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Regioselective Bisaddition to C_{60} with Bis(β-Keto Esters)

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Abstract: Reaction of C_{60} with bis(β-keto esters) in the presence of iodine and diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene provides covalent bisadducts of C_{60} with high regioselectivity.

Whereas only one monoaddition product is possible for C_{60}, monofunctionalized C_{60} possesses nine different 6-6 bonds (bonds at the junction between two six-membered rings) that can react in a second addition (*Figure 1*). Mixtures of many possible multiple adducts are produced by successive reactions at the C_{60} core, and purification is subsequently accomplished by often tedious chromatographic separations.[1] The first powerful methodology for the regioselective preparation of selected multiple adducts of C_{60} has been introduced by Diederich and coworkers[2] in 1994 and is based on tether-directed remote functionalization. Several other protocols, some of which also rely on tether control, have since been reported.[3-5] Control of the regioselectivity for the construction of polyadducts with well defined three-dimensional structure is now a central topic in fullerene chemistry and is of high importance for the preparation of fullerene derivatives with biological or material properties. We report herein the nucleophilic cyclopropanation of C_{60} starting from a β-keto ester and the direct bisfunctionnalization of C_{60} based on a cyclization reaction of the fullerene sphere with bis(β-keto esters).

The cyclopropanation of C_{60} with α-halocarbanions[6] appeared to be one of the most efficient tools for the preparation of methanofullerenes. It was also shown that nucleophilic cyclopropanation of C_{60} is possible starting directly from malonates. In this case, the α-halomalonate was generated *in situ*, and direct treatment of C_{60} with malonates in the presence of iodine[3,7] or CBr_4[8] and base afforded the corresponding methanofullerene in good yields. Similarly, we now show that direct treatment of C_{60} with ethyl acetoacetate (**1**), iodine and diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene at room temperature for 5 hrs affords methanofullerene **2** in 30% yield (*Figure 1*). The yield of monoadduct is comparable to that obtained by the

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reaction with the corresponding α-chloro-β-keto ester. When CBr_4 is used instead of iodine, the reaction appears slower (12 hrs) and compound **2** is isolated in only 21% yield.

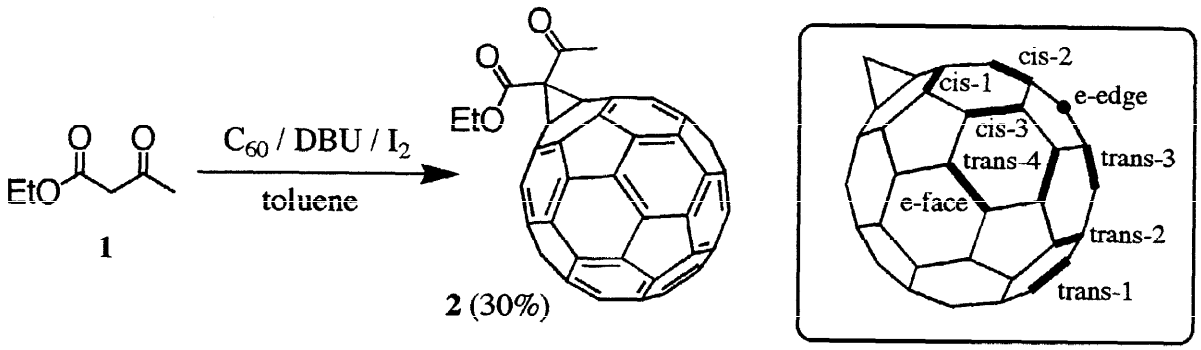

Figure 1. Monofunctionalization of C_{60} with ethyl acetoacetate and positional notation[1b,3] of the bisaddition patterns relative to a first substituent. For identical addends, a second attack onto e-edge or e-face positions leads to identical products.[2]

The generalization of this new reaction to the regioselective bisfunctionalization of C_{60} was subsequently established by starting from the bis(β-keto esters) **3-5** (*Figure 2*). Compound **3** was prepared in 66% yield by alkylation of α,α'-dibromo-*p*-xylene in THF at 0°C with an excess of the dianion from ethyl acetoacetate (**1**) which was generated by treatment of **1** with 2 eq. of lithium diisopropylamide (LDA).[9] Bis(β-keto esters) **4** and **5** were obtained in 43 and 51% yield, respectively, in a similar manner starting from the corresponding dibromide; products of monoalkylation were also isolated (32 and 34% yield, respectively) in this two cases. Treatment of C_{60} with **3-5** in the presence of iodine and DBU in toluene at room temperature afforded the corresponding macrocyclic bisadducts **6-8** in 7 to 26% yield. In a typical procedure, DBU (4.4 eq.) was added to a stirred solution of C_{60} (300 mg), **3** (1 eq.) and I_2 (2 eq.) in toluene (600 ml) at room temperature. The mixture was stirred for 5 hrs, then filtered through a pad of SiO_2 (toluene then CH_2Cl_2) and evaporated. Column chromatography on SiO_2 (CH_2Cl_2/hexane 5:3) and crystallization from $CHCl_3$/AcOEt yielded pure **6** (116 mg, 26% yield). Since the linker between the two β-keto ester moieties acted as a directing tether, the bisfunctionalization of C_{60} was highly regioselective and only one of all the possible isomeric bisadducts was formed in each case. For each bisadduct **6-8**, FAB-MS displayed the expected molecular ion peak and the relative position of the two cyclopropane rings on the fullerene core was determined based on the molecular symmetry deduced from the ^{1}H- and ^{13}C-NMR spectra as well as on the UV/VIS spectra. It was previously shown by Hirsch and coworkers[1b] that the UV/VIS spectra of the biscyclopropanated fullerene derivatives are highly dependent on the addition pattern and characteristic for each regioisomer. The UV/VIS spectra of **6-8** are fully consistent with those previously reported for the analogous bisadducts.[1b,1d] Furthermore, different diastereomers are possible for each cyclic regioisomer depending on the relative orientation of the two ethoxycarbonyl residues at the two methanobridge C atoms (in-in, in-out and out-out isomerism).[3] Actually, **6-8** were all isolated as pure compounds, therefore this cyclization reaction is not only regio- but also diastereoselective. Because of the length of the linker between the two cyclopropane rings, only the out-out isomer appeared reasonable for the e bisadduct **6**. Two C_s-

symmetrical cis-2 diastereomers (in-in and out-out) appeared possible for bis-adducts **7** and **8**. Steric considerations based on molecular modeling, however, indicated that the two ethoxycarbonyl groups should be oriented in an out-out manner, in analogy to a related macrocyclic cis-2 bisadduct for which an X-ray crystal structure was obtained.[3a]

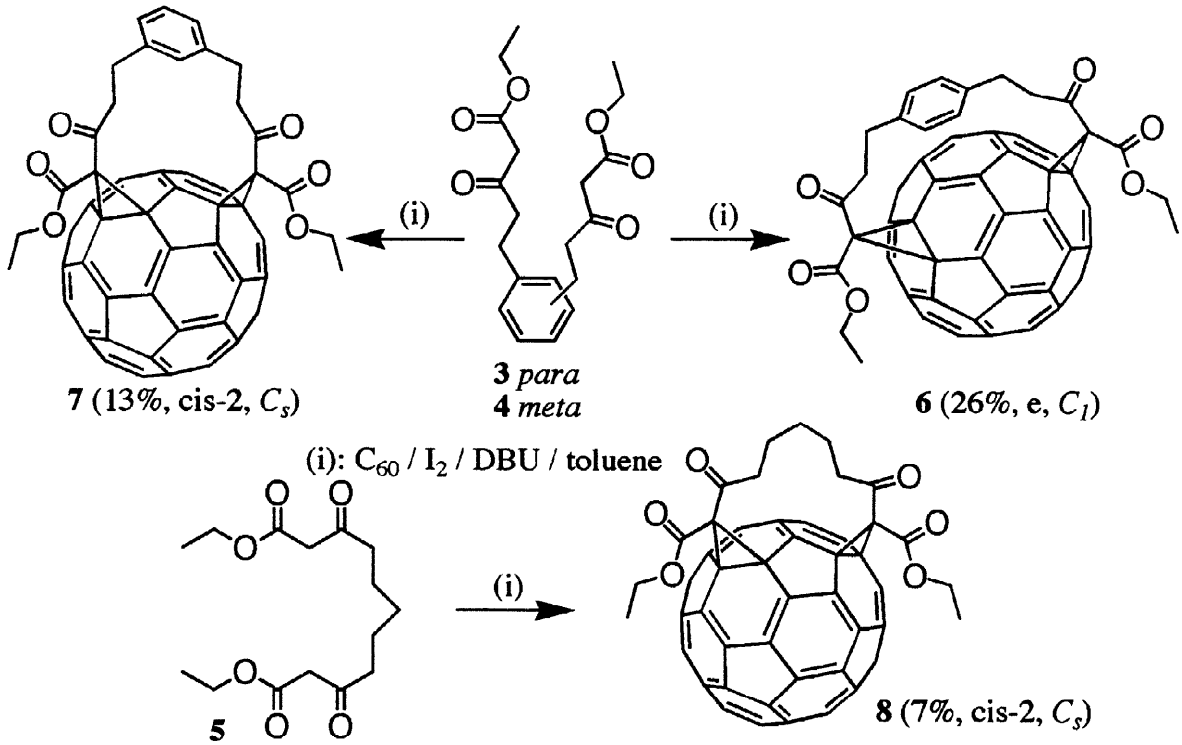

Figure 2. Regioselective bisaddition to C_{60} with bis(β-keto esters) **3-5**.

Using the same methodology, the cyclization reaction of the bis(β-keto ester) **9** yielded the two cis-2 bisadducts **10** and **11** (*Figure 3*).

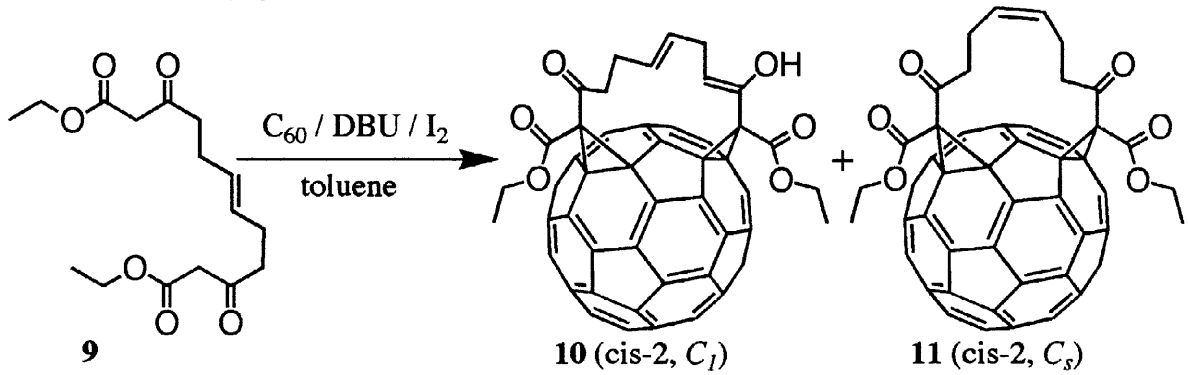

Figure 3. Bisaddition to C_{60} with bis(β-keto ester) **9**.

Compound **10** was the expected cyclization product and **11** resulted from an additional isomerization of the double bond. The relative yield of both cis-2 derivatives was found to be non reproducible. However, the overall yield was always the same (20%) and **11** was obtained as the main product in all experiments. The structure of **10** was unambiguously determined by 2D COSY experiments which showed that no double bond

migration occurred toward a conjugated system. Noteworthy was the complete enolization of one of the ketone functions of **10**. It was the only cyclic bisadduct for which such a behavior was observed and it could be the result of an important strain in the 13-membered ring containing the E-alkene moiety. Therefore the observed isomerization into the Z derivative **11** could be easily explained by a diminution of the torsional strain in the cycle with a Z-alkene fragment compared to the one with an E-alkene fragment. Further experiments with substituted alkenes and molecular modeling studies are still under investigations in order to understand this isomerization process.

In conclusion, the regioselective access to selected C_{60} multiple adduct by bisaddition of bis(β-keto esters) was established and several fullerene building blocks for material or biological applications should become available by this facile new methodology.

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