ORGANIC
LETTERS

2010
Vol. 12, No. 21
4896−4899

Synthesis of Disubstituted [60]Fullerene-Fused Lactones: Ferric Perchlorate-Promoted Reaction of [60]Fullerene with Malonate Esters

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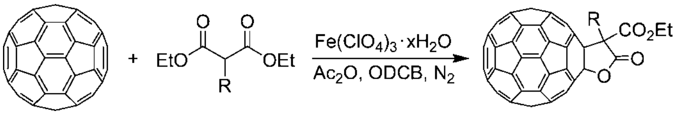
Received August 30, 2010

ABSTRACT



The ferric perchlorate-mediated reaction of [60]fullerene with substituted malonate esters in the presence of acetic anhydride afforded the rare disubstituted [60]fullerene-fused lactones. A possible reaction mechanism is proposed.

Although a large variety of reactions for the functionalization of fullerenes have been explored over the past 20 years,[1] the metal salt-mediated reactions of [60]fullerene (C_{60}) are relatively underdeveloped. Recently, our group has been interested in reactions of C_{60} mediated by metal salts such as $Mn(OAc)_3$,[2,3] $Cu(OAc)_2$,[3c] $Pb(OAc)_4$,[3h] $Pd(OAc)_2$,[4] and $Fe(ClO_4)_3$[5] to obtain a variety of novel compounds with desired moieties.

Up to now, only a few papers described the lactonization reactions of C_{60}.[3g−i,6,7] Foote et al. reported the synthesis of two C_{60}-fused γ-lactones by the [2 + 2] cycloaddition of C_{60} with diethylaminopropyne/ketene acetal, subsequent ring opening by acid hydrolysis, and final oxidative cyclization in the presence of charcoal.[6] We disclosed the preparation of four C_{60}-fused δ-lactones through the reaction of C_{60} with anthranilic acids and isoamyl nitrite in the presence of triethylamine.[7] We previously revealed the facile one-step reaction of C_{60} with carboxylic acids, or with carboxylic

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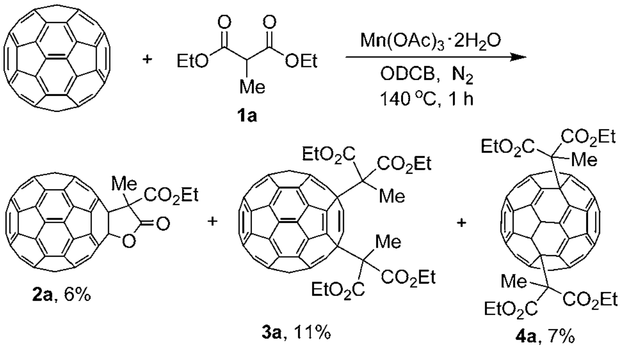
anhydrides, or with malonic acids in the presence of $Mn(OAc)_3$ to afford three C_{60}-fused γ-lactones.[3g] Recently, we further extended the $Mn(OAc)_3$-promoted reaction of C_{60} with various carboxylic acids in the presence of 4-dimethylaminopyridine to afford a series of C_{60}-fused γ-lactone derivatives.[3h,i] Unfortunately, nearly all of the reported C_{60}-fused γ-lactones are monosubstituted lactones. Only one disubstituted C_{60}-fused γ-lactone was reported, and it was formed from the $Mn(OAc)_3$-mediated reaction of C_{60} with isobutyric acid.[3h] However, the concurrent formation of a fullerenyl ester byproduct originated from the facile generation of a secondary radical via decarboxylation from isobutyric acid was unavoidable. The isolated yield (17%) of the unsymmetrical fullerenyl ester was even higher than that (10%) of the desired C_{60}-fused γ-lactone under the employed standard conditions.[3h]

It seems that the synthesis of disubstituted C_{60}-fused γ-lactones from carboxylic acids in high yields is quite challenging. This obstacle prompted us to develop an alternative efficient protocol to obtain the scarce disubstituted C_{60}-fused γ-lactones. In continuation of our interest in $Fe(ClO_4)_3$-mediated reactions of C_{60},[5] herein we describe the successful synthesis of disubstituted C_{60}-fused γ-lactones through the reaction of C_{60} with substituted malonate esters in the presence of $Fe(ClO_4)_3$ and acetic anhydride.

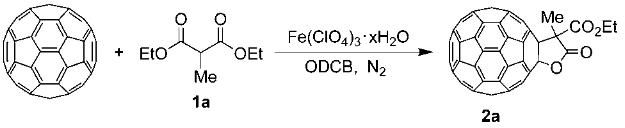
We previously reported that the $Mn(OAc)_3$-mediated reaction of C_{60} with dialkyl malonates, i.e., $CH_2(CO_2Me)_2$ and $CH_2(CO_2Et)_2$, in refluxing chlorobenzene afforded the singly bonded fullerene dimers $[(RO_2C)_2CH]C_{60}-C_{60}[CH(CO_2R)_2]$ and 1,4-adducts $C_{60}[CH(CO_2R)_2]_2$, while the corresponding reaction with $BrCH(CO_2Et)_2$ generated a 1,4-adduct and a 1,16-adduct of C_{60}.[3a] In contrast, the $Mn(OAc)_3$-promoted reaction of C_{60} with substituted malonate esters in refluxing toluene gave the benzyl-substituted unsymmetrical 1,4-adducts of C_{60}.[3b] In all of the aforementioned reactions, no C_{60}-fused lactones could be identified.[3a,b] More recently, we attempted the $Mn(OAc)_3$-mediated reaction of C_{60} with diethyl methylmalonate (**1a**) in an alternative solvent to avoid the participation of toluene. Interestingly, we obtained disubstituted C_{60}-fused γ-lactone **2a** besides 1,4-adduct **3a** and 1,16-adduct **4a** as the major products along with other byproducts from the reaction of C_{60} with diethyl methylmalonate (**1a**) and $Mn(OAc)_3$ in a molar ratio of 1:2:2 in *o*-dichlorobenzene (ODCB) at 140 °C and under nitrogen atmosphere (Scheme 1).[8]

Scheme 1. $Mn(OAc)_3$-Mediated Reaction of C_{60} with **1a** Affording C_{60}-Fused **2a**, 1,4-Adduct **3a**, and 1,16-Adduct **4a**



It should be emphasized that the protection of a nitrogen atmosphere proved to be crucial for the successful synthesis of C_{60}-fused lactone **2a** as well as 1,4-adduct **3a** and 1,16-adduct **4a**, with either little or no products being obtained in air. Nevertheless, the poor yield and selectivity for the formation of lactone **2a** led us to explore other reaction conditions to selectively obtain the rare disubstituted C_{60}-fused lactone. To our great satisfaction, we found that $Fe(ClO_4)_3$ in place of $Mn(OAc)_3$ could dramatically improve the selectivity. The reaction conditions were screened for the model reaction of C_{60} with **1a** mediated by $Fe(ClO_4)_3$ (Table 1). The reaction of C_{60} with **1a**, $Fe(ClO_4)_3{\cdot}xH_2O$ (FEP), and Ac_2O in a molar ratio of 1:2:2:20 gave lactone **2a** in 16% yield at ambient temperature (entry 1, Table 1). Raising the temperature to 60 °C enhanced the yield to 26% (entry 3, Table 1). Increasing or decreasing the amount of Ac_2O lowered the product yield (entries 4−5 vs entry 3, Table 1). The isolated yield could be further improved to 34% at the expense of recovered C_{60} by increasing the reaction temperature to 80 °C (entry 6, Table 1). The absence of Ac_2O deteriorated the yield significantly (entries 7−8 vs entry 3, Table 1). Replacing Ac_2O with AcOH gave inferior result too (entry 9 vs entry 3, Table 1). The role played by Ac_2O is not clear, yet it is known in the literature that Ac_2O is beneficial to $Fe(ClO_4)_3$-mediated radical reactions.[9b] Thus,

Table 1. Optimization of Reaction Conditions for the $Fe(ClO_4)_3$ Reaction of C_{60} with **1a**



entry	molar ratio[a]	reaction temp (°C)	reaction time (min)	yield of **2a** (%)[b]	recovered C_{60} (%)
1	1:2:2:20	25	300	16	81
2	1:2:2:20	40	120	17	80
3	1:2:2:20	60	20	26	58
4	1:2:2:10	60	60	20	62
5	1:2:2:30	60	20	25	26
6	1:2:2:20	80	20	34	38
7	1:2:2:0	60	120	9	89
8	1:2:2:0[c,d]	60	160	13	75
9	1:2:2:20[d,e]	60	10	20	42

[a] Molar ratio refers to C_{60}:**1a**:FEP:Ac_2O. [b] Isolated yield. [c] The reaction was conducted by the dissolution of $Fe(ClO_4)_3{\cdot}xH_2O$ (FEP) in **1a** (direct dissolution method). [d] An unknown product having a polarity similar to C_{60} was observed besides the desired fullerene lactone. [e] AcOH was used instead of Ac_2O.

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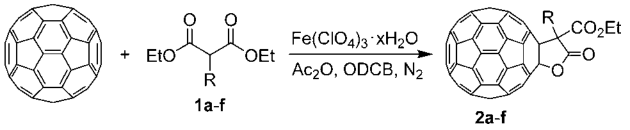
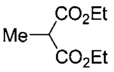
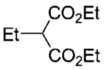
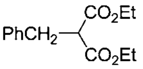
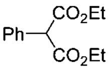
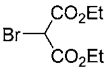
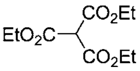
(8) After we had completed our work, the synthesis of **3a** and **4a** from the reaction of C_{60}^{2-} with diethyl 2-bromo-2-methylmalonate appeared: Kokubo, K.; Arastoo, R. S.; Oshima, T.; Wang, C.-C.; Gao, Y.; Wang, H.-L.; Geng, H.; Chiang, L. Y. *J. Org. Chem.* **2010**, *75*, 4574.

the molar ratio of 1:2:2:20 for the reagents C_{60}, **1a**, $Fe(ClO_4)_3 \cdot xH_2O$, and Ac_2O and the reaction temperature of 80 °C were chosen as the optimized reaction conditions.

Similar optimized reaction conditions could be successfully extended to the $Fe(ClO_4)_3$-mediated reaction of C_{60} with other substituted malonate esters such as diethyl ethylmalonate (**1b**), diethyl benzylmalonate (**1c**), diethyl phenylmalonate (**1d**), diethyl bromomalonate (**1e**), and triethyl methanetricarboxylate (**1f**). Table 2 lists the reaction conditions and yields for the $Fe(ClO_4)_3$-mediated reaction of C_{60} with malonate esters **1a**−**f** in the presence of Ac_2O, affording the scarce disubstituted C_{60}-fused lactones **2a**−**f**. It should be pointed out that no 1,4-adduct, 1,16-adduct, and single-bonded dimeric adduct of C_{60} could be identified from these reactions under our optimized conditions.

Table 2. Reaction Temperatures, Molar Ratios, Reaction Times, and Yields of C_{60}-Fused Lactones **2a**−**f**[a]



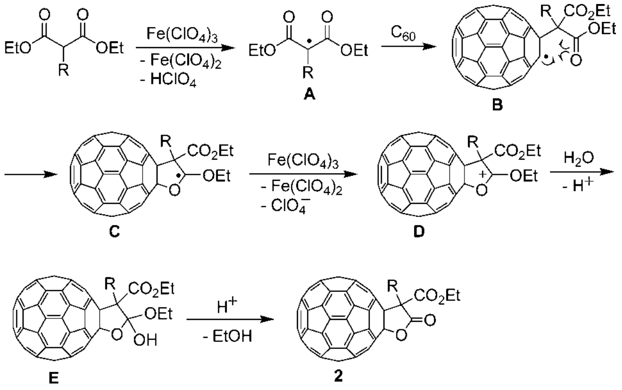
malonate ester **1**	reaction temp (°C)	reaction time (min)	yield of **2** (%)[b]
 **1a**	80	20	34 (55)
 **1b**	80	20	37 (71)
 **1c**	80	30	27 (61)
 **1d**	0[c]	180	12 (67)
 **1e**	80	30	22 (56)
 **1f**	110	20	16 (53)

[a] All reactions were carried out with a molar ratio of C_{60}:**1**:$Fe(ClO_4)_3 \cdot xH_2O$:Ac_2O = 1:2:2:20 in *o*-dichlorobenzene under nitrogen atmosphere unless indicated otherwise. [b] Isolated yield; that in parentheses was based on consumed C_{60}. [c] C_{60}:**1d**:$Fe(ClO_4)_3 \cdot xH_2O$:Ac_2O = 1:2:2:50.

As can be seen from Table 2, all examined malonate esters **1a**−**f** could be utilized to prepare disubstituted C_{60}-fused lactones **2a**−**f** in 12−37% yields (53−71% based on consumed C_{60}). Alkyl-substituted malonate esters **1a**−**c** at 80 °C afforded good isolated yields (27−37%) for monoadducts **2a**−**c**. Interestingly, phenyl-substituted malonate ester **1d** was very reactive (reaction temperature at 0 °C) yet gave lower yield due to its tendency to form some byproducts. Diethyl bromomalonate, which has been widely used in the Bingel reaction, could react with C_{60} and $Fe(ClO_4)_3$ in the presence of Ac_2O to produce lactone **2e** with the retention of the bromo substituent. Ethoxycarbonyl-substituted malonate ester **1f** was the least reactive among the investigated substituted malonate esters and required a higher reaction temperature (110 °C). It is noteworthy that acetic anhydride played a crucial role for the successful synthesis of C_{60}-fused lactones, with low and/or poor selectivity being obtained in its absence. Surprisingly, the $Fe(ClO_4)_3$-mediated reaction of C_{60} with diethyl malonate, the unsubstituted malonate ester, at 80 °C for 7 min failed to give the desired C_{60}-fused lactone, instead affording at least four unidentified products.

The structures of disubstituted C_{60}-fused lactones **2a**−**f** were fully characterized by HRMS, ^1H NMR, ^{13}C NMR, FT-IR, and UV−vis spectra. In the ^1H NMR spectra of lactones **2a**−**f**, the two methylene protons in the ethoxy group were nonequivalent and split as two double quartets due to the adjacent chiral center. In their ^{13}C NMR spectra, the chemical shifts for the lactone and ester carbons appeared at 166.49−173.56 and 162.91−169.69 ppm, and the two sp^3-carbons of the C_{60} skeleton were located at 95.57−96.43 and 68.41−72.40 ppm, close to those of reported C_{60}-fused lactone derivatives in the previous literature.[3g−i,6,7] There were at least 46 peaks in the 134−152 ppm region for the 58 sp^2-carbons of the C_{60} moiety for lactones **2a**−**e**, consistent with the C_1 symmetry of their molecular structures. In contrast, only 26 lines in the 136−149 ppm region could be found for lactone **2f**, agreeing well with its C_s symmetry. The IR spectra of **2a**−**f** showed absorptions at 1786−1798 and 1730−1760 cm^{-1} due to the lactone and ester groups. Their UV−vis spectra exhibited a peak at 415−419 nm, which is a characteristic absorption for the 1,2-adducts of C_{60} with the oxygen atom directly attached to the fullerene skeleton.[3g−i,6,7]

Scheme 2. Proposed Reaction Mechanism for the Formation of Lactones **2**



Even though the exact pathway is not quite clear for the formation of disubstituted C_{60}-fused lactones **2**, a possible reaction mechanism is proposed and shown in Scheme 2. Substituted malonate ester reacts with $Fe(ClO_4)_3$ to generate radical **A** accompanied with the formation of $Fe(ClO_4)_2$ and $HClO_4$.[9] Addition of radical **A** to C_{60} produces fullerenyl radical **B**, which undergoes intramolecular cyclization to give radical **C**. Oxidation of radical **C** by another molecule of $Fe(ClO_4)_3$ leads to cation **D** along with counteranion ClO_4^- and $Fe(ClO_4)_2$. The addition of H_2O, originated from hydrated water in $Fe(ClO_4)_3 \cdot xH_2O$ or concomitant water in the system, to cation **D** with the loss of H^+ results in **E**. Elimination of EtOH from intermediate **E** catalyzed by H^+ affords C_{60}-fused lactone **2**. The failure to obtain the expected C_{60}-fused lactone from the reaction with diethyl malonate might be due to undesired pathways such as the deprotonation of intermediate cation **D** and hydrogen atom abstraction from **E** by the ferric ion.

In summary, the reaction of C_{60} with a substituted malonate ester promoted by $Mn(OAc)_3$ afforded only a small amount of the desired disubstituted C_{60}-fused lactone along with the 1,4- and 1,16-adducts bearing two malonyl groups as the major products. However, the scarce disubstituted C_{60}-fused lactones could be selectively synthesized by simply changing the promoter from $Mn(OAc)_3$ to $Fe(ClO_4)_3$, indicating that $Fe(ClO_4)_3$ altered the reaction pathway in favor of the formation of the C_{60}-fused lactones. The synthesized disubstituted C_{60}-fused lactones have lactone and ester moieties, which can be further manipulated to make other fullerene derivatives including hydrofullerenes, fullerene hemiacetals, fullerene hemiketals, and fullerenols.[3g,10] A plausible reaction mechanism for the formation of lactones **2** is proposed. The present study hints that the metal salts have significant effects on the outcome of the reactions of C_{60}, and it is worthwhile to further explore their application in fullerene chemistry and organic synthesis in general.

Acknowledgment. The authors are grateful for the financial support from the National Natural Science Foundation of China (No. 20972145), the Specialized Research Fund for the Doctoral Program of Higher Education (No. 200803580019), and the National Basic Research Program of China (2006CB922003).

Supporting Information Available: Experimental procedures, spectral data, and NMR spectra of **2a−f**, **3a**, and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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