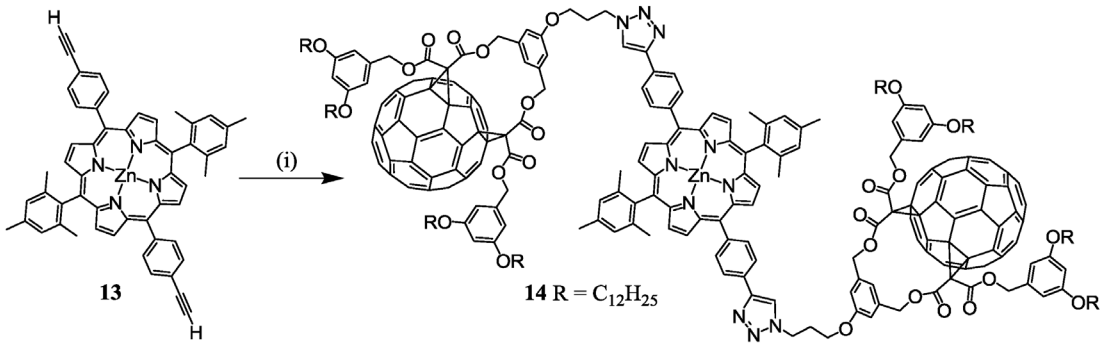

Fig. 4 Preparation of porphyrin-fullerene conjugate **14**. *Reagents and conditions*: (i) **11**, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, CH_2Cl_2/H_2O, rt (73 %).

The electrochemical and photophysical properties of the resulting multicomponent system have been investigated in detail [18]. In benzonitrile, **14** undergoes photoinduced electron transfer, and the resulting charge-separated state is relatively long-lived ($\tau = 0.48$ μs). In contrast, intramolecular energy transfer has been evidenced in toluene, with generation of the fullerene triplet level upon selective excitation of the porphyrin moiety. In this solvent, a charge-transfer (CT) emission band is observed in the near-infrared region ($\lambda_{max} = 940$ nm) as a consequence of a conformational equilibrium causing, to a minor extent, the formation of intramolecular porphyrin-fullerene tight pairs.

CLICK CHEMISTRY WITH FULLERENE HEXA-ADDUCTS

Fullerene hexakis-adducts with a T_h-symmetrical octahedral addition pattern have received increasing attention in the past few years [20]. As far as the synthesis of fullerene hexakis-adducts is concerned, most of them have been prepared by the one-pot reaction of C_{60} with malonates under the conditions initially developed by Hirsch [21] and further improved by Sun [22]. Whereas these reaction conditions are efficient for the synthesis of hexa-substituted fullerenes when starting from relatively simple malonates, structurally more complicated hexakis-adducts are generally obtained in rather low yields, and/or high-performance liquid chromatography (HPLC) is often required for their purification. In order to overcome this problem, we have decided to produce simple C_{60} hexakis-adduct derivatives bearing 12 terminal groups allowing their further functionalization. The grafting of 12 building blocks

onto this core requires however an extremely efficient reaction to obtain functionalized derivatives with good yields. Indeed, click chemistry appears to be perfectly suited for this purpose. To this end, a C_{60} hexakis-adduct bearing 12 azide groups has been prepared (Fig. 5) [23,24]. Reaction of malonyl dichloride with 3-bromopropan-1-ol (**15**) in the presence of pyridine afforded malonate **16** in 83 % yield. Subsequent treatment with sodium azide in dimethylformamide (DMF) at room temperature gave **17** in 95 % yield. Hexakis-adduct **18** was then readily synthesized by the reaction of C_{60} (1 equiv) with **17** (10 equiv), CBr_4 (100 equiv), and DBU (20 equiv) in *o*-dichlorobenzene (ODCB) at room temperature. The mixture was stirred for 72 h and evaporated. The resulting sample was separated on a silica-gel column in a relatively straightforward fashion to obtain **18** in 62 % yield. The reaction conditions for the 1,3-dipolar cycloaddition of compound **18** with terminal alkynes were first adjusted with phenylacetylene (**19a**) (Fig. 5). Under optimized conditions, a mixture of **18** (1 equiv), **19a** (13 equiv), $CuSO_4{\cdot}5H_2O$ (0.1 equiv), and sodium ascorbate (0.3 equiv) in CH_2Cl_2/H_2O was vigorously stirred at room temperature for 12 h. After work-up and purification, compound **20a** was thus obtained in 78 % yield.

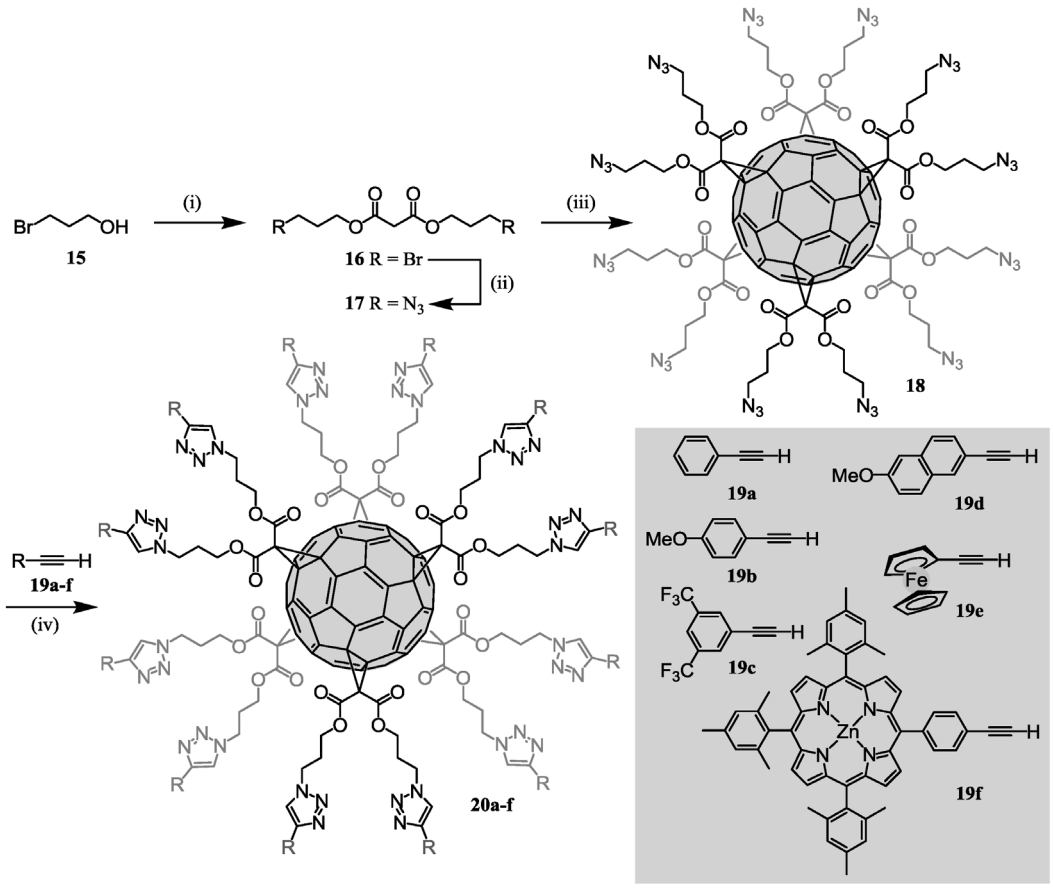

Fig. 5 Preparation of building block 18 and its subsequent reaction with terminal alkynes **19a–f** under CuAAC conditions. *Reagents and conditions*: (i) CH_2Cl_2, pyridine, 0 °C to rt, 18 h (83 %); (ii) NaN_3, DMF, rt, 16 h (95 %); (iii) C_{60}, ODCB, DBU, CBr_4, rt, 72 h (62 %); (ivi) $CuSO_4{\cdot}5H_2O$, sodium ascorbate, CH_2Cl_2, H_2O, rt, 12 h (**20a**: 78 %, **20b**: 61 %, **20c**: 56 %, **20d**: 63 %, **20e**: 81 %, **20f**: 74 %).

The reaction conditions used for the preparation of **20a** from phenylacetylene were then applied to the terminal alkynes **19b–f**. The clicked derivatives **20b–f** were thus obtained in 56–81 % yields. The structure of compounds **20a–f** was confirmed by their ^{1}H and ^{13}C NMR spectra as well as by mass spectrometry. Inspection of the ^{1}H NMR spectra clearly indicates the disappearance of the CH_2-azide signal at δ 3.33 ppm. IR data also confirmed that no azide (2092 cm^{-1}) residues remain in the final products. Importantly, the ^{1}H NMR spectra of **20a–f** show the typical singlet of the 1,2,3-triazole unit at ca. δ 7.5–7.8 ppm as well as the signal corresponding to the CH_2-triazole protons at ca. δ 4.3–4.4 ppm. Finally, the two expected resonances of the C atoms of the 1,2,3-triazole unit are clearly observed in the ^{13}C NMR spectra of **20a–f**.

The preparation of a C_{60} hexakis-adduct bearing 12 trimethylsilyl (TMS)-protected alkyne groups allowing the attachment of 12 azide units under the copper-mediated Huisgen 1,3-dipolar cycloaddition conditions has also been reported [25]. As shown in Fig. 6, compound **21** was desilylated in situ with tetrabutylammonium fluoride (TBAF) to form the corresponding hexa-adduct bearing 12 terminal alkyne units, to which a suitable azide precursor was subsequently clicked. Under typical conditions, a mixture of **21** (1 equiv), TBAF (14 equiv), **Gn-N$_3$** (13 equiv), $CuSO_4 \cdot 5H_2O$ (0.1 equiv), and sodium ascorbate (0.3 equiv) in CH_2Cl_2/H_2O was vigorously stirred at room temperature for 12 h. The resulting 1,2,3-triazole-linked fullerodendrimers **22a–c** were thus obtained in 58–84 % yield. It is worth noting that a first-generation dendritic C_{60} hexa-adduct similar to **22b** was already reported by Hirsch and co-workers [26]. The latter was obtained in a low yield (5 %) from C_{60} and the corresponding dendritic malonate, furthermore, preparative HPLC was required for its purification. In contrast, compound **22b**

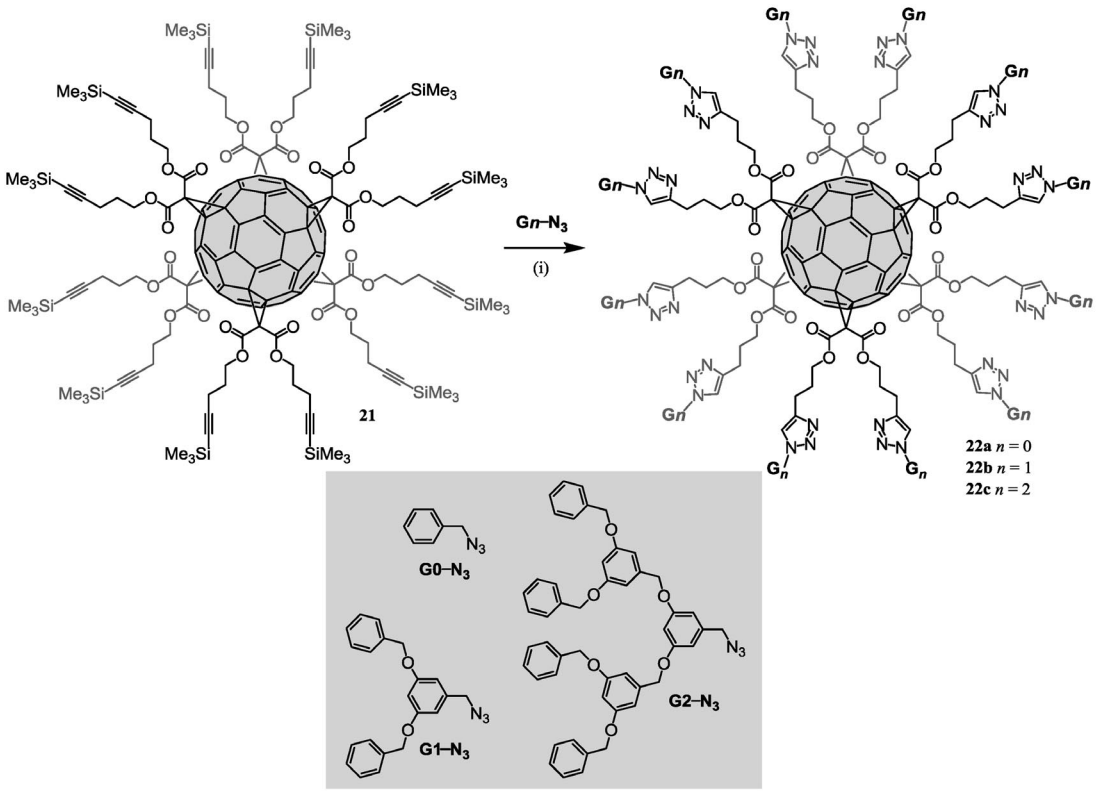

Fig. 6 CuAAC reactions with building block **21**. *Reagents and conditions*: (i) TBAF, $CuSO_4 \cdot 5H_2O$, sodium ascorbate, CH_2Cl_2, H_2O, rt, 12 h (**22a**: 58 %, **22b**: 84 %, **22c**: 67 %).

was prepared in a good yield from **21** and its purification was easily achieved on a silica-gel column. Furthermore, the second-generation derivative (**22c**) was also obtained in a good yield from **21**. Actually, the preparation of such a second-generation fullerodendrimer is nearly impossible from the corresponding malonate and C_{60}. The latter observations clearly show the advantages of the synthetic method based on the post-functionalization of a readily available fullerene hexa-adduct under the copper-mediated Huisgen reaction conditions.

The polycationic fullerene hexa-adduct derivative **23** (Fig. 7) was prepared by following the same synthetic strategy based on the post-functionalization of a readily available fullerene hexa-adduct building block [27]. Interestingly, polyplexes prepared from DNA and this globular compact polycationic derivative revealed remarkable gene delivery capabilities. Indeed, compound **23** has enough amino groups to ensure DNA compaction into stable and positively charged polyplexes that fruitfully deliver DNA into cells. Furthermore, this spherical compound exhibits high efficiency, while maintaining low toxicity. Importantly, in contrast to classical dendritic vectors for which high efficiency requires generally high-generation numbers [28], the compact hexasubstituted fullerene core led to globular systems even with low-generation dendrons, and thus the gene delivery capability is already optimum for the second-generation compound.

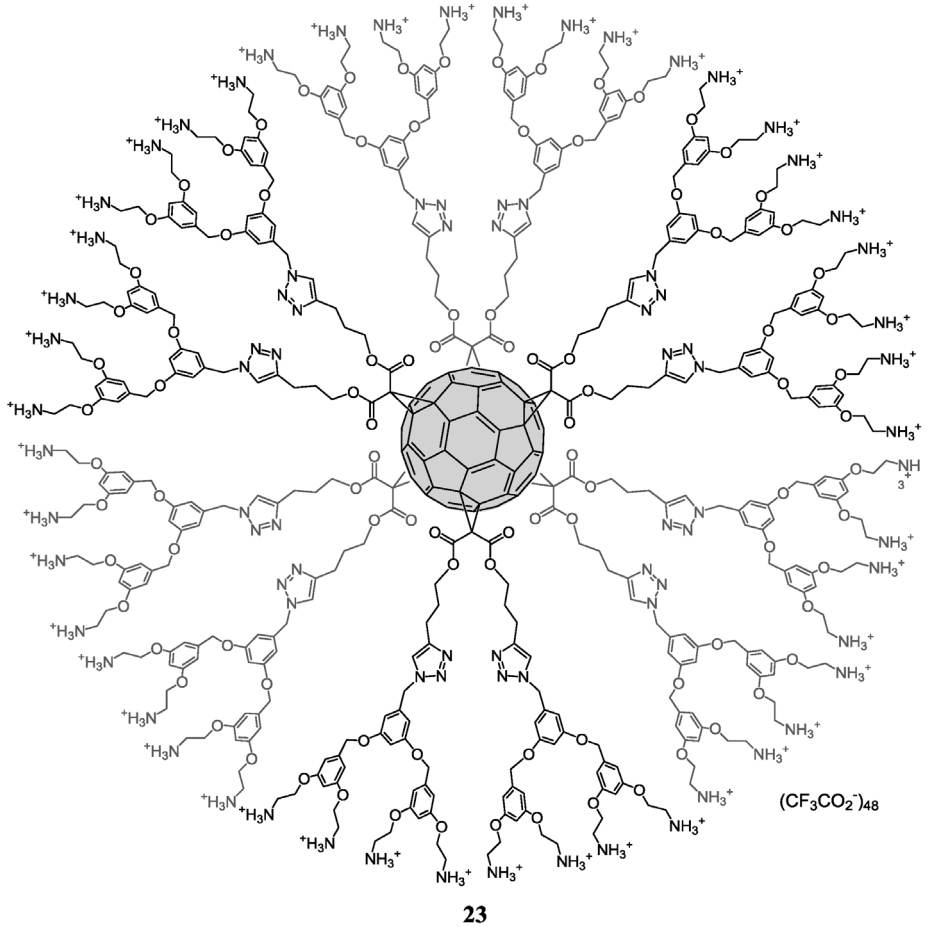

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Fig. 7 Polycationic fullerene hexa-adduct derivative **23**.

The synthetic approach based on click chemistry for the functionalization of fullerene hexakis-adduct building blocks was also used for the synthesis of fullerene glycoconjugates in which the C_{60} core is completely surrounded by sugar residues [29]. This methodology allows for the direct grafting of unprotected sugar derivatives onto the fullerene core and a large variety of fullerene sugar balls became thus easily available (Fig. 8) [29–32]. Importantly, the apparent structural sophistication of

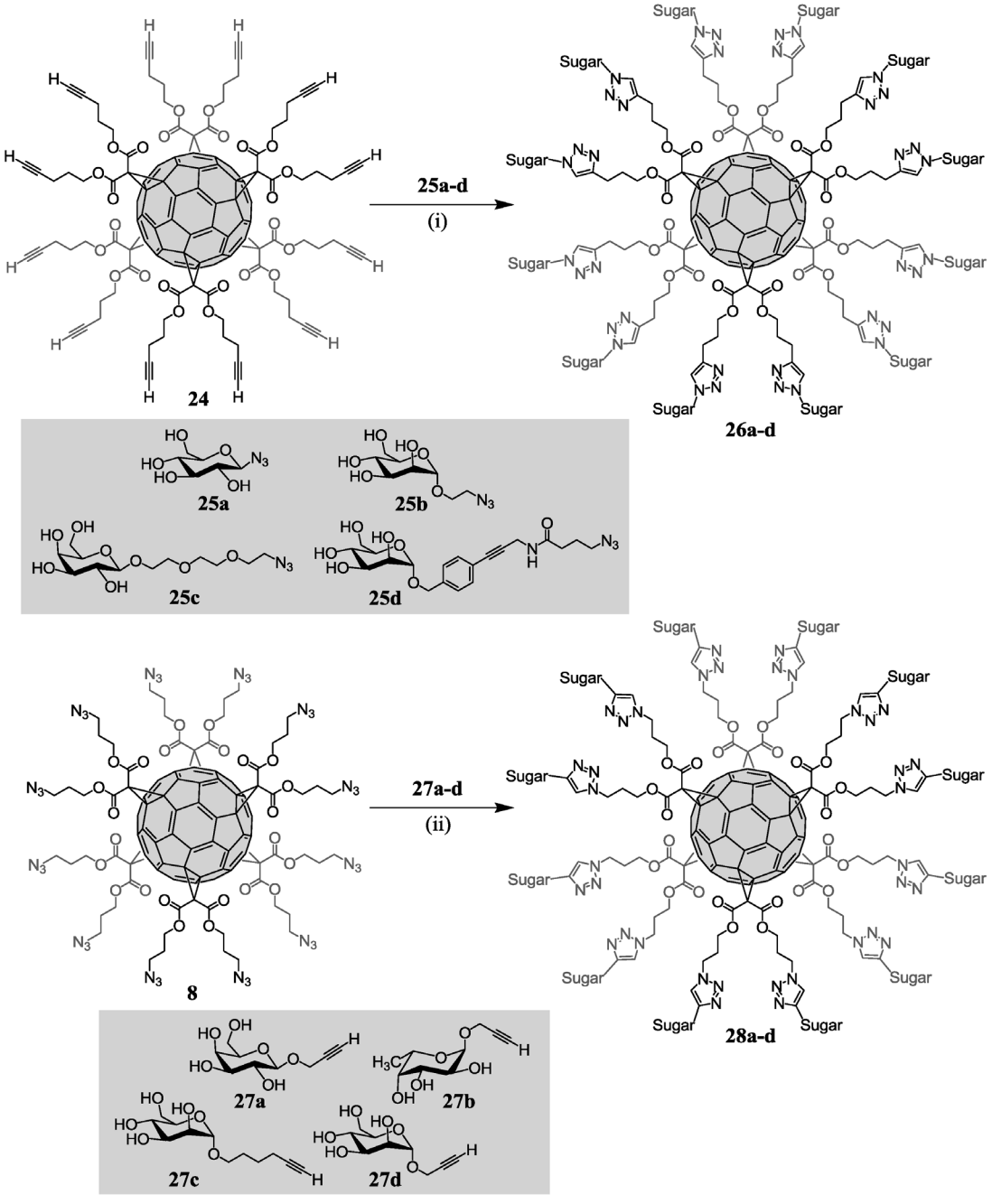

Fig. 8 Preparation of fullerene sugar balls.

compounds **26a–d** and **28a–d** is not associated with complicated synthetic routes. For example, compound **26a** has been prepared on a 500 mg scale in four synthetic steps from commercially available compounds in an overall 21 % yield. Applications of such compounds are therefore not limited by their availability. In addition, hexa-substituted fullerene derivatives are only weak electron acceptors [15] and are no longer efficient singlet oxygen sensitizers [33]. Therefore, the problems associated with the photo-toxicity of mono- or di-substituted fullerene derivatives resulting from the production of ROS (reactive oxygen species) are prevented in the case of hexasubstituted derivatives. We have recently started to evaluate the biological activities of this unique family of globular glycoconjugates. For example, fullerene hexakis-adducts **26d**, **28c**, and **28d** bearing 12 peripheral mannose moieties have been very recently assayed as inhibitors of FimH [30], a bacterial adhesin involved in the adhesion of uropathogenic *E. coli* bacterium to host cells. Remarkably, low nanomolar affinities were measured by isothermal titration calorimetry (ITC) and surface plasmon resonance (SPR). However, *no multivalent effects could be evidenced*. Indeed, contrary to many plant and bacterial lectins that are multimeric and may give rise to multivalent effects, FimH is a monomeric adhesine for which such effects are not observed. However, a single fullerene sugar ball molecule can accommodate several FimH molecules (up to 7), and thus the mannosylated fullerene derivatives displayed significantly higher inhibition levels than their corresponding monomers in hemagglutination inhibition assays.

The study of the binding affinity of glycofullerene **26b** to Concanavalin A (Con A) was carried out by ITC measurements [34]. A remarkable increase (over two orders of magnitude) of the binding constant relative to monomer sugar used as a reference was evidenced, thus showing that the high local concentration of carbohydrates around the C_{60} core in fullerene sugar balls is perfectly suited to the binding of lectins through the "glycoside cluster effect" [35]. Glycoclusters **26c** and **28a** were also evaluated as ligands of PA-IL [31], a bacterial lectin from the opportunistic pathogen *Pseudomonas aeruginosa* involved in recognition of glycoconjugates on human tissues [31]. The affinities measured by hemagglutination inhibition assay, enzyme-linked lectin assay (ELLA) and SPR displayed also a significant "glycoside cluster effect" with up to 12 000-fold increase in binding when comparing an appropriate monovalent carbohydrate reference probe with the dodecavalent fullerene-based glycoclusters. Compounds **26c** and **28a** are among the most potent ligands of PA-IL measured to date, and they can be considered as potential anti-adhesive agents against infection by *P. aeruginosa*.

CONCLUSIONS

It appears clearly that click chemistry is an interesting tool for the functionalization of fullerene building blocks. As far as fullerene mono- and bis-adducts are concerned, we have shown that the reactivity of C_{60} toward azides is not significantly competing with the cycloaddition leading to the desired 1,2,3-triazole derivatives and good yields can be obtained when fullerene derivatives with reasonable solubility are used as starting materials. In particular, bis-adduct derivatives bearing alkyne or azide groups appear to be the most promising building blocks for the synthesis of more complex fullerene derivatives. In the case of fullerene hexakis-adducts, we have shown that the synthesis of functionalized derivatives can be achieved by the post-functionalization of readily available fullerene hexa-adducts under the CuAAC reaction conditions. Importantly, this synthetic method allows for the efficient preparation of functionalized derivatives that would be nearly impossible to prepare by reaction of malonates with C_{60}. As the CuAAC reaction is modular, tolerant to a wide range of functional groups, and high yielding, a large number of functionalized fullerene hexakis-adducts are now easily accessible.

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