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

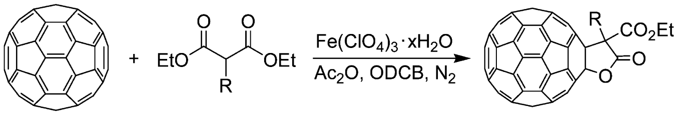
**Fa-Bao Li,[†] Xun You,[†] and Guan-Wu Wang*,[†,‡]**

*Hefei National Laboratory for Physical Sciences at Microscale, CAS Key Laboratory of Soft Matter Chemistry, and Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, P. R. China, and State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, Gansu 730000, P. R. China*

*gwang@ustc.edu.cn*

**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 $\gamma$-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 $\delta$-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

---

[†] University of Science and Technology of China.

[‡] Lanzhou University.

(1) For selected reviews, see: (a) Hirsch, A. *Synthesis* **1995**, 895. (b) Thilgen, C.; Diederich, F. *Chem. Rev.* **2006**, *106*, 5049. For some recent papers, see: (c) Murata, M.; Maeda, S.; Morinaka, Y.; Murata, Y.; Komatsu, K. *J. Am. Chem. Soc.* **2008**, *130*, 15800. (d) Filippone, S.; Maroto, E. E.; Martin-Domenech, A.; Suarez, M.; Martin, N. *Nat. Chem.* **2009**, *1*, 578. (e) Clavaguera, S.; Khan, S. I.; Rubin, Y. *Org. Lett.* **2009**, *11*, 1389. (f) Wang, G.-W.; Lu, Y.-M.; Chen, Z.-X. *Org. Lett.* **2009**, *11*, 1507. (g) Nambo, M.; Wakamiya, A.; Yamaguchi, S.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 15112. (h) Matsuo, Y.; Ichiki, T.; Radhakrishnan, S. G.; Guldi, D. M.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 6342. (i) Zhang, G.; Liu, Y.; Liang, D.; Gan, L.; Li, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 5293. (j) Tzirakis, M. D.; Orfanopoulos, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5891.

(2) For a review, see: Wang, G.-W.; Li, F.-B. *J. Nanosci. Nanotechnol.* **2007**, *7*, 1162.

(3) (a) Zhang, T.-H.; Lu, P.; Wang, F.; Wang, G.-W. *Org. Biomol. Chem.* **2003**, *1*, 4403. (b) Wang, G.-W.; Zhang, T.-H.; Cheng, X.; Wang, F. *Org. Biomol. Chem.* **2004**, *2*, 1160. (c) Wang, G.-W.; Li, F.-B. *Org. Biomol. Chem.* **2005**, *3*, 794. (d) Chen, Z.-X.; Wang, G.-W. *J. Org. Chem.* **2005**, *70*, 2380. (e) Cheng, X.; Wang, G.-W.; Murata, Y.; Komatsu, K. *Chin. Chem. Lett.* **2005**, *16*, 1327. (f) Wang, G.-W.; Yang, H.-T.; Miao, C.-B.; Xu, Y.; Liu, F. *Org. Biomol. Chem.* **2006**, *4*, 2595. (g) Wang, G.-W.; Li, F.-B.; Zhang, T.-H. *Org. Lett.* **2006**, *8*, 1355. (h) Li, F.-B.; Liu, T.-X.; Huang, Y.-S.; Wang, G.-W. *J. Org. Chem.* **2009**, *74*, 7743. (i) Li, F.-B.; Zhu, S.-E.; Wang, G.-W. *Chin. Sci. Bull.* **2010**, *55*, 2909.

(4) (a) Zhu, B.; Wang, G.-W. *J. Org. Chem.* **2009**, *74*, 4426. (b) Zhu, B.; Wang, G.-W. *Org. Lett.* **2009**, *11*, 4334.

(5) (a) Li, F.-B.; Liu, T.-X.; Wang, G.-W. *J. Org. Chem.* **2008**, *73*, 6417. (b) Li, F.-B.; Liu, T.-X.; You, X.; Wang, G.-W. *Org. Lett.* **2010**, *12*, 3258.

(6) Bernstein, R.; Foote, C. S. *Tetrahedron Lett.* **1998**, *39*, 7051.

(7) Wang, G.-W.; Zhu, B. *Chem. Commun.* **2009**, 1769.

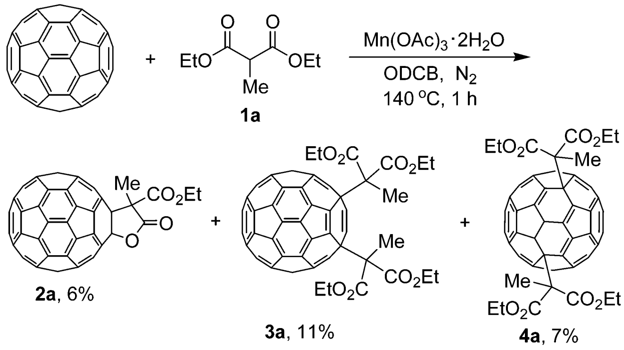
10.1021/ol102056k

anhydrides, or with malonic acids in the presence of $Mn(OAc)_3$ to afford three $C_{60}$-fused $\gamma$-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 $\gamma$-lactone derivatives.[3h,i] Unfortunately, nearly all of the reported $C_{60}$-fused $\gamma$-lactones are monosubstituted lactones. Only one disubstituted $C_{60}$-fused $\gamma$-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 $\gamma$-lactone under the employed standard conditions.[3h]

It seems that the synthesis of disubstituted $C_{60}$-fused $\gamma$-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 $\gamma$-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 $\gamma$-lactones through the reaction of $C_{60}$ with substituted malonate esters in the presence of $Fe(ClO_4)_3$ and acetic anhydride.

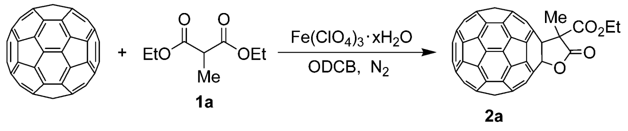
We previously reported that the $Mn(OAc)_3$-mediated reaction of $C_{60}$ with dialkyl malonates, i.e., $CH_2(CO_2Me)_2$ and $CH_2(CO_2Et)_2$, in refluxing chlorobenzene afforded the singly bonded fullerene dimers $[(RO_2C)_2CH]C_{60}-C_{60}[CH(CO_2R)_2]$ and 1,4-adducts $C_{60}[CH(CO_2R)_2]_2$, while 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 $\gamma$-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 $Ac_2O$.

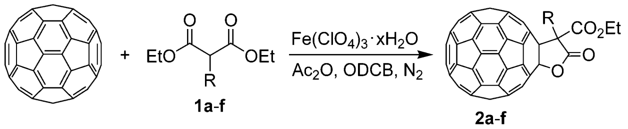
---

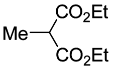
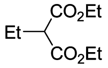
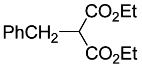
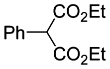
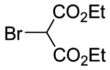
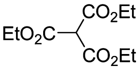
(8) After we had completed our work, the synthesis of **3a** and **4a** from the reaction of $C_{60}^{2-}$ with diethyl 2-bromo-2-methylmalonate appeared: Kokubo, K.; Arastoo, R. S.; Oshima, T.; Wang, C.-C.; Gao, Y.; Wang, H.-L.; Geng, H.; Chiang, L. Y. *J. Org. Chem.* **2010**, *75*, 4574.

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) |

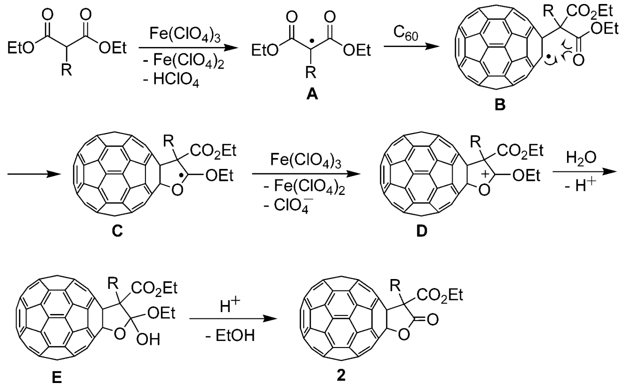
[a] All reactions were carried out with a molar ratio of $C_{60}$:**1**:$Fe(ClO_4)_3{\cdot}xH_2O$:$Ac_2O$ = 1:2:2:20 in *o*-dichlorobenzene under nitrogen atmosphere unless indicated otherwise. [b] Isolated yield; that in parentheses was based on consumed $C_{60}$. [c] $C_{60}$:**1d**:$Fe(ClO_4)_3{\cdot}xH_2O$:$Ac_2O$ = 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, $^1$H NMR, $^{13}$C NMR, FT-IR, and UV−vis spectra. In the $^1$H 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]

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.

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

OL102056K

---

(9) (a) Citterio, A.; Sebastiano, R.; Marion, A.; Santi, R. *J. Org. Chem.* **1991**, *56*, 5328. (b) Citterio, A.; Sebastiano, R.; Carvayal, M. C. *J. Org. Chem.* **1991**, *56*, 5335.

(10) Wang, G.-W.; Li, F.-B.; Xu, Y. *J. Org. Chem.* **2007**, *72*, 4774.