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[60]Fullerenoacetyl Chloride as a Versatile Precursor for Fullerene Derivatives: Efficient Ester Formation with Various Alcohols

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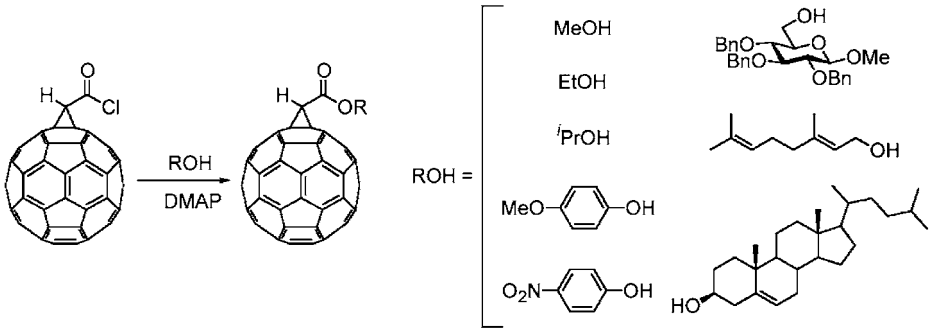
ABSTRACT



[60]Fullerenoacetyl chloride, one of the reactive derivatives of [60]fullerenoacetic acid, was isolated and identified for the first time. This acid chloride was easily synthesized in good yield from *tert*-butyl [60]fullerenoacetate through two steps. In the presence of 4-(dimethylamino)-pyridine as a base, the acid chloride smoothly reacted with various alcohols under mild conditions to give the corresponding esters including [60]fullerene−biomolecule hybrids in moderate to high yields.

Methano[60]fullerenes are a class of the most extensively studied fullerene derivatives because of their synthetic availability while maintaining the characteristic properties of [60]fullerene.[1] Although several methods have been developed for the preparation of methano[60]fullerenes,[2−4] most of them have some limitations for further facile molecular design. The Bingel reaction,[2] the most general reaction for the synthesis of methano[60]fullerenes, requires strong basic reaction conditions, and only robust functional groups can be introduced. In addition, two carbonyl units are inevitably introduced to the resultant products; such a drawback is unfavorable for the synthesis of monofunctionalized compounds. As alternative methods, addition−elimination of sulfonium ylides[3] and addition−thermal decomposition of diazo compounds[4] have been developed. Although these methods have also been widely used, they are not convenient, due to possible side reactions such as the formation of bis-adducts

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(1) Diederich, F.; Isaacs, L.; Philip, D. *Chem. Soc. Rev.* **1994**, *23*, 243.

(2) Bingel C. *Chem. Ber.* **1993**, *126*, 1957.

(3) (a) Wang, Y.; Cao, J.; Schuster, D. I.; Wilson, S. R. *Tetrahedron Lett.* **1995**, *36*, 6843. (b) Hamada, M.; Hino, T.; Kinbara, K.; Saigo, K. *Tetrahedron Lett.* **2001**, *42*, 5069.

(4) (a) Suzuki, T.; Li, Q.; Khemani, K. C.; Wudl, F.; Almarsson, O. *Science* **1991**, *254*, 1186. (b) Isaacs, L.; Wehrsig, A.; Diederich, F. *Helv. Chim. Acta* **1993**, *76*, 1231. (c)Isaacs, L.; Diederich, F. *Helv. Chim. Acta* **1993**, *76*, 2454. (d) Eiermann, M.; Wudl, F.; Prato, M.; Maggini, M. *J. Am. Chem. Soc.* **1994**, *116*, 8364.

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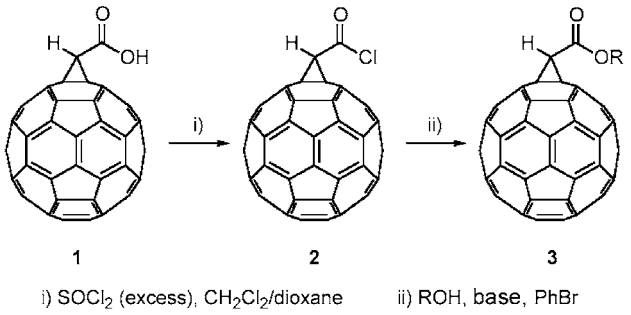
or fulleroids, and due to difficult synthetic efforts to prepare the corresponding ylides or diazo compounds. On the other hand, [60]fullerenoacetic acid is used for the formation of various [60]fullerenoacetic acid esters and amides upon treatment with alcohols and amines in the presence of a condensing agent.[4c] However, the yields of the esters and amides thus obtained are not satisfactory in general, presumably due to the low solubility of the acid in common organic solvents.[4c] Here, we describe a versatile and convenient method for the preparation of [60]fullerenoacetyl chloride and the application of the acid chloride for the synthesis of [60]fullerenoacetic acid esters.[5]

[60]Fullerenoacetyl chloride (**2**) was synthesized as follows (Scheme 1). *tert*-Butyl [60]fullerenoacetate, prepared by

Scheme 1. Synthesis of [60]Fullerenoacetic Acid Esters from [60]Fullerenoacetic Acid



following the literature method with some modification,[3a] was treated with *p*-TsOH in toluene to give [60]fullerenoacetic acid (**1**) as a brown solid.[4c,6] Although the solid was insoluble in most organic solvents, we finally found that CH_2Cl_2/dioxane (1:1 v/v) dissolves **1** very well. In this mixed solvent, **1** was efficiently converted to **2** by treatment with thionyl chloride (81−100% yield).[7] For several hours, the acyl chloride **2** was stable at room temperature, which allowed us spectroscopic characterization of **2**. The MALDI-TOF-MS spectrum showed a peak at $m/z = 795.79$, which is consistent with the calculated value (795.97 for $C_{62}HClO$).[8] IR spectroscopy also confirmed the transformation of −COOH to −COCl, since the absorption of the C═O shifted from 1700 cm^{-1} of **1** to 1780 cm^{-1} for **2**. The ^1H NMR spectrum of **2** in $CDCl_3/CS_2$ showed a singlet attributed to the proton of the bridge head at $\delta = 5.23$ (for reference, **1**: $\delta = 5.14$), and the amount of contaminated **1** was found to be significantly small.

In the presence of triethylamine as a base, **2** readily reacted with methanol and ethanol to give the corresponding esters in high yields under mild conditions (in bromobenzene at room temperature). However, in the case of the reaction with 2-propanol, which is a less-reactive alcohol, the yield was depressed. Then, to improve the yield, various bases (1.05 equiv) were employed for the condensation of **2** with 2-propanol (8.0 equiv). The data in Table 1 indicate that

Table 1. Condensation of [60]Fullerenoacetyl Chloride with 2-Propanol

entry	base	yield (%)
1	*N*,*N*-diisopropylethylamine	49
2	triethylamine	52
3	*N*-methylmorphorine	34
4	4-(dimethylamino)pyridine	61
5	pyridine	38

proton-accepting ability of the base used is an important but not a crucial factor for the efficient ester formation. In the cases of aliphatic tertiary amines with strong basicity, relatively moderate yields were attained (Table 1, entries 1 and 2), compared with pyridine with low basicity (Table 1, entry 5). Noteworthy is the fact that exceptionally good yield was realized when 4-(dimethylamino)pyridine (DMAP) was used as the base despite its weak basicity (Table 1, entry 4). These observations suggest that DMAP promotes the condensation not only as a base possessing sufficient basicity, but also as an activator of **2**. In general, it is well-known that DMAP catalyzed acyl-transfer reactions.[9]

From the viewpoint of the suppression of side reactions, DMAP is a suitable base for the condensation, too. In the condensation with 2-propanol, the use of triethylamine as a base resulted in the formation of byproducts. This side reaction is presumably the nucleophilic attack of triethylamine to the carbon atoms of **2**, which is not negligible when the nucleophilicity of the alcohol is low.[10] In sharp contrast, the use of DMAP in the place of triethylamine completely suppressed the side reaction, because of the low nucleophilicity of DMAP.

Under the optimized conditions, the condensation of **2** with various alcohols and phenols was carried out.[11] The results are summarized in Table 2. By using DMAP (1.05 equiv)

(5) For examples of in situ generation and subsequent reaction of methano[60]fullerenecarboxylic acid chlorides, see: (a) Woods, C. R.; Bourgeois, J.-P.; Seiler, P.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3813. (b) Agrawal, Y. K. *Fullerene Sci. Technol.* **1997**, *5*, 275.

(6) **Preparation of [60]Fullerenoacetic Acid (1).** A solution of *tert*-butyl [60]fullerenoacetate (214 mg, 0.26 mmol) and *p*-TsOH·H_2O (88 mg, 0.52 mmol) in toluene (150 mL) was refluxed for 8 h to afford a suspension. The brown solid thus precipitated was collected by filtration, and the solid was washed successively with toluene (100 mL) and water (30 mL). The residual solid was dissolved in CH_2Cl_2/dioxane (1:1 v/v, 30 mL), and the soluble fraction was separated by filtration. The filtrate was evaporated to dryness to afford **1** as a brown solid (145 mg, 0.19 mmol, 72%).

(7) **Preparation of [60]Fullerenoacetyl Chloride (2).** A solution of **1** (50 mg, 0.064 mmol) and thionyl chloride (5.0 mL, 67 mmol) in CH_2Cl_2/dioxane (1:1 v/v, 40 mL) was refluxed for 5 h, whereupon a black precipitate was formed. The precipitate was separated by filtration and washed with CH_2Cl_2/dioxane (1:1 v/v, 100 mL). The residual solid was dissolved in CS_2 (20 mL), and the soluble fraction was separated by filtration. The filtrate was evaporated to dryness to afford **2** as a black solid (51 mg, 0.064 mmol, quant.).

(8) In the MALDI-TOF-MS spectrum of **2**, several unidentified peaks were observed. These peaks are probably due to the reaction of **2** with the matrix (dithranol) and/or the fragmentation of **2** caused by the laser irradiation. See the Supporting Information.

(9) (a) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (b) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069.

(10) Lawson, G. E.; Kitaygorodskiy, A.; Sun, Y.-P. *J. Org. Chem.* **1999**, *64*, 5913.

Table 2. Condensation of [60]Fullerenoacetyl Chloride with Various Alcohols

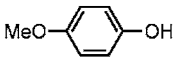
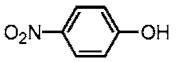
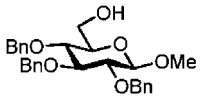
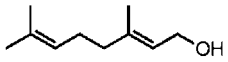
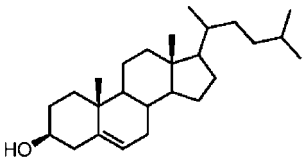
entry	ROH	DMAP (equiv)	time (h)	yield (%)
1	MeOH	1.05	3	96
2	EtOH	1.05	3	93
3	^{i}PrOH	1.05	6	61
4		2.1	6	80
5		1.05	3	74
6		2.1	3	90
7		1.05	12	60
8		2.1	12	73

Table 3. Synthesis of [60]Fullerene−Biomolecule Hybrids

entry	ROH	yield (%)
1		66
2		53
3		76

as a base, **2** smoothly reacted with primary alcohols (8 equiv), such as methanol and ethanol, to afford the methyl and ethyl esters in excellent yields (Table 2, entries 1 and 2). In contrast, 2-propanol, a representative secondary alcohol, and phenols gave the corresponding esters in moderate yields (Table 2, entries 3, 5 and 7). However, the yields were highly improved when an excess amount of DMAP (2.1 equiv) was used. The improvement is consistent with our expectation that DMAP plays a role as an activator of **2** (Table 2, entries 4, 6, and 8).

The observed efficiency of the condensation motivated us to apply the reaction for the preparation of fullerene−biomolecule hybrids (Table 3).[12] Even when natural products and their derivatives were used as alcohols, the condensation of **2** easily proceeded to give the target hybrids in moderate to good yields.

These results strongly indicate that [60]fullerenoacetyl chloride (**2**), isolated and characterized in the present study for the first time, is highly potent as an intermediate for the synthesis of [60]fullerene derivatives.

In summary, we developed a new method for the preparation of [60]fullerenoacetyl chloride (**2**) in good yield with sufficient purity for common use in organic synthesis. Taking the advantage of the high reactivity and solubility of **2**, [60]fullerenoacetic acid esters were synthesized in good yields. Thus, condensation of the acyl chloride would be a versatile and convenient method for the synthesis of hybrids of [60]fullerene and functional molecules, such as [60]fullerene-biomolecule hybrids. Considering the potential for the transformation of the acyl chloride to other functional groups, [60]fullerenoacetyl chloride would be a key intermediate of novel [60]fullerene derivatives.

Supporting Information Available: Spectral data of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) **General Procedure for the Condensation of 2 with Alcohols.** To a bromobenzene solution (15 mL) of **2** (15 mg, 0.019 mmol) was added a bromobenzene solution of methanol (0.4 M, 0.40 mL, 0.16 mmol), and DMAP (2.4 mg, 0.020 mmol) was added to the mixture. The reaction mixture was stirred at room temperature for 3 h, and then evaporated to dryness. The residue was subjected to preparative thin-layer chromatography developed with CH_2Cl_2/CS_2 to afford the methyl ester as a brown solid (14.3 mg, 0.018 mmol, 96%).

(12) For examples of [60]fullerene−biomolecule hybrids, see: (a) Murakami, H.; Watanabe, Y.; Nakashima, N. *J. Am. Chem. Soc.* **1996**, *118*, 4484. (b) Nakamura, E.; Isobe, H.; Tomita, N.; Sawamura, M.; Jinno, S.; Okayama, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 4254. (c) Ishi-i, T.; Ono, Y.; Shinkai, S. *Chem. Lett.* **2000**, 808.