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New one-pot method for the synthesis of pyrrolidinofullerenes†

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The reaction of fullerene C₆₀ with isocyanoacetates and EtMgBr in the presence of stoichiometric amounts of Ti(Oi-Pr)₄ was studied for the first time. Unlike esters and nitriles of carboxylic acids and isonitriles, isocyanoacetates were found to react with C₆₀ under the developed conditions to give *N*-unsubstituted pyrrolidinofullerenes. The electrochemical reduction of the C₆₀ derivatives we synthesized was found to proceed less easily than that of C₆₀ but more easily than that of unsubstituted pyrrolidinofullerenes.

Introduction

The interest in pyrrolidinofullerenes is caused by their potential applications in medicine,¹ in electronics and non-linear optics² and as organic ferromagnets,³ photosensitizers in the generation of singlet oxygen,⁴ molecular switches,⁵ and photoconverters of solar energy.⁶

The key method for the synthesis of pyrrolidinofullerenes is 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* to fullerenes (Prato reaction), which gives the target fulleroheterocycles in preparative yields.⁷ Alternative methods include photochemical⁸ and catalytic⁹ cycloaddition of tertiary amines to C₆₀, but these methods have not received wide use in fullerene chemistry because of low yields of the target adducts or the necessity to use starting amines of a particular structure.

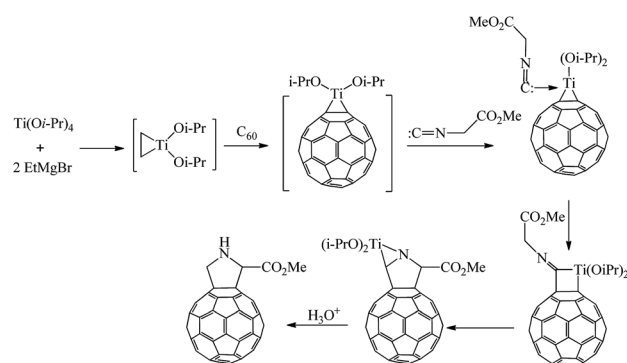
Recently,¹⁰ we developed a novel original method for functionalization of fullerene C₆₀ with various functional compounds and EtMgBr in the presence of Ti(Oi-Pr)₄, which gave, depending on the reactant structure, various acyclic or cyclic C₆₀ derivatives difficult to prepare by other methods. For example, esters of aromatic carboxylic acids give fullerenyl ketones in this reaction,^{10a} nitriles afford previously unknown

fullerotetrahydropyridines,^{10b} and cyanoacrylates and isonitriles are converted to aminomethanofullerenes previously difficult to obtain.^{10c,d}

As a continuation of this study, we investigated the reaction of C₆₀ with isocyanoacetates under the previously developed conditions.¹⁰

Result and discussion

Resorting to published data,^{10–12} we assumed that isocyanoacetates containing divalent carbon in the carbene canonical form and an active methylene group between the isonitrile and ester groups would react with fullerene C₆₀ and EtMgBr in the presence of the Ti(Oi-Pr)₄ catalyst to give pyrrolidinofullerenes, which are difficult to obtain by other methods, according to the following chart:



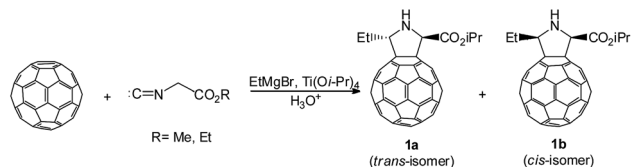
We found that the reaction of model methyl isocyanoacetate with fullerene C₆₀ and EtMgBr proceeds under argon in the presence of Ti(Oi-Pr)₄ in chlorobenzene at 80 °C at the C₆₀ : isocyanoacetate : [Mg] : [Ti] ratio of 1 : 4 : 8 : 3 and gives, after hydrolysis of the reaction mixture with 5% aqueous HCl, a mixture of pyrrolidinofullerene stereoisomers **1a** and **1b** in a ~65% total yield (in relation to taken C₆₀) and in 1 : 2 ratio, respectively (Scheme 1). A change in the ratio of the reactant and catalyst components and a decrease in the reaction

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Scheme 1 The reaction of methyl or ethyl isocyanoacetates with fullerene C₆₀ and EtMgBr in the presence of Ti(Oi-Pr)₄.

temperature result in a sharp decrease of the total yield of target pyrrolidinofullerenes **1a,b** (8–15%) and in the formation of side products *via* C₆₀ carbomagnesiation and hydrogenation.

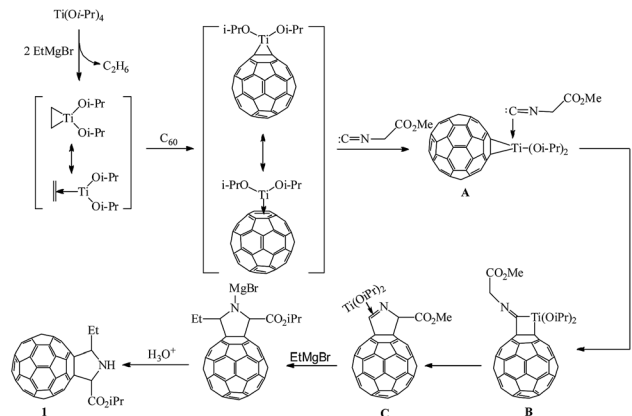
The results obtained using ethyl isocyanoacetate rather than methyl isocyanoacetate were similar.

Pyrrolidinofullerenes **1a,b** were isolated from the reaction mixture by means of preparative HPLC. According to 1D (¹H and ¹³C) and 2D (HHCOSY, HSQC, HMBC) NMR experiments and IR and MALDI TOF MS data, the reaction under conditions we developed affords a mixture of stereoisomeric cycloadducts **a** and **b**.

Indeed, the ¹³C NMR spectrum of a mixture of stereoisomers **1a,b** shows a doubled set of signals with 1 : 2 intensity ratio both for carbon atoms of the fullerene cage and for the attached addend. The intense signals at δ_C 79.38 and 78.34 ppm correspond to the sp³ hybridized atoms of the fullerene cage of *cis*-isomer **1b**, while the methine carbon atoms of the pyrrolidine ring are responsible for higher-field signals at δ_C 74.20 and 75.24 ppm, correlated with the nitrogen signal in the HMBC (NH) experiment, δ_N 60.96 ppm. For *trans*-isomer **1a**, the spectrum exhibits a set of similar signals of low intensity, belonging to the sp³ hybridized carbon atoms of C₆₀ (δ_C 76.77 and 77.58 ppm), methine carbon atoms of the heterocycle (δ_C 72.32 and 74.03 ppm), and the nitrogen atom (δ_N 55.17 ppm). The C(3') methine carbon signals of *cis*-(δ_C 75.24 ppm) and *trans*-(δ_C 74.03 ppm) isomers also show cross-peaks with the signals of the ethyl-group methylene protons (δ_H 2.20 and 2.32 ppm, respectively) in the HMBC spectra. The *cis*-configuration of the 1',3' substituents in **1b** was unambiguously proved by the cross-peaks in the NOESY experiment between the methine proton signals at δ_H (1') 5.43 ppm and δ_H (3') 4.68 ppm, whereas *trans*-isomer **1a** does not show this cross-peak.

The formation of stereoisomeric pyrrolidine cycloadducts **1a,b** of the composition C₆₈H₁₅NO₂ was confirmed by the MALDI TOF mass spectrometry. The experiments were performed in the linear (TOF) and reflection (TOF/TOF) modes and in both positive and negative ion modes using elemental sulfur as the matrix and showed the molecular ion [M + H] peak, *m/z* 878.044 (*M*_{calcd} = 877.110).

According to the published^{11,12} and our¹⁰ experimental data, we assumed a probable pathway for the formation of pyrrolidinofullerene **1** in the reaction in question (Scheme 2). In the first step, Ti(Oi-Pr)₄ reacts with EtMgBr to give dialkoxytitanacyclopentane occurring in equilibrium with the ethylene complex. Fullerene present in the reaction mixture displaces the ethylene molecule from the complex to afford the key reaction intermediate, namely, fullerotitanacyclopentane **A**.



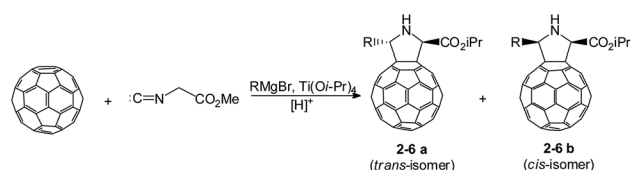
Scheme 2 Probable pathway for the formation of pyrrolidinofullerenes in the reaction of isocyanoacetates with fullerene C₆₀ and EtMgBr in the presence of Ti(Oi-Pr)₄.

The subsequent reaction of intermediate **A** with the isocyanoacetate at the metal–carbon bond yields titanacyclobutane **B**. Demetallation of **B** under the reaction conditions and subsequent transformations involving the reactive methylene group of the starting isonitrile result in the formation of pyrrolidinofullerene **C**. In view of the excess of EtMgBr and Ti(Oi-Pr)₄ in the reaction mixture, the intermediate **C** undergoes carbomagnesiation of the heterocyclic moiety at the C=N bond with simultaneous transesterification of the ester group, being thus converted to complex **D**, which is hydrolyzed to furnish the target pyrrolidinofullerene **1**.

In view of the fact that the structure of substituents in the pyrrolidine ring of the C₆₀ derivative depends on the structure of the Mg organic compound, we carried out this reaction under the developed conditions using a variety of alkyl- and arylmagnesium bromides (Scheme 3, Table 1). More bulky structure of substituent in the initial organomagnesium compound was found to lead to higher proportions of *trans*-fulleropyrrolidines, up to the selective formation of the *trans*-isomers in the case of PhMgBr. The introduction of a substituent into the aromatic ring of the organomagnesium compound reduced the selectivity, and the reaction gave a mixture of stereoisomeric pyrrolidinofullerenes **6** with a *cis* to *trans* ratio of 1 : 2, indicating that the electronic effects as well as the steric effects influence on selectivity of formation of the *cis,trans* isomers.

As model compounds, we chose phenyl-substituted fulleropyrrolidine **5** and study the electrochemical reduction.

Fulleropyrrolidine **5** can reversibly add four electrons in four steps (Fig. 1) to give stable multianions:

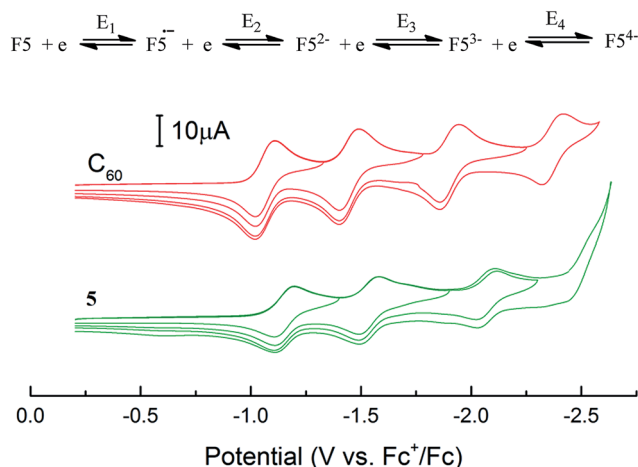


Scheme 3 Variation of alkyl- and arylmagnesium bromides in the reaction of C₆₀ with methyl isocyanoacetate.



Table 1 Effect of the structure of substituent in RMgX on the selectivity of formation of pyrrolidinofullerenes 2–6

Entry	R	Product	Yield, %	Ratio	
				<i>a</i>	<i>b</i>
1	Bu	2	50	2	3
2	i-Pr	3	55	1	1
3	Cy	4	51	8	10
4	Ph	5	45	1	0
5	<i>o</i> -MePh	6	43	2	1

**Fig. 1** Cyclic voltammograms of C₆₀ and its novel derivative 5 (10^{−3} M in 1,2-dichlorobenzene, Bu₄NBF₄).

The first reduction potentials of functionally substituted fullerene 5 are somewhat more negative than that of fullerene C₆₀, which is caused by the effect of substituents (Table 2). The fourth reduction peak is nearly merged with the background. The stability of the electrochemically reduced fullerene species (radical anion formed in the first step and polyanions formed in the subsequent steps) can be evaluated from the ratio of anodic and cathodic currents in the *i*_{pa}/*i*_{pc} peak (Table 2).

Table 2 Electrochemical characteristics of the reduction of compound

Comp.	Peak #	<i>E</i> _{pc}	<i>E</i> _{pa}	<i>i</i> _{pa} / <i>i</i> _{pc}	Δ <i>E</i>	<i>E</i> _{1/2}	<i>E</i> _{LUMO}
5	1	−1.20	−1.11	0.73	0.09	−1.16	−3.65
	2	−1.58	−1.49	1.00	0.09	−1.54	−3.27
	3	−2.12	−2.02	1.00	0.10	−2.07	−2.73
	4	−2.54	N/A	N/A	N/A	N/A	N/A
C ₆₀ ^a	1	−1.11	−1.02	0.95	0.09	−1.07	−3.74
	2	−1.49	−1.40	1.00	0.09	−1.45	−3.36
	3	−1.95	−1.86	1.00	0.09	−1.91	−2.9
	4	−2.42	−2.32	0.76	0.1	−1.37	−2.43

^a The data for C₆₀ are close to reported values,¹³ obtained under similar conditions. Due to proximity of the fourth peak to the supporting electrolyte discharge line, the calculation of *i*_{pa}/*i*_{pc} is in some cases not appropriate (this is designated as N/A). The LUMO energy (eV) was calculated as *E*_{LUMO} = −(*E*_[1/2,red vs. Fc^{+/0}] + 4.8) (eV).¹⁴

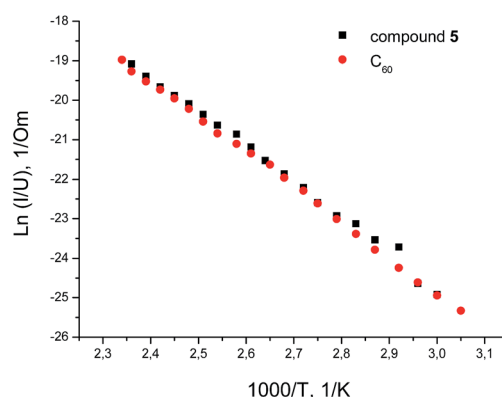
It is known that the effect of substituents present in the C₆₀ molecule on the reduction potentials is composed of two effects, namely, the change in the electronic properties of the proper fullerene sphere as a result of disruption of the common π-system of conjugation and the electron-donating or -withdrawing properties of the substituents. For example, the substituents at the exo-carbon atom of C₆₀ in methanofullerene 2 are not involved in the common fullerene π-system, which can be regarded as the reaction center of the electron transfer by two σ-bonds; therefore, they affect only slightly the reduction potentials of C₆₀ derivatives. The potential shift reported in the literature for this class of carbon clusters is in the limits of up to 200 mV.¹⁵ Meanwhile, strong electron-withdrawing substituents in methano-¹⁶ or azahomofullerenes¹⁷ can overcompensate for the loss of electron affinity as a result of disruption of π-system of conjugation. The cyclopentane and cyclohexane derivatives of C₆₀ are 100 and 80 mV more difficult to reduce than parent C₆₀,¹⁸ while the presence of a nitrogen atom in fulleropyrrolidines has a slight influence on the potentials of the first two reduction steps compared with cyclopentane derivatives.¹⁹

The electrochemical reduction of fulleropyrrolidine 5 was found to occur at more negative potentials than that of the parent C₆₀ (the difference is 60–90 mV). This distinguishes compound 5 from unsubstituted pyrrolidinofullerene. This results indicate that the introduction of an aryl substituent and ester group into the heterocyclic fragment of 5 compensates, to a certain extent although not completely, for the loss of the electron affinity caused by disruption of the π-system of conjugation.

Unfortunately, we were unable to correctly calculate the *E*_{HOMO} and thus to determine the band gap width of the acceptor (*E*_g) on the basis of cyclic voltammetry data because the

Table 3 Conductivity of 5 and C₆₀ at 60 °C

Compound	<i>G</i> , ohm ^{−1} (at 60 °C)	Δ <i>E</i> , eV
5	1.5 × 10 ^{−11}	1.54
C ₆₀	1.4 × 10 ^{−11}	1.63

**Fig. 2** Temperature dependence of the conductivity of films of 5 and C₆₀.

oxidation waves of compound **5** are multielectron, which may be caused by sample polymerization under conditions of electrochemical measurements.

Nevertheless, the band gap width can be determined by electrophysical methods, in particular, from the plot of the dependence of the film conductivity G on temperature T in the range of 300–450 K. These dependences are exponential, $G = G_0 \exp(-\Delta E/2kT)$. From the slope of the linear segments, it was possible to calculate ΔE for each sample; the result was about 1.5–1.6 eV. Meanwhile, the ΔE value can be interpreted as E_g (the gap between the LUMO and the HOMO).

It is found that the conductivity of **5** differs little from unmodified fullerene (Table 3), but is characterized by better solubility in organic solvents (Fig. 2).

Conclusions

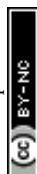
Thus, we developed a new method for the synthesis of *N*-unsubstituted pyrrolidinofullerenes by the $\text{Ti}(\text{Oi-Pr})_4$ -catalyzed reaction of C_{60} with isocyanoacetates and EtMgBr . The electrochemical reduction of model pyrrolidinofullerene occurs less easily than that of C_{60} but more easily than that of unsubstituted pyrrolidinofullerenes, which may imply that introduction of new substituents into the heterocyclic fragment compensates somewhat for the loss of electron affinity of the fullerene cage.

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