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Design and synthesis of C_{60}–benzenesulfonamide conjugates

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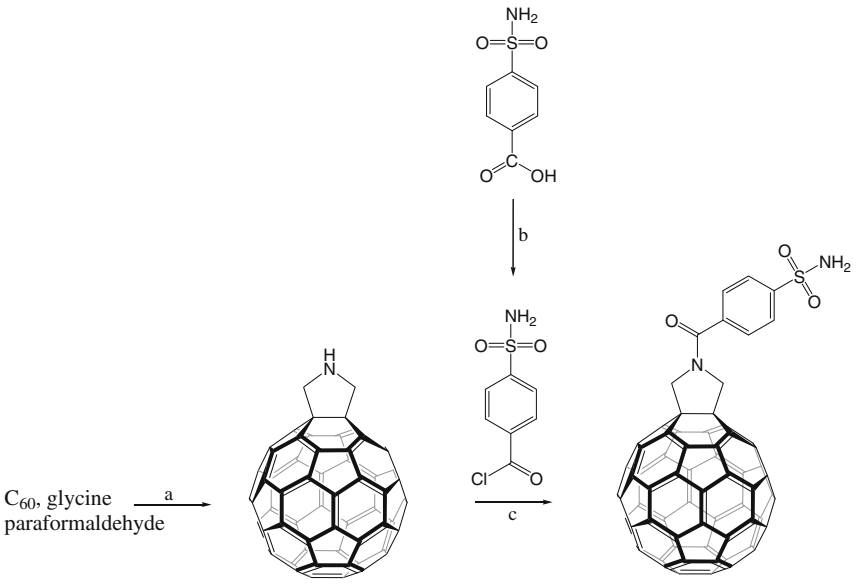
ABSTRACT

Synthesis of C_{60}–benzenesulfonamide conjugates is reported. The strategies for improving their water solubility, as required for binding to human carbonic anhydrase II, are discussed.

Since its discovery in 1985,[1] the unique physical properties and chemical reactivity of C_{60} (fullerene) have led to the exploration of its utility in myriad applications ranging from enzyme inhibitors[2] to chemical sensors[3] to superconductivity.[4] To date, the use of C_{60} for biological and medicinal purposes has largely been limited by its poor aqueous solubility, but the development of soluble host-guest encapsulation complexes[5,6] and covalent derivatization of the C_{60} scaffolding itself with polar groups[7] have facilitated the preparation of aqueous C_{60} solutions. Importantly, the substituents used to covalently modify C_{60} not only influence aqueous solubility but also influence and direct biological activity.[8] Accordingly, C_{60} derivatives have been utilized in numerous biological applications, for example, as neuroprotective agents,[9] photosensitizers for photodynamic therapy,[10] MRI contrast agents,[11] and transfection agents.[12]

A number of C_{60} derivatives have been reported to inhibit pharmaceutically important enzymes such as HIV-1 protease[13] and



Scheme 1. Reagents: (a) toluene, reflux; (b) $SOCl_2$; (c) pyridine.

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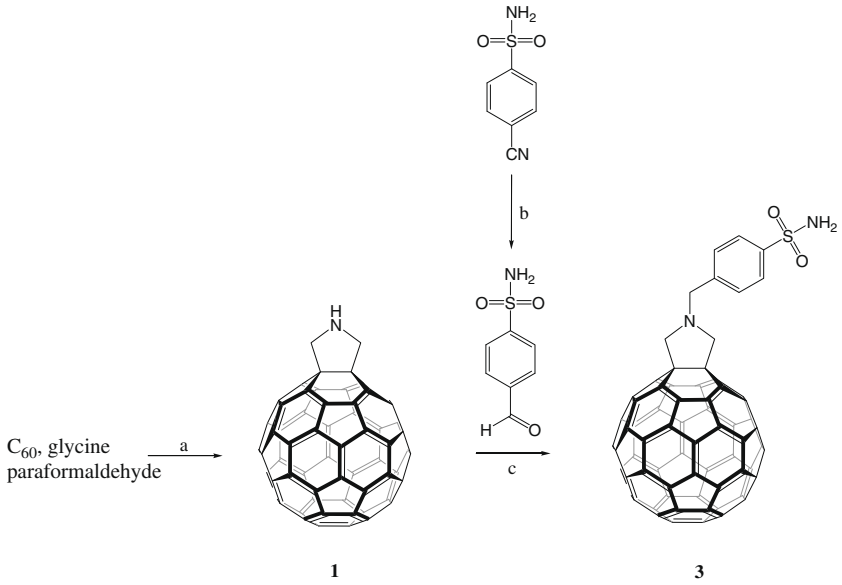


Scheme 2. Reagents and conditions: (a) toluene, reflux; (b) Raney Ni/HCOOH; (c) $NaBH(OAc)_3$, AcOH.

acetylcholinesterase.[14] In these examples, C_{60} is used as a scaffold to which appropriate functional groups are attached to make specific noncovalent interactions in enzyme active sites based on molecular modeling studies. Remarkably, while molecular models of such protein–fullerene complexes have been described,[13,15] an X-ray crystal structure determination of a protein–fullerene complex has never been reported.

With an eye toward the ultimate crystal structure determination of a protein–fullerene complex, we now describe the synthesis of C_{60}–benzenesulfonamide conjugates designed to bind to human carbonic anhydrase II (CAII). This zinc metalloenzyme serves as a useful model system for studying protein–ligand interactions.[16] Importantly, CAII contains a cone-shaped active site capable of accommodating C_{60} tethered to a benzenesulfonamide moiety that confers specificity of binding to the Zn^{2+} ion at the base of the active site; thus, the conjugation of C_{60} to the benzenesulfonamide moiety is expected to anchor C_{60} in the enzyme active site. The preparation of C_{60}–benzenesulfonamide conjugates described below represents a series of new chemical entities in the functionalization of C_{60}.

The first C_{60}–sulfonamide conjugate (compound **2**) was obtained by acylation of the previously reported fulleropyrrolidine **1**[17] (Scheme 1), which was handled in dilute solutions to prevent polymerization.

An alternative C_{60}–benzenesulfonamide conjugate (**2**) was prepared by reductive amination of 4-formylbenzenesulfonamide[18] with fulleropyrrolidine **1** (Scheme 2). Reductive amination using $NaBH(OAc)_3$ has been previously reported as an excellent method to generate N-alkylated fulleropyrrolidines.[19]

A C_{60}–benzenesulfonamide conjugate with a longer linker between C_{60} and the benzenesulfonamide moiety (compound **5**) was prepared by the acylation of aminofullerene **4**[20] with 4-aminosulfonylbenzoyl chloride[21] (Scheme 3).

Treatment of aminofullerene **6**[22] with 4-aminosulfonylbenzoyl chloride (Scheme 4) gave a conjugate with a different angle of attachment between the benzenesulfonamide moiety and C_{60}.

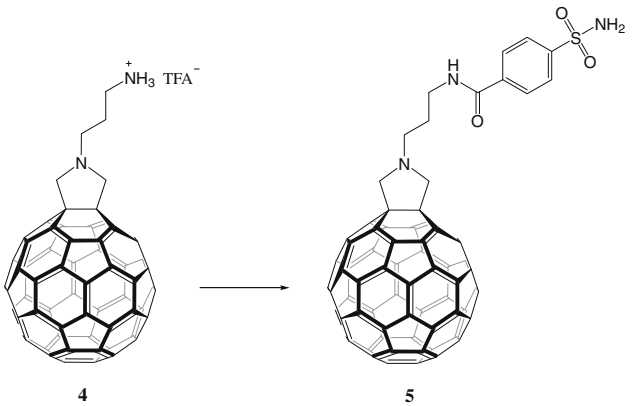
The C_{60}–benzenesulfonamide conjugate **3** was insoluble in water-miscible solvents. While all other derivatives **2**, **5**, and **7** were soluble in dimethylsulfoxide (DMSO) and dimethylformamide (DMF), our attempts to produce stable aqueous solutions with organic cosolvent content <50% (vol/vol) failed. Thus, to improve the aqueous solubility of C_{60}–benzenesulfonamide conjugates, we explored further derivatization of **7** with polar groups.

Direct derivatization of **7** with the protected water-solubilizing groups, generated by the reaction of malonyl chloride with *tert*-butyl 3-hydroxypropionate, was attempted under Bingel conditions[23] but there was no evidence for product formation. To improve the solubility of compound **7** in the nonpolar solvents commonly used for Bingel reactions, the sulfonamide was protected with 2,4-dimethoxybenzyl (DMB) groups.

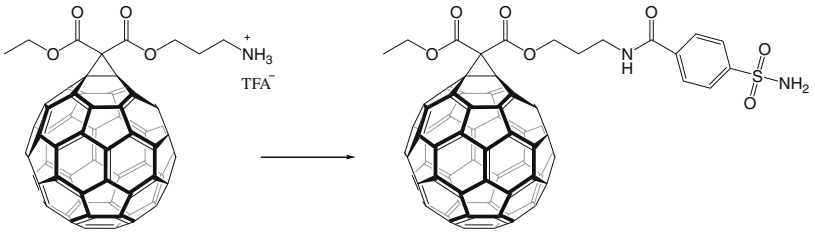
The new sequence began with compound **10** which itself was available in 3 steps from 2,4-dimethoxybenzylamine and 2,4-dimethoxybenzaldehyde (Scheme 5).

Compound **10** was derivatized with the protected water-solubilizing groups under Bingel conditions to form a mixture of regioisomers (Scheme 6). The sulfonamide and the carboxylic acid-protecting groups were then removed under acidic conditions to yield **11**.

Unfortunately, the solubility of compound **11** in DMSO/water mixtures was only slightly improved in comparison with that of compound **7**. At this stage it became evident that addition of multiple water-solubilizing groups would be desirable. Our efforts along these lines will be reported in due course.



Scheme 3. Reagents and conditions: 4-aminosulfonylbenzoyl chloride, triethylamine (TEA).



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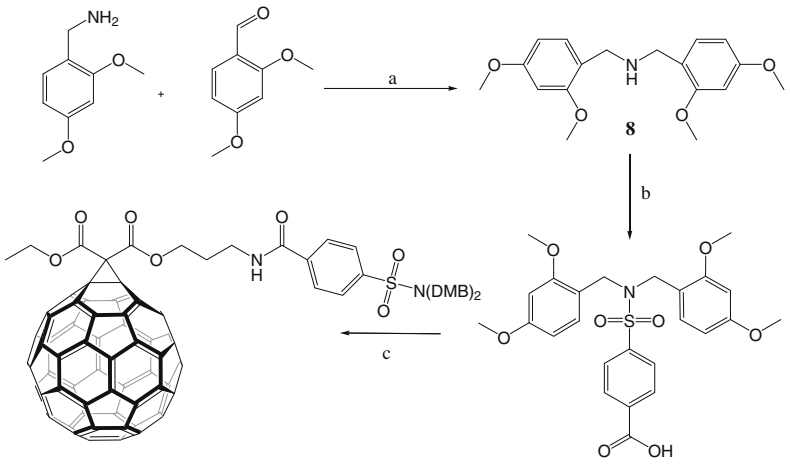
Scheme 4. Reagents and conditions: 4-aminosulfonylbenzoyl chloride, TEA.



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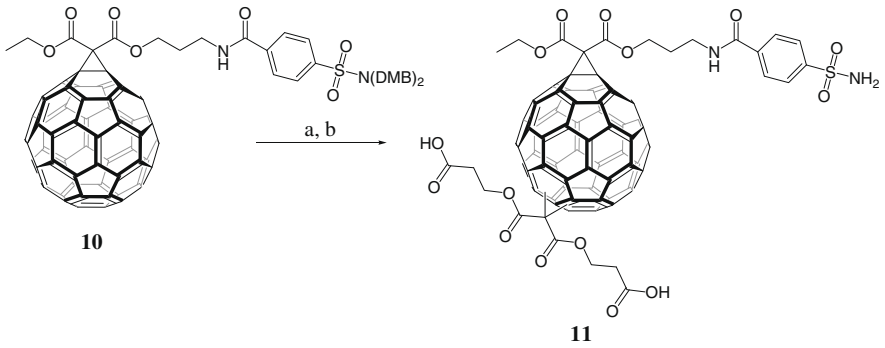
Scheme 5. Reagents and conditions: (a) $NaBH(OAc)_3$; (b) 4-(chloro-sulfonyl)benzoic acid, TEA; (c) 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), TEA, aminofullerene **6**.



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Scheme 6. Reagents and conditions: (a) 1,3-bis[3-(1,1-dimethylethoxy)-3-oxopropyl]propanedioic acid ester, I_2, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); (b) trifluoroacetic acid (TFA)/CH_2Cl_2.

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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.2010.05.017.

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