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Lead(IV) acetate: an efficient reagent for the synthesis of pyrrolidinofullerenes *via* oxidative coupling of C_{60} with amino acids esters

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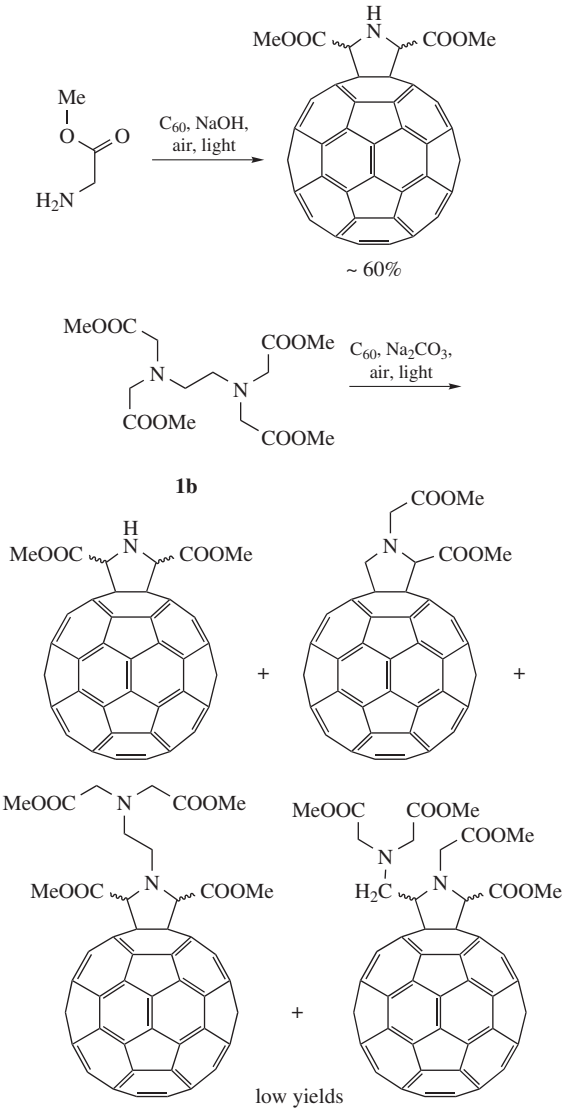
A family of pyrrolidinofullerenes bearing ester group functionalities was easily prepared starting from C_{60}, $Pb(OAc)_4$ and methyl esters of nitrilotriacetic, ethylenediaminetetraacetic and hexamethylenediaminetetraacetic acids; the obtained fullerene derivatives are considered as precursors for the preparation of corresponding water-soluble polycarboxylic acids that may serve as efficient antiviral agents and neuroprotectors *in vivo*.

Medicinal chemistry is one of the most important and exciting fields where fullerenes and their derivatives can be applied.[1,2] Fullerenes showed appreciable antiviral activities against human immunodeficiency virus (HIV) and hepatitis C virus, along with a pronounced antibacterial action.[3–7] Fullerenes are also considered as promising agents for the photodynamic and chemical therapy of cancer.[8,9] Some compounds are recommended as efficient pharmaceuticals for prevention of neuronal disorders such as Alzheimer and Parkinson diseases; clinical tests are in progress to evaluate possible side effects.[10,11]

The strongest drawback for development of medicinal chemistry of parent fullerenes is their, virtually complete, insolubility in polar media such as dimethyl sulfoxide or water. Therefore, organic derivatization was considered as a method of choice to make fullerene-based compounds soluble in water.[12] The organic chemistry of fullerenes was investigated intensely by many research groups worldwide,[13] and, in particular, in Russia.[14–18] A number of compounds called 'water-soluble fullerene derivatives' were synthesized.[1,2,12] However, only few of them possess water solubility > 1 mg cm^{-3}. High solubility in water was achieved in many cases by addition of numerous addends to the fullerene cage in defined or even undefined fashions; the shell from these addends covers almost entirely the carbon sphere and thus prohibits its interactions with biological targets. Therefore, such a type of water-soluble multiaddition products exhibit almost no or very poor pharmaceutical activity. Up to our best knowledge, there are just few examples of fullerene derivatives that possess high enough solubility in water and still have considerable area of the carbon cage without being covered by solubilizing addends.[19,20] Intense studies of these compounds *in vivo* and *in vitro* resulted in discovering a number of exciting biological effects.[1,2,12] However, the syntheses of such water-soluble fullerene derivatives require hardly available reagents and give the desired products in low to moderate yields (15–30%).[19,20] Therefore, the large amounts of the required water-soluble fullerene compounds are hardly available and quite expensive for detailed clinical studies and practical medicinal applications. To overcome this situation, some straightforward ways are necessary for the



Scheme 1

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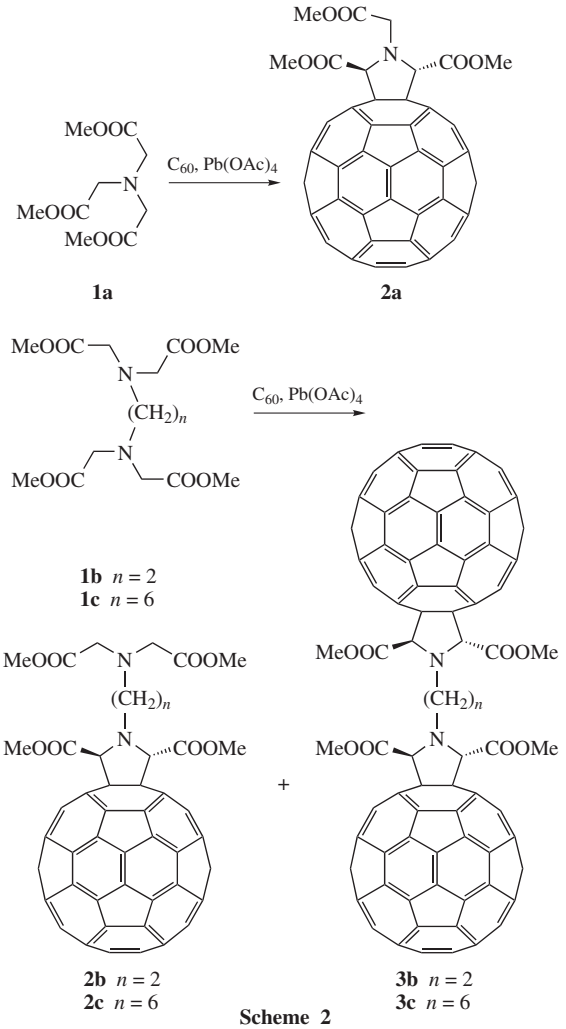
preparation of well-defined water-soluble fullerene derivatives and, at the same time, with a low number of solubilizing groups attached to the fullerene cage. We have reported recently a facile synthesis of tetraaminofullerene derivatives and their salts, which demonstrated water solubility > 200 mg cm^{-3}. Here we describe a new and efficient route developed for the preparation of pyrrolidinofullerenes bearing three to four ester functionalities. These compounds are considered as key precursors for the synthesis of corresponding water-soluble pyrrolidinofullerenes with 3–4 carboxylic groups.

Analyzing published data on the reactions of fullerenes involving free radical species, we found two main prerequisites that emphasize the potential for the application of $Pb(OAc)_4$ and similar reagents for oxidative coupling reactions of C_{60} with amino acid esters. First, note that an oxidative coupling of [60]fullerene with amino acid esters was reported previously; atmospheric oxygen played a role of oxidizer in this case while NaOH or Na_2CO_3 and UV irradiation (500 W light source) served as reaction promoters (Scheme 1).[22,23] However, a very poor selectivity was observed, especially, in the fullerene reactions with esters of ethylenediaminetetraacetic acid, where a mixture of ~7 products was formed in low yields. Some diastereomeric components of this mixture could not be fully separated even with the use of high-performance liquid chromatography (HPLC). The second argument is that manganese(III) acetate was extensively investigated as a coupling reagent for preparation of malonate-type derivatives of [60]fullerene starting from parent malonic acid diesters, $CH_2(COOR)_2$.[24,25] It is reasonable to consider that $Mn(OAc)_3$ can also be used as a reagent for oxidative addition of amino acid esters to the fullerenes. However, lead tetraacetate is even cheaper and more available reagent than $Mn(OAc)_3$; $Pb(OAc)_4$ is a commonly used oxidizer applied to alcohols, 1,2-diols, mono- and dicarboxylic acids and other types of organic compounds.[26] Therefore, we applied it as an oxidative reagent for the condensation of [60]fullerene with the methyl esters of nitrilotriacetic, ethylenediaminetetraacetic, and hexamethylenediaminetetraacetic acids **1a**–**c** (Scheme 2).‡



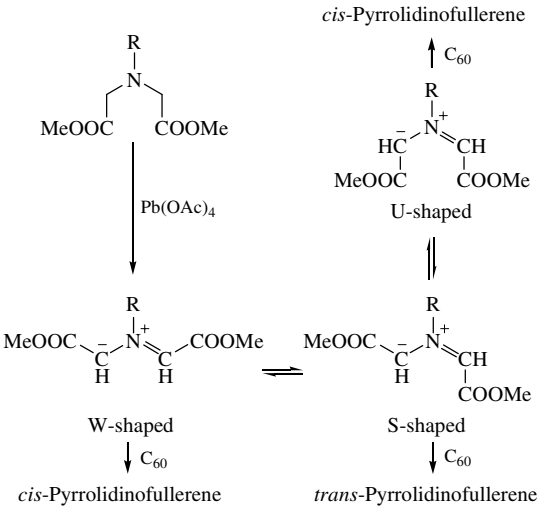
Scheme 2

As shown in Scheme 2, all studied reactions were quite selective. Only one monoaddition product **2a** was formed from C_{60} and nitrilotriacetic acid methyl ester **1a**. Moreover, this compound was represented mainly by one diastereomer (~95%) as concluded from the ^{1}H and ^{13}C NMR data (see Online Supplementary Materials). The obtained spectroscopic data and previous extensive investigations of pure *cis*- and *trans*-2′,5′-disubstituted pyrrolidinofullerenes in our group[27] and by other researchers[22,23] allowed us to assign the *trans*-configuration to two methoxycarbonyl groups in the pyrrolidine ring of **2a**. The observed stereoselectivity is a strong advantage of the developed method since Na_2CO_3/oxygen/light coupling conditions afford two diastereoisomers of **2a** in comparable ratios.[22,23]

Esters **1b**,**c** possess two reaction sites; therefore, fullerene dimers **3b**,**c** were obtained in the reaction along with expected monoaddition products **2b**,**c** (Scheme 2). Both types of compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy (see Online Supplementary Materials), which revealed that **2b**,**c** and **3b**,**c** are also represented mainly (> 90%) by the isomers with the *trans*-arrangement of substituents attached at the 2′- and 5′-positions of the pyrrolidine rings. For comparison, the investigated previously reaction of C_{60} with ester **1b** conducted under Na_2CO_3/oxygen/light conditions gives four structurally different pyrrolidinofullerenes (different sites of the parent ester were affected by oxidation); three out of four products consist of two diastereoisomers (Scheme 1).

The NMR data also revealed restricted rotations of substituents attached to the pyrrolidine ring nitrogen. For example, two doublets appearing at 4.15 and 4.32 ppm correspond to the N–C*H*$_2$ group in the spectrum of compound **2a**. The signals from pyrrolidine N–C*H*$_2$ groups in the spectra of other compounds are splitted into multiplets, first, because of presence of adjacent CH_2 group and, second, because of hindered rotation around pyrrolidine N–CH_2 bond. Remarkably, two fullerene units in compound **3b** are non-equivalent because of the hindered rotations around all three bonds in the N–CH_2–CH_2–N fragment; this results in the appearance of two singlets in the ^{1}H NMR spectrum corresponding to the pyrrolidine ring methine protons together with two sets of signals from COOMe groups. On the contrary, both fullerene units are equal in **3c**, which has a longer spacer in between, while the restricted rotation around pyrrolidine ring N–CH_2 bonds is still present. Surprisingly, the signals from the methylene groups in the N(CH_2COOMe)$_2$ moiety of **2b** are also splitted into two doublets and appeared

‡ *Typical synthetic procedure*: a solution of [60]fullerene (300 mg, 0.42 mmol) in 1,2-dichlorobenzene (50 ml), an excess of the amino acid ester (4.2 mmol) and 1.5–2 equiv. of lead tetraacetate (279–372 mg, 0.63–0.84 mmol) were placed in a 100 ml two-necked round-bottom flask equipped with a thermometer and a reverse condenser. The reaction system was degassed and then filled with argon for three times. Afterwards, the reaction solution was stirred at 80–100 °C for *ca.* 3 h to reach a fullerene conversion of about 50–60% (TLC). Then, the system was cooled to room temperature, the reaction mixture was filtered, and the filtrate was diluted with toluene (~500 ml) and hexane (100 ml). The resulting solution was filtered, and the filtrate was poured onto a silica gel column (silica Acros 40–60 μ, 60 Å). Unreacted fullerene was eluted with toluene–hexane (5:1, v/v), while reaction products **2a**–**c** and **3b**,**c** were eluted with toluene or toluene–methanol (see Online Supplementary Materials).



Scheme 3

in the ^{1}H NMR spectrum at 3.74 and 3.89 ppm. Perhaps, some π–π interactions between fullerene cage and the lone electron pair of the non-pyrrolidine nitrogen fix the structure in some preferable conformation thus making non-equivalent methylene protons in the $N(CH_2COOMe)_2$ functionality.

The exact origins of the observed high selectivity of the fullerene couplings with **1a–c** promoted by $Pb(OAc)_4$ are not clear at present. It seems that $Pb(OAc)_4$ is a mild reagent to affect the selective oxidation of the parent amino acid ester to only one azomethine ylide (Scheme 3). This explains the regioselectivity of the reaction. Perhaps, a high degree of *cis*/*trans* diastereoselectivity arises from the existence of some kind of thermodynamic equilibrium in the reaction system between three configurations of the intermediate ylides called W-shaped, U-shaped and S-shaped. S-shaped isomers of 1,2,3-trisubstituted ylides are usually more stable than other forms;[27,28] therefore, they should be accumulated under the equilibrium conditions. The addition of the S-shaped ylides to the fullerene cage should afford *trans* isomers of pyrrolidinofullerenes; indeed, the selective formation of *trans* products was observed in this work. To support this explanation, some theoretical calculations will be performed to compare the stabilities of different forms of azomethine ylides, as well as that of the *cis* and *trans* isomers of the prepared pyrrolidinofullerenes.

Considering the possible applications of the synthesized fullerene derivatives, note that ester groups in **2a–c** can be hydrolyzed to give corresponding carboxylic fullerene derivatives. The target polycarboxylic fullerene derivatives should give highly water-soluble salts with alkali metals that will become available for biological studies. We expect that these compounds will exhibit appreciable antiviral activities, particularly, against HIV.

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Online Supplementary Materials

The eluent compositions used for chromatographic isolation, product yields and NMR spectra for all compounds are presented in Online Supplementary Materials which can be found in the online version at doi:10.1016/j.mencom.2007.03.021.

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