Easy Access to [60]Fulleroalkaloids *via* Photoinduced Reactions of Tertiary Amines with [60]Fullerene

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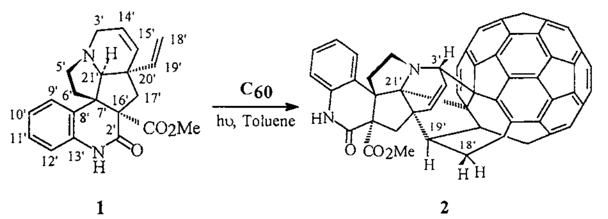
Photoinduced reactions of tertiary amines with [60]fullerene (C_{60}) were successfully applied to the synthesis of [60]fulleroalkaloids. This method is easy and effective for constructing C_{60} derivatives containing natural alkaloids for the purpose of checking the influence of the carbon cage on the biological activities of the alkaloids. In this letter, the preparation and characterization of [60]fulleroscandine is reported.

Recently, we have been interested in the preparation of C_{60} derivatives that contain potentially biologically active moieties. In this letter, we report a novel and easy approach for introducing natural alkaloids, which are endowed with a range of biological activities, to the C_{60} cage in order to evaluate the biological properties of these novel and interesting molecules. In this approach, an alkaloid moiety was attached directly to the C_{60} cage by the use of photoinduced reaction of C_{60} with an alkaloid containing a tertiary amino group. Although a few examples of alkaloid-C_{60} are already known in the literature, for instance, Prato *et al* have reported the synthesis of a nicotine analogue *via* 1,3-dipolar cycloaddition of an azomethine ylide to C_{60},[1] there appears to be no report in the literature concerning the synthesis of alkaloid-C_{60} derivatives *via* a photochemical method.

The photoinduced reactions of tertiary amines with C_{60} have been previously studied.[2-4] However, little attention has been directed to seeking the synthesis of more complex photoadducts that may expand the scope of this reaction. Aiming to expand the scope and seek an easy access to constructing C_{60} derivatives containing complex alkaloids for the purpose of checking the influence of the carbon cage on the biological activities of the alkaloids, we investigated the reaction of C_{60} with complex alkaloids that contain tertiary amino groups. The results are encouraging. So far, 10-hydroxyscandine,[5] tazettine, gramine, vobasine, vindoline and scandine[6] (**1**), *etc.* have successfully reacted with C_{60} under the similar reaction conditions and their major products have been isolated and purified. Among them, the structure of the C_{60}-scandine derivative (**2**), which we called [60]fulleroscandine, has been fully elucidated. The characterization of the other derivatives and the preliminary evaluation of biological properties of all these derivatives are presently underway. Herein, we describe the preparation and full characterization of the [60]fulleroscandine as the first example of this approach. Interestingly, in addition to the expected reaction of C_{60} with a tertiary amino group, the reaction of C_{60} with scandine unexpectedly involves a [2+2] cycloaddition between a vinyl group and a double bond adjacent to the one involved in the first addition.



1 **2**

Scheme 1.

The reaction was carried out as follows. 37.2 mg of C_{60} (0.052 mmol) and 53.4 mg of **1** (0.152 mmol, 2.9 equiv.) were dissolved in 20 ml toluene, and the solution was stirred at ambient temperature and was irradiated with a 60 W bulb for two hours. The color of the solution changed from purple to dark brown. Flash chromatography on silica gel first using toluene as eluent furnished unreacted C_{60} (13.5 mg), then using a mixture of methylene chloride and ethyl acetate (25:1) as eluent afforded product **2** (14.5 mg, yield 41.2% based on consumed C_{60}). Prolongation of reaction time to 4 hours resulted in a lower yield of **2** due to marked increase in the proportion of products arising from multiple additions to the cage.

The time of flight secondary ion mass spectrum (TOF-SIMS) of **2**, which displayed a peak at *m/z* 1069 (relative intensity 34%, $[MH]^+$ for $C_{81}H_{21}N_2O_3$) as well as the base peak for C_{60} at *m/z* 720 which arises from loss of $C_{21}H_{21}N_2O_3$, showed that one molecule of **1** was incorporated into C_{60} with loss of two hydrogens. Its UV-Vis spectrum was similar to that of C_{60} in 190-300 nm region, but was different in the weakly absorbing region between 300-500 nm. The FT-IR spectrum (KBr pellet) gave absorption bands at 3427.0(NH), 1740.6(ester C=O), 1678.1(amide C=O), along with a very strong band at 525.0 cm^{-1} characteristic of the parent fullerene.

The NMR spectra gave the most important information for the structure of **2**. Each proton in the ^1H NMR spectrum was individually identified by the ^1H-^1H COSY experiment.[7] The asymmetric structure of **2** yielded separate signals for each carbon except one overlapping signal at δ 144.81 in the ^{13}C NMR spectrum. Based on the HMQC and HMBC experiments, all assignable carbon signals in the ^{13}C NMR spectrum have been assigned.[7] The detailed analysis of the NMR spectra showed that the expected reaction of C_{60} with the tertiary amino group of **1** has indeed occurred. As shown in previous studies,[2-4] the tertiary amino group should be added to 6-6 ring junction of C_{60}, forming a 6-6 closed structure. This conclusion is consistent with ^{13}C NMR spectrum of **2** in which the carbon atoms of the addition site appeared at δ 79.08 and 76.72 respectively, which revealed they had been sp^3-hybridized. In the HMBC spectrum, $H_{3'}$ (δ 4.98) showed two and three bonds correlations with both of the sp^3 carbons of the C_{60} skeleton. Undoubtedly, $C_{3'}$ is one of the connecting sites. Another connecting site must be $C_{21'}$ because in the ^{1}H NMR spectrum only $H_{21'}$ signal was absent, and in the HMBC spectrum no other hydrogen except $H_{3'}$ showed correlations with either of such two sp^3 carbons of the C_{60} skeleton. The quaternary carbon signal at δ 100.94 was assigned to $C_{21'}$ on the ground of the fact that $C_{21'}$ showed distinct cross peaks with $H_{3'}$, $H_{5'}$, $H_{15'}$ and $H_{17'}$, respectively, in the HMBC spectrum.

Much to our surprise, in parallel with the above expected reaction, there is an intramolecular [2+2] cycloaddition between C_{60} and the vinyl group of scandine moiety. In the ^{1}H NMR spectrum, $H_{19'}$ resonated at δ 4.19 (1H, dd, J 3.79, 10.10 Hz) and two $H_{18'}$ resonated at δ 3.74 (1H, dd, J 3.79, 13.05 Hz), 3.52 (1H, dd, J 10.10, 13.05 Hz), respectively. Their chemical shifts and coupling constants revealed that they had not been vinyl protons. The HMQC spectrum showed $C_{18'}$ and $C_{19'}$ signals appeared at δ 33.33 and 53.91 respectively, unequivocally demonstrating they have been sp^3-hybridized carbons. Since the 6-6 double bonds of C_{60} behave like electron-deficient alkenes, it is reasonable to assume that the [2+2] cycloaddition reaction has taken place at the 6-6 ring junction. There are also examples of [2+2] cycloaddition across the 6-6 ring junction of C_{60} in the literature.[8] Moreover, the assumption is in agreement with the ^{13}C NMR spectrum in which the two quaternary carbon signals at δ 68.93 and 61.70 are assigned to the sp^3 bridgehead carbons of the C_{60} cage which are the sites of attachment of the vinyl group. This assignment was confirmed by the HMBC spectrum, in which the carbon signal at δ 61.70 showed correlations with $H_{19'}$ and both of $C_{18'}$ hydrogens, respectively; and the carbon at δ 68.93 showed a cross peak with the $H_{18'}$ at δ 3.74. Usually, alkenes do not undergo photoaddition to C_{60}. In this case, however, the reaction occurred unexpectedly and easily, most likely because it was an intramolecular reaction *via* a presently unknown route. Although the exact cause is still unknown, the spatial proximity and the activation of a double bond adjacent to the first due to the increased localization of the electrons in the double bonds in a hexagon of C_{60}, once a first addition has occurred, are likely the driving forces for the unexpected reaction with the vinyl group.

Based on the above information and in view of the NOE effects (shown by ROESY spectrum) between $H_{19'}$ / $H_{17'\alpha}$ and $H_{18'}$ / $H_{15'}$, the structure of **2** is proposed as depicted in Scheme 1. Molecular model examinations are in excellent agreement with the structure. The tertiary amino group and the vinyl group on the scandine moiety are fused to two 6,6-ring junctions of the same six-membered ring on the C_{60} moiety.

The scope of this reaction and the bioactivity of the derivatives obtained will be reported in due course.

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References and Notes

1 T.D. Ros, M. Prato, F. Novello, M. Maggini, and E. Banfi, *J. Org. Chem.*, **61**, 9070 (1996).

2 G.E. Lawson, A. Kitaygorodskiy, B. Ma, C.E. Bunker, and Y.-P. Sun, *J. Chem. Soc., Chem. Commun.*, **1995**, 2225.

3 K.-F. Liou and C.-H. Cheng, *Chem. Commun.*, **1996**, 1423.

4 S.-H. Wu, D.-W. Zhang, G.-W. Wang, L.-H. Shu, H.-M. Wu, J.-F. Xu, and X.-F. Lao, *Synth. Commun.*, **27**, 2289 (1997).

5 Y.-L. Zhou, J.-H. Ye, Z.-M. Li, and Z.-H. Huang, *Planta Med.*, **4**, 315 (1988).

6 J. Buckingham, "The Dictionary of Organic Compounds," 5th ed, Chapman and Hall, New York, London, Toronto (1982), T-00103, D-05504, P-00635, V-00180, S-00144.

7 Spectral data for **2** : TOF-SIMS (*m/z*) 1069 (M^++1, $C_{81}H_{21}N_2O_3$, 34%), 720 (C_{60}, 100); UV-Vis (CH_2Cl_2) λmax/nm 228s, 255s, 336w, 354w, 366w, 435w; FT-IR ν(KBr)/cm^{-1} 3427.0s, 1740.6s, 1678.1s, 1593.7m, 1237.5s, 746.9s, 525.0s; ^{1}H NMR [600 MHz; CS_2-$(CD_3)_2CO$, 10:1] δ 9.15 (1H, s, NH), 7.38 (1H, br. d, J 6.31 Hz, $H_{9'}$), 6.84 (1H, d, J 9.26 Hz, $H_{15'}$), 6.76 (2H, m, $H_{10'}$, $H_{11'}$), 6.65 (1H, dd, J 9.26, 5.40 Hz, $H_{14'}$), 6.31 (1H, br. d, J 7.16 Hz, $H_{12'}$), 4.98 (1H, d, J 5.40 Hz, $H_{3'}$), 4.19 (1H, dd, J 3.79, 10.10 Hz, $H_{19'}$), 3.74 (1H, dd, J 3.79, 13.05 Hz, $H_{18'}$), 3.52 (1H, dd, J 10.11, 13.05 Hz, $H_{18'}$), 3.47 (3H, s, OCH_3), 3.38 (1H, m, $H_{5'}$), 3.25 (2H, d + m, $H_{17'\alpha}$ + $H_{5'}$), 3.17 (1H, m, $H_{6'}$), 2.51 (1H, d, J 13.89 Hz, $H_{17'\beta}$), 2.23 (1H, m, $H_{6'}$); ^{13}C NMR [150.9 MHz; CS_2-$(CD_3)_2CO$, 10:1] δ (number of carbon atoms) 169.43 (ester C=O), 167.46 (amide C=O), 153.10 (1), 152.88 (1), 150.66 (1), 150.36 (1), 149.33 (1), 149.15 (1), 148.94 (1), 148.64 (1), 148.25 (1), 148.19 (1), 148.06 (1), 147.37 (1), 147.32 (1), 146.95 (1), 146.78 (1), 146.71 (1), 146.56 (1), 146.37 (1), 146.15 (1), 145.98 (1), 145.89 (1), 145.68 (1), 145.65 (1), 145.40 (1), 145.28 (1), 145.17 (1), 145.09 (1), 144.91 (1), 144.81 (2), 144.75 (1), 144.43 (1), 144.39 (1), 144.35 (1), 144.29 (1), 144.11 (1), 143.90 (1), 143.52 (1), 143.22 (1), 143.12 (1), 143.03 (1), 142.86 (1), 142.77 (1), 142.72 (1), 142.55 (1), 142.44 (1), 142.31 (1), 142.17 (1), 141.91 (1), 141.84 (1), 141.02 (1), 138.37 ($C_{13'}$), 138.17 (1), 138.03 (1), 137.97 (1), 137.18 (1), 136.09 (1), 133.88 ($C_{15'}$), 130.47 ($C_{9'}$), 129.36 ($C_{11'}$), 127.65 ($C_{14'}$), 123.87 ($C_{8'}$), 123.64 ($C_{10'}$), 117.02 ($C_{12'}$), 100.94 ($C_{21'}$), 79.08 (sp^3-C of C_{60}), 76.72 (sp^3-C of C_{60}), 68.93 (sp^3-C of C_{60}), 64.89 ($C_{16'}$), 61.85 ($C_{3'}$), 61.70 (sp^3-C of C_{60}), 57.46 ($C_{7'}$), 56.10 ($C_{20'}$), 53.91 ($C_{19'}$), 52.65 (OCH_3), 43.52 ($C_{5'}$), 42.99 ($C_{17'}$), 41.91 ($C_{6'}$), 33.33 ($C_{18'}$).

8 S.R. Wilson, N. Kaprinidis, Y. Wu, and D.I. Schuster, *J. Am. Chem. Soc.*, **115**, 8495 (1993); S.R. Wilson, Q. Lu, J. Cao, H. Zhao, and D.I. Schuster, *Proc. Electrochem. Soc.*, **95-10**, 1179 (1995); S.H. Hoke II, J. Molstad, D. Dilettato, M.J. Jay, D. Carlson, B. Kahr, and R.G. Cooks, *J. Org. Chem.*, **57**, 5069 (1992); X. Zhang and C.S. Foote, *J. Am. Chem. Soc.*, **117**, 4271(1995).