ORGANIC LETTERS

2006
Vol. 8, No. 7
1463−1466

Convergent Synthesis of a Polyfunctionalized Fullerene by Regioselective Five-Fold Addition of a Functionalized Organocopper Reagent to C_{60}

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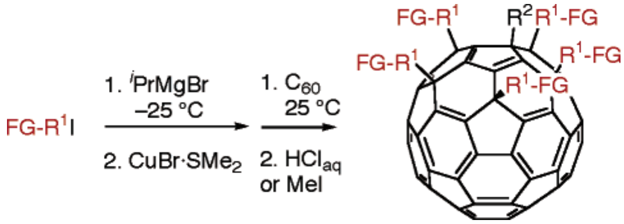
Received February 1, 2006

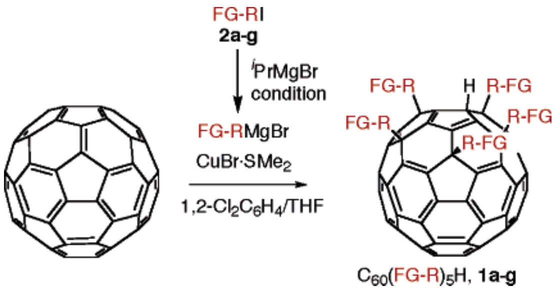
ABSTRACT



A method for one-step preparation of polyfunctionalized fullerene derivatives by regioselective penta-addition of an organocopper reagent is described. A functionalized aryl iodide is first converted to the corresponding Grignard reagent and then to a copper reagent and finally is allowed to react with C_{60}. The method allows introduction of five functional groups to the C_{60} skeleton in a convergent manner. The shuttlecock-like molecules crystallize into a columnar packing structure.

We discovered some time ago that an organocopper reagent prepared by transmetalation between a Grignard reagent and $CuBr{\cdot}SMe_2$ added regioselectively to C_{60} to provide penta-arylated,[1] alkenylated,[2] methylated,[3] and silyl-methylated[4] compounds ($C_{60}R_5H$) in a good to quantitative yield. If the R group could bear a wide variety of functional groups, this reaction would provide a uniquely short, general approach to the synthesis of densely functionalized molecules such as polysaccharides that would tightly bind to proteins,[5] more generally represented as **1** in Scheme 1. However, this idea has thus far not been fully materialized because the original method relying on conventional preparation of the necessary Grignard reagent from aryl halides and magnesium turnings is too harsh to tolerate functional groups on the Grignard

Scheme 1. Convergent Synthesis of Functionalized C_{60} Derivatives



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10.1021/ol060282t CCC: $33.50

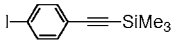
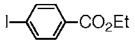
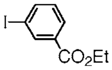
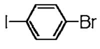
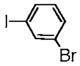
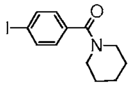
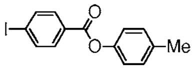
part. We report herein that a mild iodine/magnesium exchange procedure pioneered by Knochel[6] removes some of the limitations and allows one- or two-step syntheses of functionalized fullerene compounds $C_{60}(R{-}FG)_5R$ and their derivatives in good to high yield (Schemes 1 and 2).

We employed the transmetalation reaction between an aryl iodide and ^{i}PrMgBr to prepare the desired functionalized Grignard reagents,[6b] which were then in situ transmetalated to the corresponding copper reagent by reaction with CuBr·SMe$_2$.[1] The conditions for the iodide/magnesium exchange reaction depended on the Grignard reagent. The aryl Grignard reagent bearing an electron-withdrawing group required a lower reaction temperature. Nine equivalents of aryl iodide was enough for complete conversion of the starting material when the reaction was run on a large scale. A typical procedure is shown in footnote 7. In the preliminary, small-scale investigations, however, the synthesis using 12 equiv of the aryl iodide allowed us to obtain the desired products in generally high yields. These results are summarized in Table 1.

The reaction of 4-(trimethylsilylethynyl)phenyl iodide (**2a**) (entry 1) was examined to investigate the feasibility of the iodine/magnesium transmetalation protocol for the penta-addition reaction. When the iodide (12.0 equiv to C_{60}) was treated with ^{i}PrMgBr (11.0 equiv) at 25 °C for 3 h and then with CuBr·SMe$_2$ (12.0 equiv), an orange copper reagent was generated. The copper reagent was added to C_{60} (1 equiv) in a THF/1,2-dichlorobenzene mixture at 25 °C,[1] and the product **1a** was isolated in high yield and purity. The use of a slight excess of the aryl iodide and CuBr·SMe$_2$ over ^{i}PrMgBr was important to obtain the product in high purity.

When the method was applied to an aryl iodide bearing a Grignard-reagent-sensitive substituent, the iodine/magnesium exchange was carried out at low temperature. The iodides **2b**−**e** were treated with ^{i}PrMgBr at −25 °C for 1.0 h and then with CuBr·SMe$_2$ at the same temperature. After stirring for 10 min, the solution of the copper reagent was warmed to 25 °C, and a solution of C_{60} was added at the same temperature. In this manner, adducts **1b**−**e** were prepared in high yields (entries 2−5). The aryl iodide **2f** containing an amide group posed some difficulty because of the low solubility of the Grignard intermediate in THF. The exchange was carried out in a mixture of THF and NBP (*N*-butylpyrrolidinone) (v/v, 5:1),[8] and 4 equiv of CuBr·SMe$_2$ relative to ^{i}PrMgBr was used to ensure total conversion to the copper reagent. The desired reaction took place, though less clean than other reactions, to give the expected adduct **1f** in 66% yield (entry 6).

Table 1. Penta-Addition of a Functional Copper Reagent to C_{60}[a]

entry	FG-RI (**2**)	conditions[b]	**1**	yield (%)[c]
1	 **2a**	25 °C/3.0 h	**1a**	95
2	 **2b**	−25 °C/1.0 h	**1b**	93
3	 **2c**	−25 °C/1.0 h	**1c**	90
4	 **2d**	−25 °C/1.0 h	**1d**	96
5	 **2e**	−25 °C/1.0 h	**1e**	90
6[d]	 **2f**	−30 °C/1.0 h	**1f**	66[e]
7[d]	 **2g**	−45 °C/0.5 h	**1g**	45[e]

[a] The synthesis was carried out following the typical procedure described in footnote 7. Details are reported in the Supporting Information. Unless otherwise noted, the reaction was carried out with 0.1 mmol of C_{60}, 1.2 mmol of FG-RI, 1.1 mmol of ^{i}PrMgBr, and 1.2 mmol of CuBr·SMe$_2$. [b] The conditions for the I/Mg exchange step. [c] All products were obtained with HPLC purity better than 90%, except in the cases of **1d** and **1e** with purities of 85%. [d] The reaction was run on a 0.05 mmol scale of C_{60}. [e] Yield of isolated product after purification by preparative HPLC.

The phenyl benzoate ester compound **1g** is a structurally inversed analogue (i.e., $C_{60}{-}C_6H_4{-}COOAr$ instead of $C_{60}{-}C_6H_4{-}OCOAr$) of the shuttlecock-shaped fullerenes that were previously reported to form columnar stacks in crystals and liquid crystals.[9] Because the aryl *p*-iodobenzoate moiety **2g** is sensitive to nucleophiles, the iodine/magnesium exchange must be carried out at −45 °C for a shorter time period (0.5 h). The product **1g** was obtained this way in a modest isolated yield of 45%. Further optimization of the conditions will be necessary if any specific compound is found to be useful for practical applications.

Crystal structure analysis indicated that a large concave cavity forms above the fullerene core of **1g** (Figure 1), and the molecules stack with each other one dimensionally in

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(7) Typical procedure: A solution of 4-iodobenzoic acid ethyl ester **2b** (1.5 mL, 9.0 mmol) in 40 mL of THF was treated with 8.0 mmol of isopropylmagnesium bromide (11.5 mL of 0.7 M solution in THF) at −25 °C and stirred for 1 h. CuBr·SMe$_2$ (1.8 g, 9.0 mmol) was then added. After stirring for 10 min, the mixture was brought to room temperature and a solution of C_{60} (720 mg, 1.0 mmol) in 50 mL of *o*-dichlorobenzene was added. Stirring was continued until C_{60} disappeared as monitored by HPLC. The reaction was then quenched with 1.0 mL of saturated aqueous ammonium chloride solution and 100 mL of degassed toluene. The solution was filtered through silica gel and concentrated. A portion of 200 mL of methanol was then added. The resulting precipitate was collected after filtration and washed with methanol to afford 1.35 g of the desired product **1b**, with a yield of 93% and a HPLC purity of 96%.

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(9) Sawamura, M.; Kawai, K.; Matsuo, Y.; Kanie, K.; Kato, T.; Nakamura, E. *Nature* **2002**, *419*, 702.

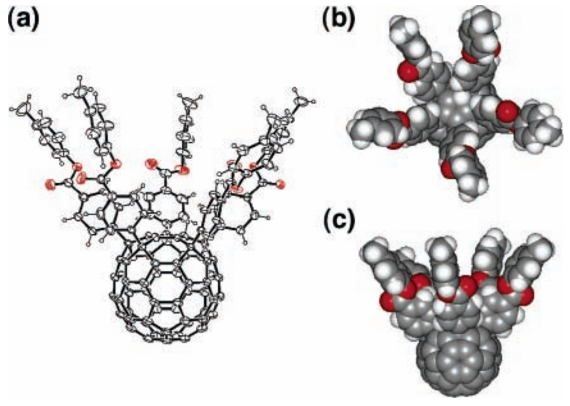


Figure 1. Molecular structure of **1g**. (a) ORTEP drawing. (b) Top view of a CPK model. (c) Side view of a CPK model.

crystals (Figure 2). The stacking period is 11.27 Å, a distance similar to the one observed previously for the structurally inversed analogues.[9] The crystal packing as viewed along the *B* axis is disordered hexagonal, similar to previously reported analogues.

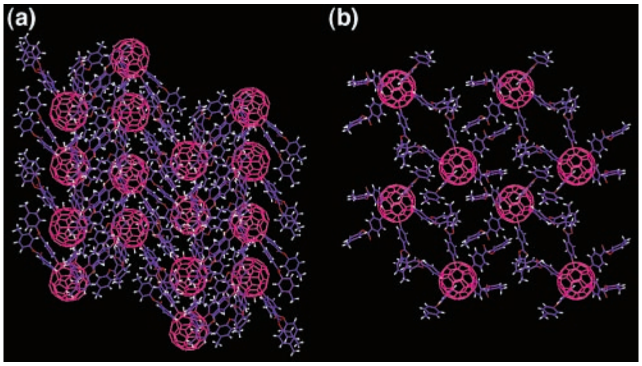
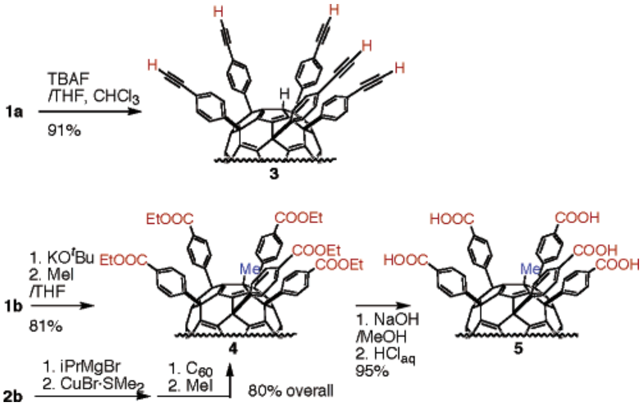


Figure 2. Crystal packing of **1g**. (a) View along *A* axis. (b) View along *B* axis.

These compounds are readily amenable to further modifications through elaboration of the functional groups. The five trimethylsilyl groups in **1a** were removed by treatment with tetra(butyl)ammonium fluoride (TBAF) to obtain a free terminal acetylene compound **3** (Scheme 2), which would be useful for further studies.[10,11]

The acidic cyclopentadienyl proton in **1** can be replaced with a methyl group as previously reported.[12] Thus, the methylation reaction was achieved either by first isolating the protio compound **1b** and subjecting it to the base/MeI treatment[12] or by directly methylating in situ the copper intermediate (80% overall from C_{60}). Crystallographic analysis of the methylated compound **4** (Figure 3) indicated that the cavity has been made somewhat shallower by the methyl group (marked in blue) but that the molecules still form the one-dimensional stacking structure (Supporting Information). Basic hydrolysis of the ester group in **4** followed by acidification of the mixture afforded the free carboxylic acid **5** in good overall yield.

Scheme 2. Further Conversions of Products **1**



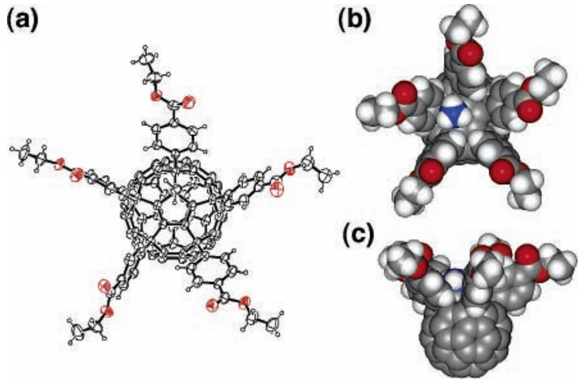


Figure 3. Crystal structure of **4**. (a) ORTEP drawing. (b) Top view of a CPK model. (c) Side view of a CPK model.

The pentacarboxylic acid compound **5** is highly soluble in alkaline water, THF, DMF, MeOH, and EtOH and will be useful for engineering applications and for derivatizations into dendrimers.[13]

Functionalized fullerene derivatives have found use in chemistry, biology, and material sciences,[14] and the $C_{60}R_5H$

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class of compounds has been employed to explore the chemistry of transition-metal complexes,[15] liquid crystal materials,[4,9] vesicles,[16] and others.[17] The present synthetic method will further expand the utility of polyfunctionalized fullerene compounds.

Supporting Information Available: Experimental procedures, full spectroscopic data for all new compounds, and CIF files for **1g** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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