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N-methyl-2-(4-styrylphenyl)-3,4-fulleropyrrolidine synthesis and structure

New stilbene fulleropyrrolidine has been synthesized by C_{60} fullerene triple-component condensation with sarcosine and trans-4-stilbene carboxaldehyde in Prato reaction conditions. It was demonstrated that primary factor having influence on this reaction *final* product yield is the homogeneity of the reaction medium. The highest yield of N-methyl-2-(4-styrylphenyl)-3,4-fulleropyrrolidine is observed when reaction performed in xylene and reactive medium is heated. Synthesized compound structure has been studied by IR-, UV-, NMR ^{1}H and ^{13}C spectroscopy as well as by two-dimensional COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C) spectra data. The purity and individuality of obtained fulleropyrrolidine have been evaluated using HPLC analysis. N-methyl-2-(4-styrylphenyl)-3,4-fulleropyrrolidine synthesis proceeds by the 1,3-dipolar addition to fullerene C_{60} mechanism through formation of active azomethinilides. N-methyl-2-(4-styrylphenyl)-3,4-fulleropyrrolidine and poly-N-vinylpyrrolidone water-soluble complex has been obtained in dichloromethane. It was shown that complex formation is outcome of fulleropyrrolidine solubilization by PVP chains and lactamic group physical interaction with the fullerene sphere.

Keywords: fullerene C_{60}, trans-4-stilbencarboxaldehude, sarcosine, fulleropyrrolidine, Prato reaction, NMR specters, poly-N-vinylpyrrolidone, three-component condensation.

Introduction

Nowadays biological properties of fullerenes and their functional derivatives are massively researched for the purpose of creating new pharmaceuticals and biomaterials based on them. Compounds found among fullerene derivatives possess various types of pharmacological activity. The development of C_{60} fullerene functionally substituted derivatives synthesis methods is essential for creating new materials and obtaining biologically active substances. Fulleropyrrolidine derivatives obtained through Prato reaction are some of the most promising for this purpose within the wide range of derivatives known today. This way, natural fullerene-containing aminoacid derivatives, such as fulleropyrrolidineglutamine acid and fulleroproline, have been synthesized. Some biologically active peptides and other derivatives advantageous for use in medicine and engineering have been obtained based on them [1–3].

A highly promising fulleropyrrolidine research area is the study of pyrrolidine scaffold containing new «pharmacophoric» groups [4]. One of such «pharmacophoric» groups is stilbene fragment, as stilbene (1,2-diphenyletilene) functional derivatives are widespread in plant life and have been used in traditional medicine for a long time [5–8]. These compounds' (as well as other arylpolyenes) electronic structure peculiarities provide strong physiological activity and valuable physical-chemical properties for their molecules. Synthetic stilbenoids with various functions and stilbenoid-containing polymers are used for the production of laser dyes, sensors, light-sensitive markers and composite materials [9]. Stilbenoids show antioxidant, anticarcinogenic, antibacterial and other therapeutic activities. Due to high derivative pharmacological activity stilbene fragment is considered as one of privileged structure blocks while creating pharmacologically important substances [10, 11]. However, compounds containing both stilbene fragment and fullerene sphere are not sufficiently researched.

Experimental

NMR ^{1}H and ^{13}C (DMSO-d_6) spectra were registered at JNM-ECA Jeol400 spectrometer (399.78 and 100.53 MHz respectively) regarding deuterated solvent carbon residual protons or atoms signals. IR spectra (KBr) were registered at Nicolet 5700 spectrometer. The reaction progress and the identity of the synthesized

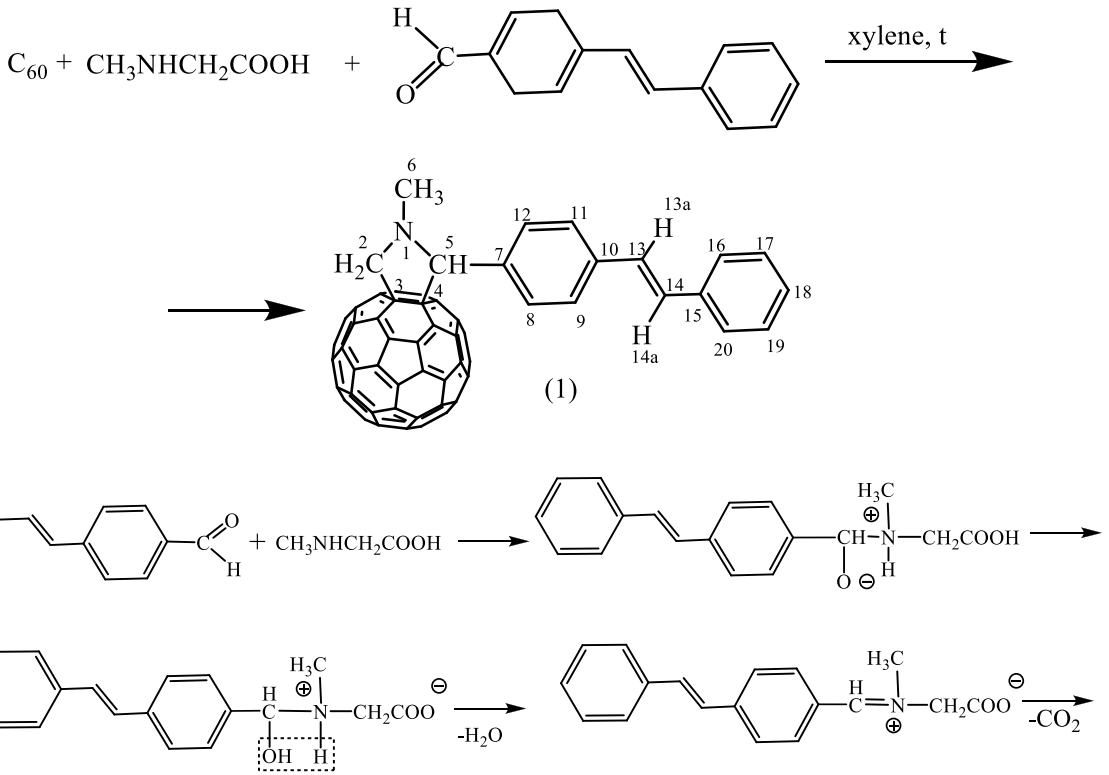
compounds were monitored by TLC on Sorbfil plates (Russia). Plates development was done in isopropyl alcohol — ammonia (25 % in water) — water (7:2:1), treatment by iodine vapor.

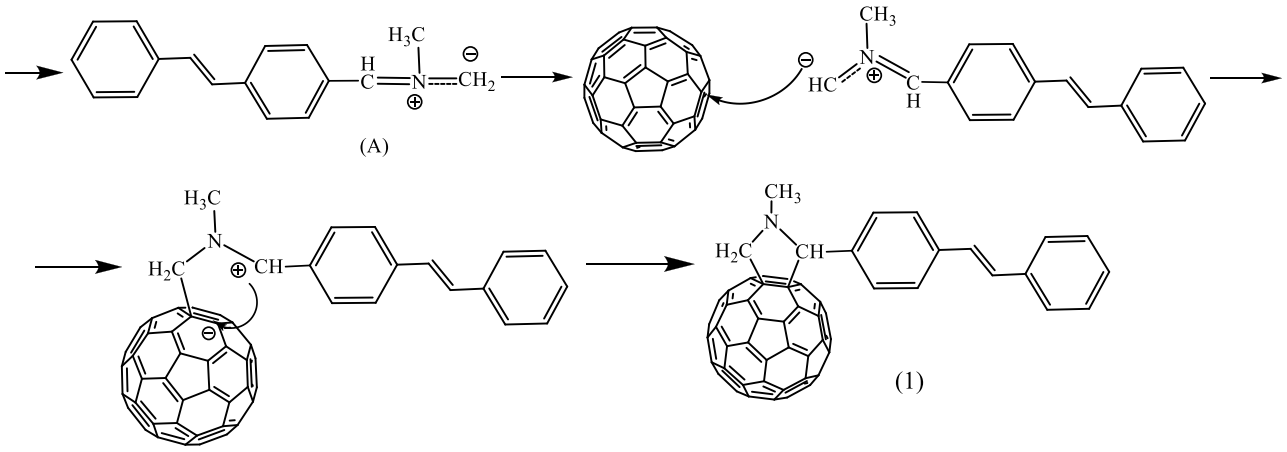
N-methyl-2-(4-styrylphenyl)-3,4-fulleropyrrolidine (1). **1**00 mg C_{60} solution (0.1388 mmol) in 20 ml xylene was added to 57.81 mg (0.2776 mmol) trans-4-stilbencarboxaldehyde and 123.6 mg (1.388 mmol) sarcosine (reacting agents' molecular ratio was 1:2:5 respectively). Reaction mixture was boiled for three hours at 110–120^{0}C. After solvent removal residue was chromatographed on silicagel column eluting unreacted C_{60} and the product with toluene. Product yield was 14.7 mg (10.8 %). NMR spectra ^{1}H, δ, ppm (J, Hz): 2.87 s (3H, H-6,6,6), 4.31 d (1H, H-2ax, ^{2}J 9.2), 4.98 s (1H, H-5), 5.02 d (1H, H-2eq, ^{2}J 9.2), 7.0 d (1H, H-14, ^{3}J 3.6), 7.25 t (1H, H-18, ^{3}J 7.2), 7.27 d (2H, H-17,19, ^{3}J 8.4), 7.34 t (2H, H-16,20, ^{3}J 7.6), 7.47 d (2H, H-9,11, ^{3}J 7.6), 7.57 d (2H, H-8,12, ^{3}J 8.0), 7.81 w. s (1H, H-13). NMR spectra ^{13}C, δ_C, ppm: 40.12 (C-6), 70.12 (C-2), 83.47 (C-5), 126.70 (C-9,11), 126.99 (C-8,12), 127.85 (C-18), 128.36 (C-14), 128.79 (C-16,20), 129.36 (C-13), 137.73 (C-15), 139.69 (C-10), 156.22 (C-7).

Complex obtaining technique (1a). 2 mg fulleropyrrolidine1 solution in 2 ml xylene were added to 200 mg PVP in 3 mg xylene. Reaction mixture was stired for 30 minutes at room temperature. After solvent removal the residue was dried in vacuum.

Results and Discussion

Considering stilbenoids and fullerenes derivatives' scientific and applied prospects, we have performed synthesis and NMR spectroscopic research of new fulleropyrrolidine structural peculiarities. C_{60} fullerene, sarcosine and trans-4-stilbenecarboxaldehyde triple-component condensation took place in Prato reaction conditions. One of major factors having influence on this reaction final product yield is the homogeneity of the reaction medium. So stilbenefulleropyrrolidine 1 synthesis was done in medium of various solvents such as benzene, toluene, chlorobenzene and xylene and while reactive medium was heated for 4–5 hours. It is possible that present in reaction medium amino acid (which is a zwitterionic compound) has negative impact on the reaction rate (heterogeneity factor). The highest yield of target fulleropyrrolidine 1 was obtained in xylene medium. Obtained fulleropyrrolidine 1 purity and individuality were analyzed using HPLC analysis.





New obtained fulleropyrrolidine 1 structure was found using IR, NMR ^{1}H and ^{13}C spectroscopy as well as two-dimensional COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C) spectra data.

There are pyridine ring C-N bond lines and fullerene scaffold, C-H and N-H vibrational frequencies in compound 1 IR spectra. Compound 1 UV spectra has 254, 319 and 431 nm peaks. Low intensity peak at 431 nm is typical for all C_{60} fullerene [6, 8] closed adducts (Fig. 1).

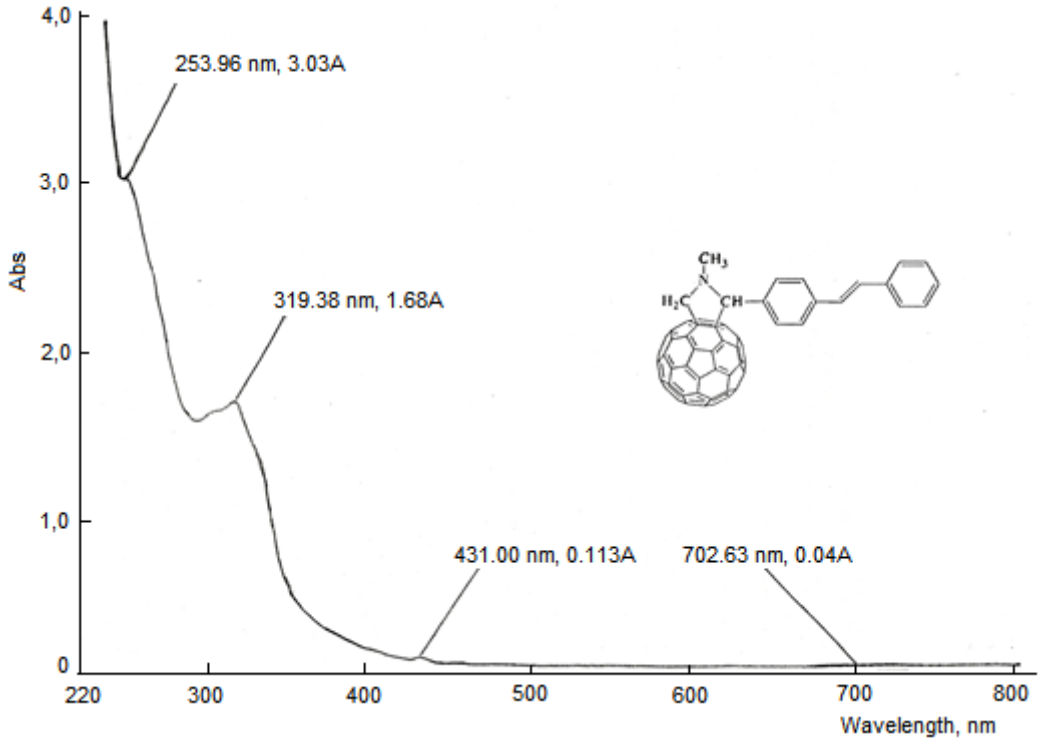
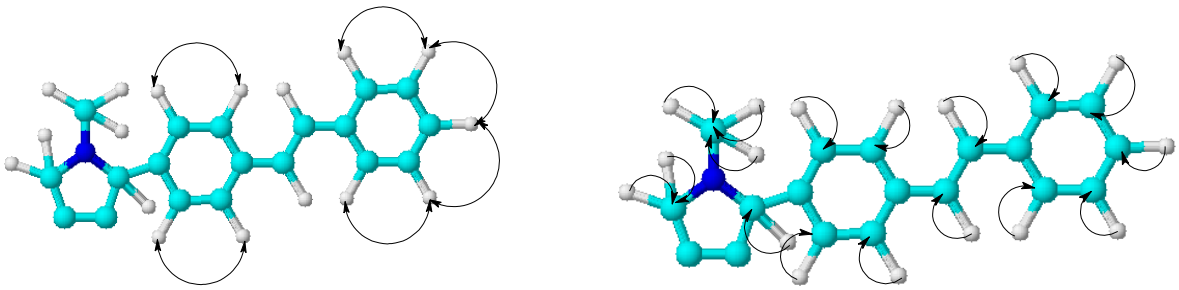


Figure 1. Compound 1 UV spectra

Compound 1 NMR ^{1}H spectra is characterized by three-proton singlet signal presence at 2.87 ppm of H-6,6,6 N-methyl fragment protons in pyrrolidine ring. One-proton singlet signal at 4.92 ppm indicates presence of H-5 methyne proton in pyrrolidine cycle. Two one-proton duplicate signals appearance at 4.31 and 5.02 ppm with the same spin-spin interaction constant ^{2}J9.2 Hz proves presence of two pyrrolidine ring H-2ax and H-2eq protons (axial and equatorial) connected to fullerene nucleus. H-14 and H-13 protons of ethane chain appear as one-proton duplicate at 7.09 ppm and ^{3}J3.6 Hz extended one-proton singlet at 7.81 ppm respectively. Aromatic protons H-18 and H-9,11 appear as one- and two-proton triples at 7.25 ppm and ^{3}J 7.2 Hz and 7.34 ppm and ^{3}J 7.6 Hz respectively. H-17 and H-19 protons appear as two-proton duplicates at 7.27 ppm and ^{3}J 8.4 Hz, H-9 and H-11 protons appear as two-proton duplicates at 7.47 ppm and ^{3}J 7.6 Hz, H-8 and H-12 protons appear as two-proton duplicates at 7.57 ppm and ^{3}J 8.0 Hz respectively.

Pyrrolidine ring signals with N-methyl substituent can be seen at 40.12 (C-6), 70.12 (C-2) and 83.47 (C-5) ppm in compound 1 NMR ^{13}C spectra. Aromatic and unsaturated fragments carbon atoms resonated at 126.70 (C-9,11), 126.99 (C-8,12), 127.85 (C-18), 128.36 (C-14), 128.79 (C-16,20), 129.36 (C-13), 137.73 (C-15), 139.69 (C-10) and 156.22 (C-7) ppm. Multiple signals in 136–148 ppm area belong to fullerene nucleus sp^2-hybridized carbon atoms.

Compound 1 structure was also confirmed by two-dimensional NMR COSY (^1H-^1H) and HMQC (^1H-^{13}C) spectroscopy data, which allowed finding spin-spin interactions of homo- and heteronuclear nature. Correlations observed in molecule are shown in Figure 2. In compound 1 ^1H-^1H COSY pectras there are spin-spin correlations through two bonds of methylene protons H^{2ax}-H^{2eq} (4.31, 5.02 and 5.02, 4.31) ppm and through three bonds of protons in adjacent methyne groups $H^{16,20}$-H^{18} (7.34, 7.26 and 7.26, 7.34), $H^{16,20}$-$H^{9,11}$ (7.34, 7.48 and 7.48, 7.34), and $H^{8,12}$-H^{13} (7.56, 7.81 and 7.81, 7.56) ppm aromatic rings. Protons and carbon atoms heteronuclear interactions through one bond were found using ^1H-^{13}C HSQC for the following couples present in the compound: H^6-C^6 (2.87, 40.12), H^{2ax}-C^2 (4.31, 70.16), H^{2eq}-C^2 (5.02, 70.16), H^5-C^5 (4.98, 83.47), H^{14}-C^{14} (7.10, 128.36), H^{18}-C^{18} (7.24, 127.84), $H^{16,20}$-$C^{16,20}$ (7.34. 129.11), $H^{9,11}$-$C^{9,11}$ (7.48, 126.70), $H^{8,12}$-$C^{8,12}$ (7.57, 126.99), H^{13}-C^{13} (7.80, 129.36).

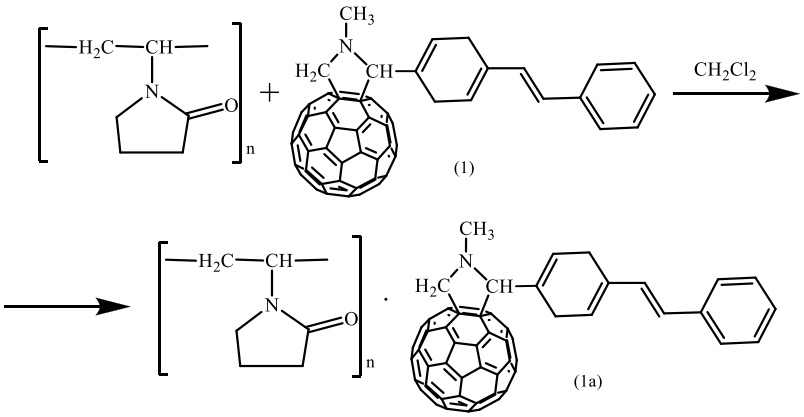


a b

Figure 2. Compound 1 correlations in COSY (1H-1H) (a) and HMQC (1H-13C) (b) spectra

The insolubility of fullerenes in water is the main problem that impedes the biological studies of fullerene derivatives and the creation of therapeutic agents based on them. One of the possible ways to overcome this problem is to obtain water-soluble polymers approved for use in medicine, for example, with poly-N-vinylpyrrolidone.

In this regard, a complex of compound 1 with poly-N-vinylpyrrolidone in dichloromethane medium was obtained:



1a complex formation proceeds as a result of fullerenepyrrolidine 1 solubilization by PVP chains and lactamic group physical interaction with fullerene sphere. Obtained complex 1a dissolves well in water.

Conclusion

New stilbenefulleropyrrolidine has been synthesized by C_{60} fullerene triple-component condensation with sarcosine and trans-4-stilbenecarboxaldehyde in Prato reaction conditions. It was demonstrated that the

homogeneity of the reaction medium is the primary factor having influence on this reaction final product yield. The highest yield of N-methyl-2-(4-styrylphenyl)-3,4-fulleropyrrolidine was observed when reaction performed in xylene and reactive medium heated. N-methyl-2-(4-styrylphenyl)-3,4-fulleropyrrolidine compound water-soluble complex with poly-N-vinylpyrrolidone in dichloromethane has been obtained. Synthesized compound structure has been studied by IR-, UV-, NMR ^{1}H and ^{13}C spectroscopy as well as two-dimensional COSY (^{1}H-^{1}H) and HMQC (^{1}H-^{13}C) spectra data.

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N-Метил-2-(4-стирилфенил)-3,4-фуллеропирролидиннің синтезі және құрылымы

Стильбенқұрамды фуллеропирролидинге әкелетін *транс*-4-стильбенкарбоксальдегидтің C_{60}-фуллеренге Прато реакциясы бойынша циклоқосылу реакциясы зерттелген. Бұл реакцияда соңғы өнімнің шығуына әсер ететін негізгі фактор реакциялық ортаның гомогенділігі болып табылады. N-метил-2-(4-стирилфенил)-3,4-фуллеропирролидиннің ең жоғары шығымы ксилол ортасында реакция жүргізу және реакциялық ортаны қыздыру кезінде байқалады. Синтезделген қосылыстың құрылысы ИҚ-, УК-, ЯМР ^{1}H және ^{13}C спектроскопия әдістерімен, сондай-ақ COSY (^{1}H-^{1}H) және HMQC (^{1}H-^{13}C) екі өлшемді спектрлерінің деректерімен зерттелген. Алынған фуллеропирролидиннің даралығы мен тазалығы ЖТСХ талдауды қолдана отырып, анықталған. N-метил-2-(4-стирилфенил)-3,4-фуллеропирролидиннің түзілуі белсенді азометинилидтердің аралық түзілуі арқылы C_{60} фуллереніне диполярлы қосылыс механизмі бойынша жүреді. Дихлорметан ортасында N-метил-2-(4-стирилфенил)-3,4-фуллеропирролидинді поли-N-винилпирролидонмен қосудың суда еритін комплексы алынған. Комплекстің фуллеренопирролидинді ПВП тізбектерімен солюбилизациялау және лактам тобының фуллерендік сферамен физикалық өзара әрекеттесуі нәтижесінде пайда болатыны көрсетілген.

Кілт сөздер: фуллерен C_{60}, *транс*-4-стильбенкарбоксальдегид, саркозин, фуллеропирролидин, Прато реакциясы, ЯМР-спектрлер, поли-N-винилпирролидон, үшкомпонентті конденсация.

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Синтез и строение N-метил-2-(4-стирилфенил)-3,4-фуллеропирролидина

Изучена реакция [2+3] циклоприсоединения *транс*-4-стильбенкарбоксальдегида к C_{60}-фуллерену по реакции Прато, приводящая к стильбенсодержащему фуллеропирролидину. Показано, что основным фактором, влияющим на выход конечного продукта в этой реакции, является гомогенность реакционной среды. Наиболее высокий выход N-метил-2-(4-стирилфенил)-3,4-фуллеропирролидина наблюдается при проведении реакции в среде ксилола и нагревании реакционной среды. Строение синтезированного соединения исследовано методами ИК-, УФ-, ЯМР ^{1}H и ^{13}C спектроскопии, а также данными двумерных спектров COSY (^{1}H-^{1}H) и HMQC (^{1}H-^{13}C). Чистота и индивидуальность полученного фуллеропирролидина проанализированы с применением ВЭЖХ анализа. Образование N-метил-2-(4-стирилфенил)-3,4-фуллеропирролидина протекает по механизму1,3-диполярного присоединения к фуллерену C_{60} через промежуточное образование активных азометинилидов. Получен водорастворимый комплекс соединения N-метил-2-(4-стирилфенил)-3,4-фуллеропирролидина с поли-N-винилпирролидоном в среде дихлорметана. Показано, что образование комплекса происходит в результате солюбилизации фуллеренпирролидина цепями ПВП и физического взаимодействия лактамной группы с фуллереновой сферой.

Ключевые слова: фуллерен C_{60}, *транс*-4-стильбенкарбоксальдегид, саркозин, фуллеропирролидин, реакция Прато, ЯМР-спектр, поли-N-винилпирролидон, трехкомпонентная конденсация.

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