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Synthesis of A Novel Fulleroaziridine Carrying 4-Deoxy-4′-demethylepipodophyllotoxin

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Abstract: A novel fulleroaziridine **2** with a closed 6,6-ring junction was synthesized from [60]fullerene and 4-azido-4-deoxy- 4′-demethylepipodophyllotoxin **1** in 1, 2-dichlorobenzene at 110℃ for 45 h, in a yield of 39.3 % based on consumed C_{60}. The structure of the product was characterized by NMR and MS.

Keywords: Podophyllotoxin derivative, azide, [60]fullerene, fulleroaziridine, cycloaddition.

Functionalization by cycloaddition reactions[1] represents a useful strategy to modify fullerenes[1,2]. Stable cycloadducts are interesting in regarding to the development of new materials with unique physical properties or biological activities[3]. One of the typical reactions is the cycloadditions of C_{60} with azide compounds. Wudl and Miyata *et al*. reported that C_{60} reacted with alkyl azides[4] or benzyl azides[5] to give the same kind of adduct azafulleroids with an opened 6,5-ring junction by thermally induced [3+2] cycloaddition. In contrast to these results the thermal reaction of an azioformate leading to the formation of a fulleroaziridine with a closed 6,6-ring junction was reported by Banks *et al*.[6] as well as the photoreaction of arylazides[7] or aroylazides[8]. The divergent formation of fulleroids and fulleroaziridines can probably be explained either *via* [3+2] 1, 3-dipolar addition of alkyl azides followed by N_2-elimination from the intermediately formed triazoline adduct or *via* nitrene [1+2] cycloaddition[6].

In this communication we report the result of our work on the cycloaddition reaction of C_{60} with a special benzylazide **1** (**Scheme 1**), which was from podophyllotoxin **3**, affording a novel fulleroaziridine **2** with a closed 6,6-ring junction adduct, other than fulleroid with an opened 6,5-ring junction. This result clearly conform the nitrene addition to be the key step for the formation of fulleroaziridine derivatives by thermally induced reactions[6]. A podophyllotoxin derivative moiety **1** was chosen for the reaction, because it is a well known natural product owing to its antimitotic activity, and to the ability of derived epiglucosides to inhibit DNA synthesis, this has led to the development of drugs such as etoposide **4** and teniposide **5** which have been widely used for the treatment of cancers[9-11]. As a result, the adduct **2** may have interesting biological activities or physical properties. The aim of the work described here was also to

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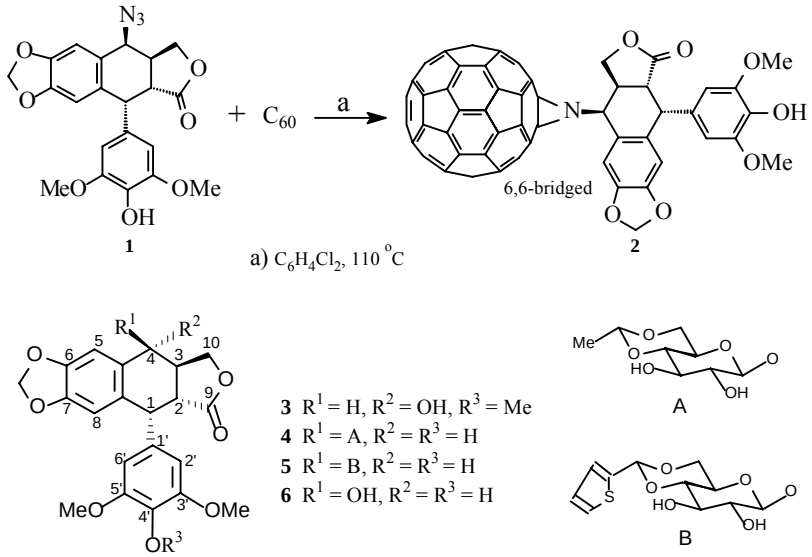
examine the cycloaddition reaction of C_{60} with podophyllotoxin azide derivative **1** to establish a general way to introduce podophyllotoxin derivatives into fullerenes utilizing the cycloaddition reaction of fullerenes with benzyl podophyllotoxin azides.

Scheme 1 Formation of fulleroaziridine **2**



Results and Discussion

The starting azide **1** was synthesized by the reaction of 4′-demethylepipodophyllotoxin **6** with HN_3 in the presence of $BF_3{\cdot}Et_2O$ at –15℃[12]. The structure of **1** was confirmed by MS, NMR and IR spectra. Considering the solubility of starting materials and steric hindrance of the azide **1**, various solvents and different temperatures were investigated for the reaction. The results are summarized in **Table 1**. When the reaction was refluxed in chlorobenzene (132℃) for 14 h, a complex mixture of products with a partially broken lactone was produced due to the partial decomposition of the azide **1** according to ^{1}H NMR and IR spectra. When the reaction mixture was refluxed in carbon disulphide, benzene or toluene for 128 h, 81 h or 13 h respectively, no reaction was observed according to TLC. When the reaction mixture was stirred in a mixed solvents of 1:1 chlorobenzene-toluene at 110℃, the adduct was isolated in 12.9% yield based on consumed C_{60}. When the reaction mixture was stirred in chlorobenzene at *ca*. 115℃ for 53 h, a good yield of 27.6 % (based on consumed C_{60}) of the product was obtained. Finally, when the reaction mixture was stirred in *O*-dichlorobenzene, the best solvent in solubility for C_{60}, at 110℃ for 45 h, the maximum yield (39.3 %, based on consumed C_{60}) of the product was isolated. The molar ratios of the starting materials of C_{60} and azide **1** in all the reactions discussed above were 1:1.

The structure of adduct **2** was characterized by analysis of its NMR and MS spectra[13]. The ^{13}C NMR spectrum of **2** displays only 16 resolved or partially resolved signals for sp^2 fullerene moiety carbons in the region of quaternary carbon atoms between 128 and 150

ppm, together with one signal of sp^3 bridgehead fullerene carbon at 90.0 ppm. The number and chemical shifts of the fullerene moiety signals are only consistent with a closed 6,6-bridged structure for the adduct **2** having a C_{2v} symmetry of the molecule[8], rather than an adduct with an open 6,5-ring junction[4]. The remaining 18 signals belong

Table 1 Effect of solvents and temperatures for synthesis of **2**

Entry	Solvent (solubility[a])	Tempt.(℃)	Time(h)	Yield[b] (%)
1	C_6H_5Cl (7.0)	132	14	?[c]
2	CS_2 (7.9)	46	128	0[d]
3	C_6H_6 (1.7)	80	81	0[d]
4	$C_6H_5CH_3$ (2.8)	110	13	0[d]
5	C_6H_5Cl /$PhCH_3$[e]	110	54	12.9
6	C_6H_5Cl (7.0)	118	53	27.6
7	$C_6H_4Cl_2$ (27)	110	45	39.3

[a] For C_{60} (mg/mL);
[b] Based on consumed C_{60};
[c] The cyclic lactone of the product was partially broken according to IR and ^{1}H-NMR spectra;
[d] No work;
[e] In a 1:1 ratio.

to the azide moiety carbon atoms, of which 7 signals are attributed to the aryl quaternary carbon atoms within the area of fullerene signals. Most of them have downfield shifts, compared with the starting azide **1**, due to the electronwithdrawing influence of the carbon sphere. The ^{1}H NMR spectrum of the adduct **2** is similar to the starting azide **1** with remarkable downfield shifts as they did in ^{13}C NMR spectrum. Because the aziridinofullerene moiety is located at 4-β position of the molecule of 4-deoxy-4′-demethylepipodophyllotoxin, β-aliphatic protons at both H-2 and H-10β cause the biggest downfield shift with more than 1 ppm. Whereas all the α-protons at H-3, H-5 and H-10α have just caused a medium shift with *ca*. 0.5 ppm. The remaining protons only have few shifts as they are far away from C_{60} sphere. The MALDI-TOF mass spectrum gives the molecular ion cluster at *m/z* 1116.1, supporting the formula of $C_{81}H_{18}O_7N$ (M-1). The UV-vis spectrum of the adduct **2** is similar to that of C_{60} with a slight blue-shift occurred at 228, 255 and 322 nm from 230, 258 and 328 nm in the spectrum of C_{60}, due to 60 π electrons in C_{60} while 58 π electrons in C_{60} moiety of adduct **2**.

In conclusion, we have demonstrated the feasibility of the fullerenation of an azapodophyllotoxin derivative affording the fulleroaziridine **2** with a closed 6,6-ring junction**,** *via* nitrene [1+2] cycloaddition reaction of C_{60} with an azide of podophyllotoxin derivative. We have also demonstrated that using *O*-dichlorobenzene as the solvent to guarantee a sufficient solubility of the reagents and the reaction could proceed at lower temperature (*ca*. 110℃) to avoid decomposition of the podophyllotoxin derivative moiety. These would be the best conditions for this reaction.

Acknowledgments

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13. Selected data for compound **2**: ^{1}H NMR ($CDCl_3$): δ 4.99 (d, 1H, *J*=3.4, H-1), 4.33 (dd, 1H, *J* =5.6, 13.8, H-2), 3.42 (m, 1H, H-3), 4.93 (d, 1H, *J*=5.5, H-4), 7.43 (s, 1H, H-5), 6.73 (s, 1H, H-8), 4.75 (dd, 1H, *J*=8.0, 15.4, H-10α), 5.38 (dd, 1H, *J*=8.7, 11.2, H-10β), 6.411s (s, 2H, H-2′6′), 6.03 (ABq, 2H, *J*=1.3, OCH_2O), 3.85 (s, 6H, H-3′5′-OMe). ^{13}C NMR ($CDCl_3$): δ 174.9 (C=O), 148.8, 147.2, 146.6, 145.6, 145.5, 145.2, 145.1, 144.9, 144.1, 144.0, 143.3, 143.2, 142.4, 142.3, 141.3, 134.4, 133.8, 131.4, 130.6, 128.8, 127.8, 111.6 (C-8), 109.6 (C-5), 108.3 (C-2′6′), 101.8 (OCH_2O), 90.0 (sp^3 bridgehead fullerene carbon), 68.2 (C-10), 56.8 (C-4), 56.7 (3′,5′-OMe), 44.6, 41.9, 38.7 (C-1～C-3). MALDI-TOF MS: 1116.1 (M-1). IR (KBr): 1779, 1427, 1186, 527 cm^{-1}

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