Chemical Derivatization of Organofullerenes through Oxidation, Reduction, and C–O and C–C Bond-Forming Reactions

Shigeru Yamago, Hidetoshi Tokuyama, and Eiichi Nakamura*

Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

Maurizio Prato† and Fred Wudl

Institute for Polymers and Organic Solids, Department of Chemical Physics, University of California, Santa Barbara, California 93106

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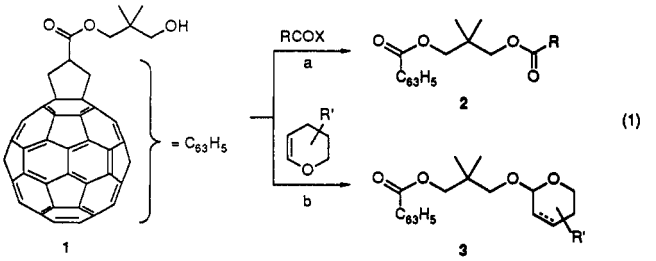
Summary: Fullerenes bearing olefin, aldehyde, alcohol, sugar, and amino acid functional groups were synthesized by oxidation, reduction, and C–O and C–C forming reactions.

Chemical modifications of fullerenes by selective bond formation provide a vital tool in fullerene science and technology.[1] Intensive efforts in the past few years have successfully laid an "organic foundation" on the C_{60} sphere[2] that includes three-,[3] four-,[4] five,[3b,5] and six-membered[6] ring systems. The next step is to construct useful functionalities on such "foundations". However, knowledge of the chemical reactivities of fullerenes is to scant to permit the synthetic design of most desired structures, at present.[7] In this paper, we report our preliminary data on several chemical modifications of organofullerenes, using alcohol 1 as a prototype. Existing knowledge suggested that fullerenes are quite reactive compounds, particularly under basic conditions (e.g., aqueous KOH at room temperature[8]). We found, however, that the C_{60} moiety survives the acidic to weakly basic conditions required to carry out a range of C–O and C–C forming reactions as well as oxidation and reduction. These reactions thus provide flexible synthetic routes to fullerenes bearing functional groups such as olefin, aldehyde, alcohol, sugar, and amino acid residues. The functionalized fullerenes are stable compounds and are much more soluble in various solvents than C_{60} itself, opening up new possibilities in fullerene research.

In our investigations of the stability of the C_{60} group against bond-forming reaction conditions, we first examined esterification reactions under mildly basic conditions (eq 1a). The alcohol 1, available from the [3 + 2] cycloaddition of a dipolar trimethylenemethane,[5] was treated with benzoyl chloride (2 equiv) and pyridine (2 equiv) in toluene at 50 °C for 3 h. The benzoate **2a** was isolated in 62% isolated yield by silica gel chromatography (Table I, entry 1a). The same benzoate could be obtained more conveniently by condensation with benzoic acid (2 equiv), dicyclohexylcarbodiimide (DCC) (2 equiv), and 4-(dimethylamino)pyridine (DMAP, 0.2 equiv) in CH_2Cl_2 at room temperature (entry 1b). Similarly, methacrylic ester **2b** was prepared in quantitative yield (entry 2). In relation to our interests in the biological activities of fullerenes,[9] we have examined the possibility of connecting the fullerene unit to amino acids. Thus, condensation of 1 with the *N*-Boc-protected 4-aminopyrrolecarboxylic acid gave the ester **2c** (entry 3) and that with *N*-Boc-phenylalanine gave the ester **2d** (entry 4). These were found to be stable compounds, offering good prospects for the design and synthesis of biochemical tools based on the fullerene core. Throughout the present studies, we have noted that excess reagents were necessary to achieve the full conversion of 1 within a reasonable period of time, because the low solubility of 1 necessitated the use of a relatively low concentration of reactants (ca. 0.01 M).



(1)

C–O bond formation could also be achieved under acidic conditions (eq 1b). For example, the tetrahydropyranyl ether **3a** was prepared by treatment of 1 with dihydropyran (20 equiv) and pyridinium *p*-toluenesulfonate (0.2 equiv) in quantitative yield (entry 5). The acidic etherification conditions were found to be useful for glycosidation of 1 with a glycal.[10] Thus, the reaction of 1 with tri-*O*-acetylglycal (10 equiv) in the presence of *p*-toluenesulfonic acid (0.4 equiv), as shown in entry 6 afforded the sugar derivative **3b** as a 4:1 mixture of α- and β-anomers.

† On leave from CMRO-CNR and Department of Organic Chemistry, University of Padova, Italy. Current address: Dipartimento di scienze Parmaceutiche, Pizzale Europa 1, 34127 Trieste, Italy.

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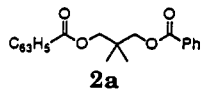
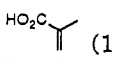
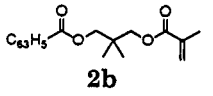
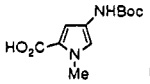
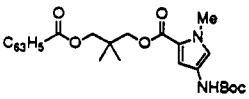
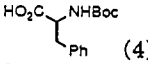
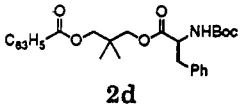
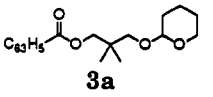
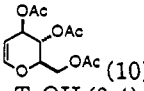
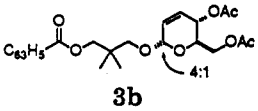
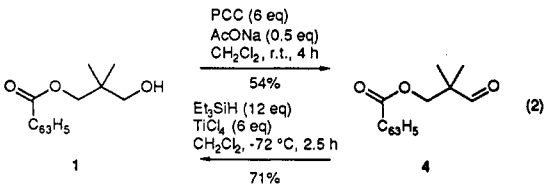
Table I. Synthesis of Organofullerenes[a]

entry	reagents (equiv)	time (h)	product	% yield[b]
1a	PhCOCl (2), pyridine (2)	8	 **2a**	62
1b	$PhCO_2H$ (2), DCC (2)/DMAP (0.2)	12	**2a**	100
2	 (10), DCC (10)/DMAP (0.8)	10	 **2b**	100
3	 (5), DCC (5)/DMAP (0.5)	26	 **2c**	64
4	 (4), DCC (4)/DMAP (0.4)	18	 **2d**	81
5	 (20), PPTS (0.2)	12	 **3a**	85
6	 (10), TsOH (0.4)	12	 **3b**	62

[a] The reaction was carried out in CH_2Cl_2 at room temperature except for entry 1a, where it was carried out in toluene at 50 °C. [b] Based on pure isolated material.

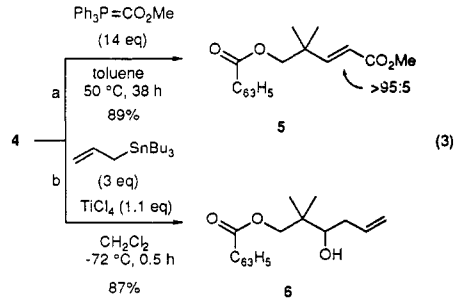
Oxidation and reduction of oxygen functionalities could also be achieved in the presence of the fullerene core (eq 2). Thus, oxidation of the hydroxyl group in 1 with



(2)

pyridinium chlorochromate (PCC)[11] in CH_2Cl_2 at room temperature cleanly (TLC) afforded the aldehyde 4 in 58% isolated yield. Swern oxidation,[12] on the other hand, resulted in the recovery of 1. While attempted conversion of 4 back to 1 with diisobutylaluminum hydride was unsuccessful due to a competitive reaction with the C_{60} core, reduction under acidic conditions proved to be successful. Thus, reduction of the aldehyde group of 4 with Et_3SiH (12 equiv) in the presence of $TiCl_4$[13] (3.6 equiv) in CH_2Cl_2 at −72 °C afforded 1 in 74% yield. The C_{60} core remained intact despite the use of excess reducing agent.

The potential of C–C bond elongation reactions was next examined for the aldehyde group in 4. Initial attempts to add alkyllithium[14] and magnesium[15] reagents failed due to competitive reactions of the C_{60} moiety. It was rather disappointing that much milder conditions using fluoride activation technology[16] also failed to induce selective C–C bond formation at the aldehyde group. Hence, the aldol reaction of 4 with the trimethylsilyl ketene acetal of metal isobutyrate in the presence of tris(diethylamino)sulfur (trimethylsilyl) difluoride[17] gave several products due to reactions of the C_{60} moiety. We found, however, that a stabilized ylide does react selectively with the aldehyde group to give the unsaturated ester 5 as an *E*-isomer (>95:5) in 89% yield (eq 3a). Lewis-acid mediated reaction



(3)

was also found to be effective for C–C bond formation.[18] The reaction of the aldehyde 3 with allyltributyltin[19] (3 equiv) and $TiCl_4$ (1.1 equiv) at −72 °C gave the homoallylic alcohol 6 in 87% yield (eq 3b).[20]

While the parent C_{60} is sparingly soluble in various solvents, the fullerene derivatives described above were found to be considerably more soluble in aromatic hydrocarbons and halogenated and ethereal solvents. While there was a possibility that the attached polar groups in the present studies might interact with the C_{60} core in either an intramolecular or intermolecular manner, ^1H NMR spectroscopy, which provides a measure of the spatial proximity between the C_{60} core and a nearby proton,[2c] indicated no sign of anomaly due to such interactions.

In summary, we have established that the organofullerenes are amenable to functional group modifications under weakly basic to strongly acidic conditions and that

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(20) Typical reaction procedure. Oxidation: to a mixture of the alcohol 1 (45.6 mg, 50 μmol), AcONa (2.1 mg, 25 μmol), and Al_2O_3 (0.20 g) in 5 mL of CH_2Cl_2 was added PCC (17.0 mg, 79 μmol) at room temperature. PCC was added repeatedly (10–14 mg, ca. 1 h period) until the alcohol 1 disappeared on TLC (total amount of PCC; 64 mg, 0.29 mmol). Toluene (15 mL) was added, and the resulting mixture was passed through a pad of silica gel (silica gel 5 g, elution with toluene). Removal of the solvent followed by purification by silica gel chromatography (silica gel 2 g, elution with toluene followed by 10% ethyl acetate in toluene) afforded 1 (6.7 mg, 15% recovery) and 3 as a black powder (24.2 mg, 54%). Allylation to a mixture of the aldehyde 4 (15.4 mg, 17 μmol) and allyltributyltin (16.9 mg, 51 μmol) in 2 mL of CH_2Cl_2 was added $TiCl_4$ (1.01 M in CH_2Cl_2, 19.0 μL, 19 μmol) at −72 °C, and the resulting solution was stirred for 0.5 h at this temperature. Water (0.1 mL) was added, and the reaction mixture was warmed to room temperature. Purification of the crude product obtained after aqueous workup (silica gel 0.6 g, elution with toluene and then 5% ethyl acetate in toluene) afforded the homoallyl alcohol 6 in 87% yield (13.8 mg).

these reactions provide a variety of useful compounds for further fullerene studies.

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Supplementary Material Available: Experimental procedures and spectral data for compounds **2–6** and UV–vis spectra of **2a** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.