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CuBr/PMDETA-Mediated Reactions of [60]Fullerene with Active Halides: Preparation of Methano[60]Fullerene Derivatives

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Hai-Tao Yang,^{*[a]} Zong-Yong Tian,^[a] Xiao-Jiao Ruan,^[a] Min Zhang,^[a] Chun-Bao Miao,^[a] and Xiao-Qiang Sun^{*[a]}

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An efficient protocol for the synthesis of methano[60]fullerene derivatives linked with a single electron-withdrawing group has been developed through one-step reaction of [60]fullerene with active halides mediated by CuBr/pentamethyldiethylenetriamine. Many functional groups including

Introduction

The fascinating structure and properties of fullerenes have led to rapid development of their chemistry in the last two decades. The functionalization of [60]fullerene with various organic functional groups is an important subject in fullerene chemistry, as these derivatives can be used in materials and medicinal applications. Among a large number of functionalized [60]fullerene compounds, methano[60]fullerene derivatives have been one of the most intensively studied classes.^[1] Since Wudl showed that watersoluble methano-bridged C₆₀ compounds inhibited certain HIV enzymes,^[2] several methods for the synthesis of methano[60]fullerenes have been developed (Scheme 1): (1) The reaction of C₆₀ with halogenated active methylene compounds in the presence of base (Bingel reaction) is one of the most widely applied reactions in fullerene chemistry to give various cyclopropanated fullerene derivatives.^[3] (2) The addition of diazo compounds to C₆₀ followed by photolysis or thermolysis of the pyrazoline compounds produces the methanofullerenes and fulleroids through extrusion of N₂.^[4] (3) The reaction of phosphonium ylides or sulfonium ylides with C_{60} gives selectively [6,6]-methanofullerenes.^[5] (4) Fluoride ion mediated reactions of silvlated nucleophiles with [60]fullerene affords selectively [6,6]-methanofullerenes.^[6] (5) The addition of free carbene to C_{60} has also been studied.^[7] Cu^{II} acetate or Mn^{III} acetate mediated reaction of carbonyl compounds with C₆₀ to form methanofullerene as a byproduct has also been reported.^[8] Nevertheless, these reactions have some limitations. As for the Bingel reaction,

esters, ketones, amides, and sulfonyl groups could be easily introduced onto the fullerene skeleton by using this methodology. A plausible reaction mechanism, but not the atom transfer radical process, was proposed for the formation of the methano[60]fullerene derivatives.

the substrates are restricted to active methylene compounds often with two electron-withdrawing groups. Sulfonium ylides, phosphonium ylides, and silylated nucleophiles need to be prepared from halide compounds. The diazo compounds always yield fulleroids as byproducts and the carbene is difficult to prepare. Therefore, an easier method for the preparation of cyclopropanated [60]fullerenes is still needed. Herein, we report a convenient method for the synthesis of methano[60]fullerenes linked with a single electron-withdrawing group through reaction of [60]fullerene with active halide compounds mediated by CuBr/PMDETA (pentamethyldiethylenetriamine).



Scheme 1. Previous methods for the preparation of methano[60]fullerene derivatives.

Free radical reactions of fullerenes were amongst the first to be investigated and are still attractive protocols to synthesize fullerene derivatives.^[9] Most recently, it was reported the reaction of C_{60} with active alkyl bromides in the presence of CoCl₂/Mn/ligand/H₂O system gave the monoalkylated [60]fullerene probably through a radical process.^[10] On

 [[]a] School of Petrochemical Engineering, Changzhou University, Changzhou 213164, P. R. China E-mail: yanght898@yahoo.com.cn chemsxq@yahoo.com.cn

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the other hand, the atom transfer radical reaction (ATR) process has been extensively investigated in polymerization and cyclization reactions.^[11] A radical species was generated from an organic halide or a related compound through a reversible redox process catalyzed by a transition metal complex. A number of groups have reported that transition metal-catalyzed atom transfer radical reactions of halogenated compounds with olefins for the formation of C–C bonds.^[12] However, there are rare reports on the application of this ATR reaction to functionalization of [60]fullerene in the field of polymer science up to now.^[13] We were wondering whether the carbon radical generated from halide compound by the copper(I) halide could be captured by C_{60} , and generated 1,2- or 1,4 adducts of C_{60} .

Results and Discussion

Ethyl bromoacetate (**1aa**) was chosen as a model substrate, and the reaction of C_{60} with **1aa** was carried out in the presence of different copper(I or II) salts and ligands (Table 1). A mixture of C_{60} (0.05 mmol) and **1aa** (2 equiv.) was treated with CuBr (1 equiv., purified according to a reported procedure^[14]) and PMDETA (1 equiv.) in toluene

Table 1. Screening of reaction conditions.[a]



[a] Unless otherwise specified, all reactions were performed with C_{60} (0.05 mmol), **1aa** (0.10 mmol), and the given amount of CuBr/ligand in toluene (12 mL) at 110 °C for the designated time. [b] Isolated yield. The yield in parentheses is based on consumed C_{60} . [c] Performed under a N₂ atmosphere.

(12 mL) at 110 °C for 6 h. To our surprise, no anticipated radical addition product was observed. Instead, undesired methano[60]fullerene derivative 2a was obtained in 10% yield along with 87% of recovered C₆₀ (Table 1, entry 3). Atmospheric oxygen did not show a marked influence on the reaction (Table 1, entry 4). Although no radical addition product was isolated, this procedure provides an efficient method for the preparation of methano[60]fullerenes linked with a single electron-withdrawing group through the direct reaction with halides. However, the conversion efficiency and product yield needed to be further improved. When the amount of CuBr and PMDETA were increased to 4 equiv., the yield of 2a improved to 45% (Table 1, entry 6). A further increase in the amount of CuBr and PMDETA to 6 equiv. resulted in generation of more byproducts (Table 1, entry 7). It should be emphasized that CuBr and the PMDETA ligand were both crucial to the success of this reaction, as no conversion was observed in the absence of either one (Table 1, entries 1 and 2). Replacing CuBr with CuI, CuCl, or Cu₂O resulted in a decrease in the yield (Table 1, entries 8-10). Cu^{II} could not initiate the reaction under similar conditions (Table 1, entries 11 and 12). Other ligands such as TMEDA (N,N,N',N')-tetramethylethylenediamine), DMEDA (N,N'-dimethylethylenediamine), TETA (triethylenetetramine), 2,2'-bipyridine, EDTA-4Na (ethylene diamine tetraacetic acid tetrasodium), DABCO, and PPh3 were also tried. Unfortunately, they were all ineffective in this reaction (Table 1, entries 13–19). Eventually, the reagent molar ratio of C₆₀/1aa/CuBr/ PMDETA = 1:2:4:4 and a reaction temperature of 110 °C were chosen as the optimal reaction conditions (Table 1, entry 6).

With the optimized conditions in hand, this kind of cyclopropanation reaction was extended to various halide compounds (Table 2). All examined halides **1aa-1k** (except 1d and 1l) could be utilized to prepare methano[60]fullerenes 2 in 15–55% yield (41–96% based on consumed C_{60}). As for the bromoacetate, when R was an aliphatic ester group the reaction proceeded well and gave good yields of 2 (Table 2, entries 1, 4, and 6), and the *tert*-butyl group was found to be superior to both the ethyl and methyl groups. However, when R was a phenyl ester, no conversion was observed (Table 2, entry 7). Meanwhile, the halogen atom of the halide compound also had an influence on this reaction, and the active sequence is I > Br > Cl (Table 2, entries 1-5). From the viewpoint of easy preparation and stability, the bromide was selected for most substrates. α -Halide ketones were also suitable for this reaction, but a lower reaction temperature was needed (Table 2, entries 8–12). α -Bromoaromatic ketones gave better results than did α haloaliphatic ketones. The presence of both electron-donating and electron-withdrawing groups on the phenyl ring was tolerated, and 2 could be obtained in good yield (Table 2, entries 8–10). Bromomethylaryl sulfone 1j also participated in the reaction to afford 2j in moderate yield when the reaction temperature was increased to 140 °C in chlorobenzene (Table 2, entry 12). The sulfone structure has never been reported to undergo this type of reaction. Secondary amide

2



1k was also tolerant to this reaction (Table 2, entry 13).

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Nevertheless, the primary amide failed to react with C_{60} under similar conditions.

Table 2. CuBr/PMDETA-mediated reaction of C_{60} with active halides.^[a]



[a] Unless otherwise specified, the molar ratio of $C_{60}/1/CuBr/PMDETA = 1:2:4:4.$ [b] Isolated yield. The yield in parentheses was based on consumed C_{60} . [c] Molar ratio of $C_{60}/1i/CuBr/PMDETA = 1:10:4:4.$ [d] Molar ratio of $C_{60}/1j/CuBr/PMDETA = 1:20:4:4$, solvent: chlorobenzene.

All of the known products were confirmed by comparison of their spectroscopic data with those reported in literature. The identification of new compounds 2h and 2j was fully confirmed by their MS, ¹H NMR, and ¹³C NMR spectra. As an example, the APCI mass spectrum of 2h showed a molecular ion peak at m/z = 834. The ¹H NMR spectrum of **2h** showed a singlet at $\delta = 5.79$ ppm for the methine proton, triplets at $\delta = 4.53$ ppm, and quartets at δ = 1.53 ppm for the ethoxy group protons. In the ^{13}C NMR spectrum of **2h**, there were two signals at $\delta = 183.7$ and 159.7 ppm for the two carbonyl carbon atoms, 29 peaks due to sp² carbon atoms of the C₆₀ skeleton at δ = 136.69– 147.63 ppm, one peak at $\delta = 71.91$ ppm for the sp³ carbon atom of the C₆₀ cage, one peak at $\delta = 40.96$ ppm for the methine carbon atom, and two peaks at $\delta = 63.38$ and 14.25 ppm for the ethoxy group, agreeing well with its C_s symmetry. Compound 2j was also fully characterized in a similar way and exhibited spectral patterns similar to those of 2j.

A possible ATR mechanism based on those reported in the literature is depicted in Scheme 2. Carbon radical **3** generated from halide compound **1** in the presence of CuBr/



PMDETA attacks C_{60} to produce fullerene radical 4, which

reacts with CuBr₂ to form 1,2-adduct 5. PMDETA can also

act as a base to generate carbanion 6, and subsequent intramolecular S_N reaction gives methano[60]fullerene derivative

Scheme 2. Possible ATR process for the generation of 2.

To substantiate this mechanism, monoalkylated fullerene 7 was prepared according to a literature procedure.^[10] We expected that bromination of 7 under basic conditions would generate intermediate $5^{[17]}$ and that subsequent intramolecular S_N reaction would afford methanofullerene 2a. Nevertheless, treatment of 7 with Br₂ (1 equiv.) and PMDETA (3 equiv.) in orthodichlorobenzene (ODCB) at room temperature for 1 h gave single-bonded fullerene dimer 8 in 80% yield (Scheme 3, conditions a). Further investigation revealed that 7 could be converted into 8 directly under basic conditions (PMDETA or tBuOK) in the absence of Br_2 (Scheme 3, conditions b and c). This proved that conversion of 7 into 8 is a radical process. Under basic conditions, monoanion RC_{60}^{-} (R = CH₂CO₂Et) generated from 7 underwent one-electron oxidation by O2 to afford fullerene radical 4. Coupling of the monomer radicals would give dimer 8. A similar process for the formation of a singly bonded C₆₀ dimer using I₂ as the oxidant or catalyzed by (CuOAc)₂ has been reported.^[18] If the generation of 2 is an ATR process, as shown in Scheme 2, capturing radical intermediate 4 with CuBr₂/PMDETA would yield 2. However, when 7 was treated with PMDETA (4 equiv.), CuBr (3 equiv.), and CuBr₂ (1 equiv.) at 110 °C for 1 h, all the starting material disappeared and methanofullerene 2a was not detected. Instead, dimer 8 and lactone 9 were isolated in 61% and 20% yield, respectively (Scheme 3, conditions d). When tBuOK was used as the base and the amount of CuBr₂ was increased to 6 equiv., 7 could be converted into lactone 9 (82%) completely after 4 h at 110 °C (Scheme 3, conditions e). Moreover, 8 also could be transformed into lactone $9^{[19]}$ in 87% yield upon treatment with 5 equiv. of CuBr₂ at 100 °C for 3 h (Scheme 3, conditions f). These results proved that the reaction of [60]fullerene with active halides under ATR conditions is not a radical pro-

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cess, which also could be supported by the fact that no reaction was observed when C₆₀ was treated with benzyl bromide (Table 2, entry 15).



Scheme 3. Mechanism investigation. Conditions: (a) Br₂ (1 equiv.), PMDETA (3 equiv.), ODCB, r.t., 1 h, 80%; (b) PMDETA (3 equiv.), ODCB, r.t., 6 h, 50%; (c) tBuOK (2 equiv.), r.t., 30 min, 94%; (d) PMDETA (4 equiv.), CuBr (3 equiv.), and CuBr₂ (1 equiv.), ODCB, 110 °C, 1 h, gave a mixture of 8 (61%) and 9 (20%); (e) tBuOK (3 equiv.), CuBr₂ (6 equiv.), ODCB, 100 °C, 4 h, 82%; (f) CuBr₂ (5 equiv.), ODCB, 100 °C, 3 h, 87%.

The exact reaction mechanism for the formation of 2 is currently unknown. An alternative plausible reaction pathway is proposed in Scheme 4. Interaction of active halide 1 with CuBr and PMDETA generates Cu^{III} intermediate 10. In path A, elimination of HBr from 10 results in the formation of carbenoid 11, which undergoes [2+2] cycloaddition with C_{60} to generate 12. Subsequent reductive elimination



Scheme 4. Plausible mechanism for the formation of 2.

generates 2. In path B, deprotonation of 10 generates carbanion 13, which attacks C_{60} to form 14 and subsequent intramolecular S_N reaction affords 2.

Conclusions

In conclusion, a wide variety of methano[60]fullerenes linked with a single electron-withdrawing group were synthesized conveniently through the one-step reaction of active halides with C₆₀ mediated by CuBr/PMDETA. A possible reaction pathway, but not the ATR mechanism, was proposed to explain the cyclopropanation of C_{60} .

Supporting Information (see footnote on the first page of this article): General methods; experimental procedures for the preparation of methanofullerenes 2, 8, and 9; spectral data for products 2h, 2j, 8, and 9; ¹H NMR and ¹³C NMR spectra of the products.

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