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'Click' chemistry as a tool for the facile synthesis of fullerene glycoconjugate derivatives

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ABSTRACT

A bis-malonate C_{60} derivative bearing terminal alkyne groups prepared by the Bingel reaction has been used as a building block under copper-catalyzed azide–alkyne cycloaddition conditions to produce a series of new fullerene glycoconjugate derivatives.

Almost twenty years have passed since fullerene C_{60} was made accessible for researchers in large quantities by the Krätschmer-Huffman method.[1] The chemistry of C_{60} is a well established field of research and the knowledge accumulated in the last two decades has revealed both potentials and limitations of this molecule and its derivatives. Chemically modified fullerenes have found very promising applications in two main fields: nanomaterial sciences[2] and medicinal chemistry.[3] For the latter, the potential of C_{60} can be exemplified by the use of certain derivatives in DNA cleavage,[4] enzymatic inhibition,[5] and cytotoxicity by generating singlet oxygen under light.[6]

For biological use, many different strategies have been explored to render the fullerene C_{60} biocompatible.[7] Covalent chemical functionalization of fullerenes seems of fundamental importance for this end and the design of fullerene derivatives containing a sugar on its surface is particularly interesting. It is known that sugar moieties in biomolecules have important roles including cellular transport and adhesion phenomena.[8] It has yet been shown that fullerene glycoconjugates have an activity similar to lectins and participate in molecular recognition between cells.[9] Based on previous work, it is also reasonably clear that the sugar linkage to C_{60} may bring about notable biological and physicochemical properties.[10]

Since Vasella et al.[11] reported the fullerene glycoconjugate derivatives obtained through addition of glycosylidene carbenes, different types of procedures have been employed to synthesize this type of compound. Among the methods cited in the literature to produce fullerene-carbohydrates, cycloaddition reactions are the most useful. Dondoni and Marra[12] have synthesized a fulleropyrrolidine glycoconjugate by a [3+2] cycloaddition with *C*-glycosyl azomethine ylides. Mikata et al.[13] reported a [3+2] cycloaddition reaction of 2′-azidoethyl per-*O*-acetyl-α-D-mannopyranoside to C_{60} furnishing a fullerene glycoconjugate which produced singlet oxygen under laser irradiation and exhibited photocytotoxicity. Based on the Diels–Alder reaction, Liu and co-workers[14] prepared a fullerene bearing β-cyclodextrin as an efficient photodriven DNA-cleavage reagent. Recently, Tanimoto et al.[15] have described the use of a fullerene glycoconjugate hybrid obtained by cycloaddition in the photodegradation of HIV-protease.

Considering the high potential of fullerene glycoconjugates, the development of general methodologies to build these compounds is necessary. A method rarely used to obtain fullerene-carbohydrates is Bingel's cyclopropanation.[16] This reaction, very useful in the chemistry of fullerenes, has been used only once to obtain glycoconjugates. Enes et al. produced a fullerene glycoconjugate mono-adduct with a good oxygen quantum yield.[17] The authors obtained the target fullerene by reaction between a sugar malonate and C_{60} under Bingel conditions. Thus, most of the fullerene glycoconjugate derivatives have been prepared by the direct functionalization of C_{60} in the final step in low to moderate yields. Actually, the use of fullerene building blocks in multi-step synthesis has been very scarcely considered in the literature. This is mainly due to the chemical reactivity of the fullerene, which reacts readily with nucleophiles or unsaturated compounds. Therefore, the range of reactions that can be used for the further transformations of fullerene derivatives is quite limited. The 'click' chemistry appears to be an attractive tool for fullerene chemistry as click reactions are

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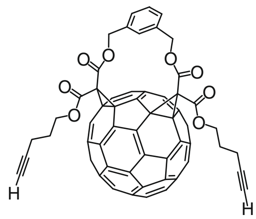


1

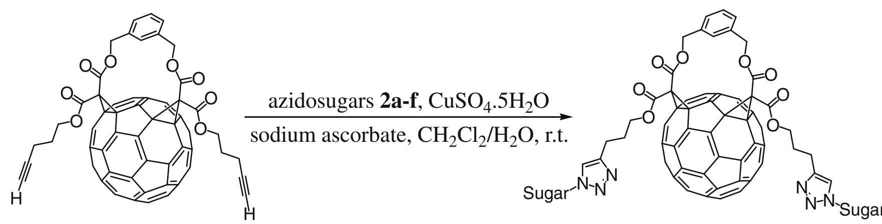
Figure 1.

tolerant to a wide range of functional groups, clean, and high yielding. The most popular 'click' reaction, the copper-catalyzed azide-alkyne cycloaddition (CuAAC) has been used recently to obtain highly functionalized fullerene derivatives.[18] However, most of the methods described are specific and only one example is known for the synthesis of fullerene glycoconjugates via a 'click' reaction.[19]

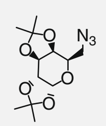
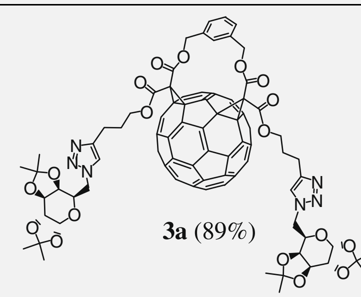
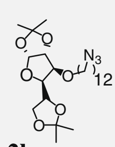
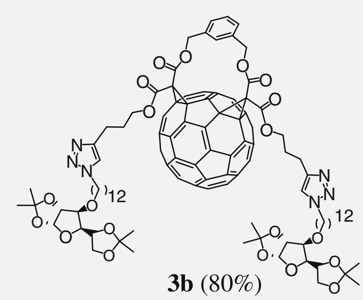
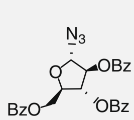
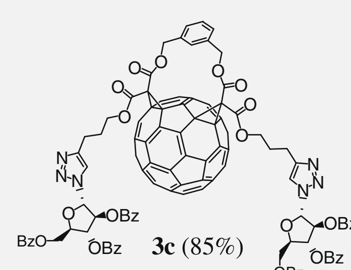
As part of our research program on fullerene derivatives, we have evaluated the use of a stable fullerene bis-adduct building block (**1**) bearing two terminal alkynes (Fig. 1) to produce fullerene glycoconjugate derivatives under CuAAC conditions. To the best of our knowledge, there are no examples in the literature of bis-adduct fullerene glycoconjugates obtained through a combination of Bingel's cyclopropanation conditions and the 'click' reaction.

Fullerene derivative **1** was prepared as described in the literature.[20] The preparation takes advantage of the regioselective reaction with bis-malonate derivatives[21] which leads to macrocyclic bis-adducts of C_{60} by a double Bingel cyclopropanation at the *C*-sphere.

Table 1
One-pot synthesis of fullerene bis-adducts

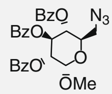
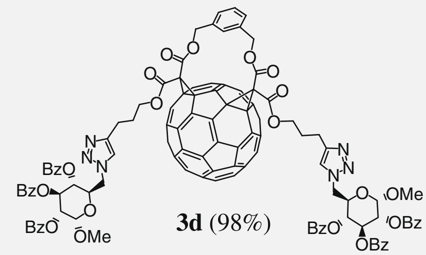
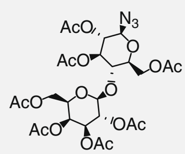
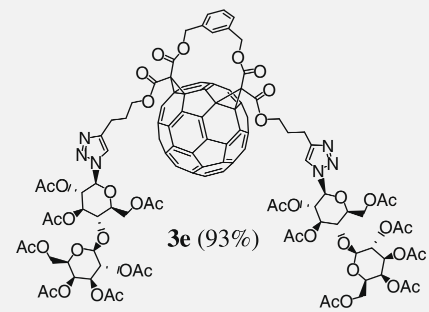
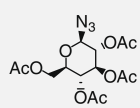
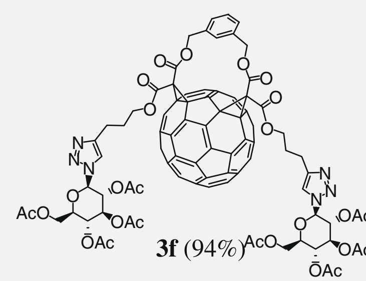


1 3a-f

Entry	Azidosugar	Bistriazole carbohydrate fullerene
1	 **2a**	 **3a** (89%)
2	 **2b**	 **3b** (80%)
3	 **2c**	 **3c** (85%)

(*continued on next page*)

Table 1 (*continued*)

Entry	Azidosugar	Bistriazole carbohydrate fullerene
4	 **2d**	 **3d** (98%)
5	 **2e**	 **3e** (93%)
6	 **2f**	 **3f** (94%)

We have chosen a bis-adduct bearing two terminal alkyne groups and not a mono-adduct to decrease the reactivity of the C_{60} moiety toward the azide reagents[20] and increase the solubility of fullerene for the 'click' reaction. It is important to observe that in the Bingel reaction for preparation of compound **1** we must use a limited number of equivalents of iodine. An excess of iodine frequently produces a mixture of side products which complicates purification. The reaction of **1** with sugar azides **2a–f** in the presence of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in CH_2Cl_2/H_2O gave the corresponding 1,2,3-triazole fullerene glycoconjugates with yields of 80–98%.[22] The organic azides were prepared using classical reactions of sugars.[23] We have used sugars bearing different protecting groups to show the generality of the method. The results are summarized in Table 1. The structures of all fullerene glycoconjugates were confirmed by ^{1}H and ^{13}C NMR, IR, and mass spectrometry.[24] Deprotection of the hydroxyl groups in fullerene glycoconjugate **3a** with trifluoroacetic acid[25] afforded the corresponding deprotected derivative in 78% yield.[26] Under similar reaction conditions, deprotection of the hydroxyl groups in compound **3b** led to a solid insoluble both in water and in organic solvents. The lack of solubility of that product prevented its structural characterization.[25]

In conclusion, we have shown that the CuAAC reaction of azide-containing sugars and alkyne-fullerene **1** is an interesting tool to obtain fullerene glycoconjugate derivatives. Several methods are cited in the literature to produce fullerene glycoconjugates. However, the use of the 'click' reaction combined with the Bingel reaction to produce fullerene glycoconjugates is an innovative route. Additionally, the use of the 'click' reaction as the last step to functionalize the fullerene presents the advantage of higher global yields when compared with a cycloaddition reaction or the Bingel reaction using highly functionalized malonates. The approach is very simple and general, and the introduction of other biomolecules (such as amino acids) and labels (for example biothin) can also be easily made by this approach.

Acknowledgments

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References and notes

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22. To a mixture of azide **2a** (37 mg, 0.130 mmol) and bis alkyne fullerene **1** (50 mg, 0.043 mmol) in 2 mL of dichloromethane, was added $CuSO_4{\cdot}5H_2O$ (1.0 mg, 0.004 mmol) and 2 mL of an aqueous solution of sodium ascorbate, previously prepared from ascorbic acid (2.3 mg, 0.013 mmol) and sodium bicarbonate (2.5 mg, 0.013 mmol). The mixture was stirred for 24 h at room temperature, the organic layer was diluted with dichloromethane, and washed with water. The organic phase was dried over anhydrous Na_2SO_4 and filtered. The crude mixture was concentrated and purified by column chromatography (SiO_2, CH_2Cl_2 then CH_2Cl_2/MeOH 99/1). *Compound* **3a**: IR (neat): ν 3054 (C–H aromatic), 2984 (C–H), 1745 (C=O), 1246 (C–O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.27, 1.36, 1.38, 1.48 (s, 24H), 2.14 (pseudo qn, 4H), 2.82 (t, J = 7.2 Hz, 4H), 4.18–4.20 (m, 4H), 4.43–4.64 (m, 8H), 5.21 (d, J = 12.8 Hz, 2H), 5.49 (d, J = 2.8 Hz, 2H), 5.89 (d, J = 12.8 Hz, 2H), 7.32–7.50 (m, 4H), 7.54 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 22.12, 24.61, 25.08, 26.13, 26.20, 28.37, 49.52 (methano bridge), 50.74, 66.41, 67.25 ($2C_{60}$-sp^3), 67.52, 67.72, 70.53, 70.94, 71.41, 96.41, 109.23, 110.06, 122.58, 124.14, 127.04, 128.89, 131.09, 134.98, 136.11, 136.14, 136.52, 136.87, 137.96, 140.24, 141.26, 142.58, 141.26, 143.23, 143.52, 143.85, 144.04, 144.24, 144.43, 144.63, 144.86, 145.28, 145.27, 145.46, 145.90, 145.99, 146.20, 146.23, 146.33, 147.26, 147.77, 148.91, 162.96, 163.14. ESI-MS m/z calcd for $C_{108}H_{60}N_6O_{18}$ $[M+H]^+$ 1728.4, found 1729.4.
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24. *For example compound* **3c**: IR (neat): ν 3059 (C–H aromatic), 2965 (C–H), 1726 (C=O), 1262 (C–O). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.12–2.15 (m, 4H), 2.84–2.87 (m, 4H), 3.80–4.46 (m, 8H), 4.52–5.24 (m, 2H), 5.30 (br s, 2H), 5.81–5.96 (m, 4H), 6.19–6.28 (m, 4H), 7.28–7.35 (m, 4H), 7.49–8.18 (m, 32H). ^{13}C NMR ($CDCl_3$, 50,32 MHz): δ 21.82, 27.91, 53.50 (methano bridge), 65.93, 65.94, 67.00, 67.43, 68.96, 70.65 ($2C_{60}$-sp^3), 71.47, 86.71, 119.58, 123.84, 128.43, 129.71, 133.70, 135.86, 136.22, 136.59, 140.00, 141.01, 141.29, 142.31, 142.93, 143.26, 143.56, 143.76, 143.98, 144.20, 144.32, 144.56, 144.97, 145.18, 145.36, 145.60, 145.73, 146.05, 147.28, 147.46, 148.63, 162.71, 162.91, 164.64, 165.38, 165.59. ESI-MS m/z calcd for $C_{136}H_{64}N_6O_{22}$ $[M+H]^+$ 2132.4 found 2133.3. *Compound* **3f**: IR (neat): ν 3144 (C–H aromatic), 2955 (C–H), 1744 (C=O), 1220 (C–O). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.71 (s, 6H), 2.03–2.07 (s, 22H), 2.83 (t, J = 7.2 Hz, 4H), 3.98–4.32 (m, 4H), 4.32–4.42 (m, 2H), 5.27–5.43 (m, 12H), 5.86–5.93 (m, 4H), 7.27–7.53 (m, 4H), 7.55 (s, 2H); ^{13}C NMR ($CDCl_3$, 50,32 MHz): δ 20.24, 20.62, 20.78, 21.95, 28.01, 49.20 (methano bridge), 61.69, 66.07, 67.11, 67.62, 67.84, 70.39 ($2C_{60}$-sp^3), 70.76, 72.68, 75.13, 85.75, 119.75, 124.12, 126.93, 128.79, 136.73, 146.23, 140.11, 141.13, 141.40, 141.44, 141.45, 143.08, 143.40, 143.73, 144.46, 144.73, 145.13, 145.33, 145.53, 145.86, 145.21, 147.27, 147.65, 148.76, 163.03, 163.04, 168.94, 169.44, 169.96, 170.55.
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26. ESI-MS m/z calcd for $C_{96}H_{44}N_6O_{18}$ $[M+H]^+$ 1569.27 found 1569.1.