Synthesis of Derivatives of closo-Dodecaborate Anion Based on Amino Acid Esters

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Received April 19, 2021; revised June 3, 2021; accepted June 15, 2021

Abstract—This work proposes a new method for the synthesis of \((\text{N})\)-borylated amino acids based on nucleophilic substitution reactions in the \([\text{B}_{12}\text{H}_{11}\text{IPh}]^–\) anion. Esters of glycine and L-phenylalanine were used as nucleophiles. The structure of the products has been determined by multinuclear NMR spectroscopy, IR spectroscopy, and ESI mass spectrometry.

Keywords: closo-dodecaborate anion, amino acid esters, phenyliodonium derivative

DOI: 10.1134/S0036023621110036

INTRODUCTION

Boron cluster anions are widely used as components of photovoltaic devices \([1–6]\), catalysts \([7, 8]\), biosensors \([9, 10]\), and molecular magnets \([11, 12]\). One of the most important areas of application of closo-borate anions is boron neutron capture therapy of malignant tumors \([13–18]\).

The main interest of researchers is focused on the development of methods for the directed functionalization of boron cluster anions. Thus, along with the processes of electrophilic \([19–21]\) and nucleophilic substitution \([22, 23]\) of hydrogen atoms in the boron cluster, the process of ipso-substitution \([24–26]\) can be considered as an effective method of functionalization.

Halonium ions are one of the types of such groups, which can react with a number of nucleophilic reagents. This approach was successfully extended to iodonium derivatives of carboranes \([27]\), which react with various nucleophiles with selective substitution of the arylgalonium substituent. Monocarboranes and boron cluster anions have a negative charge, and aryliodonium zwitterions based on them differ from derivatives of neutral carboranes in terms of reactivity and selectivity of the processes. The preparation of derivatives of hypervalent iodine through the oxidation of iodo-closo-borates is described in the literature \([28]\). It should be noted that this approach has a number of disadvantages, since it leads to the formation of oxidation products of the cluster fragment. The use of hypervalent iodine compounds can significantly increase the yield of target closo-borates \([29, 30]\). Iodonium derivatives can enter into substitution reactions of PhI groups with a number of nucleophiles (pyridines, thioureas, cyanide ion, azide ion, etc.) \([31–35]\). In \([36, 37]\), the possibility of using phenyliodonium derivatives of the closo-dodecaborate anion and substituted analogs for the targeted introduction of various functional groups into the cluster was shown.

Thus, the use of iodonium functional substituents as leaving (ipso) groups is a rather powerful tool for creating new boron-containing compounds with a given set of properties. In this regard, the aim of this work was the creation of new substituted derivatives of the closo-dodecaborate anion and natural amino acids based on the processes of nucleophilic substitution in the \([\text{B}_{12}\text{H}_{11}\text{IPh}]^–\) anion.

EXPERIMENTAL

Elemental analysis for carbon, hydrogen, and nitrogen was performed on a CHNS–3 FA 1108 Elemental Analyzer (Carlo Erba). Boron was determined by ICPMS on an iCAP 6300 Duo inductively coupled plasma atomic emission spectrometer at the Center for Collective Use of the Research Scientific Analytical Center of the IREA Federal State Unitary Enterprise (State Scientific-Research Institute of Chemical Reagents and High Furity Chemical Substances).

IR spectra of the synthesized compounds were recorded on an Infralum FT-08 IR Fourier spectrom-
eter (NPF AP Lumex) in the range 4000–400 cm⁻¹ with a resolution of 1 cm⁻¹. Samples were prepared as potassium bromide pellets.

1H, 11B, and 13C NMR spectra of solutions of the investigated substances in CD₃CN were recorded on a Bruker Avance II-300 spectrometer at frequencies of 300.3, 96.32, and 75.49 MHz, respectively, with internal deuterium stabilization. Tetramethylsilane or boron trifluoride etherate were used as external standards.

ESI mass spectra of solutions of the investigated substances in CH₃CN were recorded on a Bruker MicrOTOF-Q spectrometer (Bruker Daltonik, Germany). Ionization conditions: Apollo II electrospray ionization source, ion spray voltage +(−)4500 V, temperature 200°C, flow 3 μL/min.

Tetraphenylphosphonium phenylidododecaborate (Ph₄P)[B₁₂H₁₁IPh]. Acetonitrile (15 mL) and trifluoroacetic acid (2 mL) were added to (Ph₄P)[B₁₂H₁₂] (2.0 g, 2.4 mmol). PhI(OAc)₂ (0.77 g, 2.4 mmol) was added to the resulting solution, and the mixture was stirred in an atmosphere of dry argon with moderate heating (up to 40°C) for 2 h. After that, the solution was concentrated on a rotary evaporator and the product was recrystallized from a mixture of acetonitrile and diethyl ether. The resulting solid was washed with glacial acetic acid and diethyl ether, then dried under oil pump vacuum. Yield, 1.45 g (88%).

11B NMR (CD₃CN, ppm): –12.1 (s, 1B, B–N); –15.5 (m, 11B, B–H); 1H NMR (CD₃CN, ppm): 7.98, 7.74, 7.65 (20H, aromat., Ph₄P); 7.76, 7.38, 7.15 (m, 5H, aromat., C₆H₄); 2.25–0.15 (br m, 11H, B–H).

Derivative of glycine ethyl ester (Ph₄P)[B₁₂H₁₁NH₂CH₂CH(OEt)COOEt]. A mixture of (NH₂CH₂CH(OEt)COOEt)·HCl (0.47 g, 3.4 mmol) and 4-dimethylaminopyridine (0.43 g, 3.4 mmol) in anhydrous THF (20 mL) was prepared. The resulting suspension was stirred in a dry argon atmosphere at room temperature until complete precipitation of dimethylaminopyridine hydrochloride (~0.5 h). Then the precipitate was filtered off, and (Ph₄P)[B₁₂H₁₁IPh] (0.50 g, 0.7 mmol) was added to the mother solution. The flask was purged with argon, the resulting reaction mass was stirred with stirring to 80°C for 4 h. After the completion of the reaction, the resulting solution was evaporated on a rotary evaporator, and the solid residue was recrystallized from a mixture of methanol and diethyl ether. The resulting crude product was dissolved in dichloromethane and washed with 0.1 M HCl solution. The organic phase was separated, washed with water until neutral pH, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The product was dried under vacuum. Yield, 0.33 g (75%).

IR (KBr, cm⁻¹, selected bands): 3301, 3240 (ν(N–H)); 2470 (ν(B–H)); 1750 (ν(C=O)); 1505 (δ(B–B–H)).

RESULTS AND DISCUSSION

The synthesis of phenylidonium derivative of the closo-dodecaborate anion in anhydrous medium is proposed. The reaction of the [B₁₂H₁₂]²⁻ anion with PhI(OAc)₂ was carried out in a mixture of acetonitrile.
and trifluoroacetic acid (Fig. 1). The reaction progress was monitored on the basis of $^{11}$B NMR spectroscopy data. Thus, the $^{11}$B NMR spectrum of salts of the $[B_{12}H_{11}IPh]^-$ anion is represented by two signals: $\delta_1 = -12.5$ ppm and $\delta_2 = -15.6$ ppm with an integrated intensity ratio of 1 : 11. The structure of the substituent in the derivative was determined using $^1$H NMR spectroscopy. Thus, in the spectrum of compound $(PBu_4)[B_{12}H_{11}IPh]$, along with the signals of protons from the tetrabutylammonium cation, signals at 7.76, 7.39, and 7.16 ppm are observed in the region of aromatic protons (m, 5H, aromat., $C_6H_5I$), which corresponds to the phenyl substituent at the iodine atom. In addition, the spectrum contains signals from hydrogen atoms bound to the boron cage. They appear as a broadened multiplet in the range 2.20–0.16 (br m, 11H, B–H).

In the second stage, derivatives based on esters of amino acids were obtained, which were used as nucleophilic reagents. Since the amino acid esters in the form of free bases are unstable, we used the corresponding hydrochlorides. In this case, the deprotonated forms of esters were obtained in situ under the action of organic bases in the medium of tetrahydrofuran (THF). The use of triethylamine as a base led to the formation of a significant amount of the chlorination byproduct of the closo-dodecaborate anion, which is obviously related to the solubility of the hydrochloride in THF. Therefore, we decided to use 4-dimethylaminopyridine as a base; its hydrochloride is easily removed from the reaction mixture by filtration.

The addition of the ester of $(Ph_4P)[B_{12}H_{11}IPh]$ to the solution results in the substitution of the phenyliodonium group for the amino acid residue. The reaction takes place already at room temperature, but the rate of this process is low. Heating the reaction mixture to 80°C makes it possible to achieve complete conversion of the initial iodonium derivative in 4 h. It should be noted that the studied process is sensitive to the presence of water and chloride ions in the system, which leads to side processes and reduces the yield of the target product.

The reaction progress was monitored on the basis of $^{11}$B NMR spectroscopy data. Thus, the $^{11}$B NMR spectra of the target ammonium-type derivatives contain two signals in the range $-7.2...-7.7$ ppm (s, 1B, B–N) and $-16.5...-16.8$ ppm (m, $^{11}$B, B–H). The introduction of a more electronegative ammonium group leads to a shift of the signal from the substituted boron atom to a weaker field as compared to the spectrum of the initial iodonium derivative.

The structure of functional groups in the obtained products was determined using $^1$H and $^{13}$C NMR spectroscopy. Thus, in the $^1$H NMR spectrum of compound $(Ph_4P)[B_{12}H_{11}NH_2CH_2COOEt]$ along with the signals of the cation protons, the signals of the protons of the amino acid residue are observed. The ammonium group is represented by a broadened singlet at 6.86 ppm (2H, NH$_2$), the protons of the methylene group appear as a doublet at 3.99 ppm (2H, CH$_2$COO, $J = 6$ Hz). This signal splitting is typical of amino acid derivatives with a rigid spatial structure [38]. The $^{13}$C NMR spectrum of compound $(Ph_4P)[B_{12}H_{11}CH_2COOEt]$ shows signals of carbon atoms of the carbonyl group at 171.0 ppm and a methylene group at 45.4 ppm. In the IR spectrum of this compound, absorption bands of stretching vibrations of the N–H bond appear at 3320 and 3258 cm$^{-1}$, absorption bands of stretching vibrations of the C=O bond are observed at 1745 cm$^{-1}$, and the absorption bands of the phenyliodonium fragment disappear. Replacement of the exopolyhedral substit-
uent has little effect on the position and shape of the band of stretching vibrations of the boron–hydrogen bond.

In addition, the formation of the target compounds was confirmed by ESI-mass spectrometry. Thus, in the anionic part of the mass spectra of the products, there are intense peaks of ions \([\{\text{B}_{12}\text{H}_{11}\text{NH}_{2}\text{CH}_{2}\text{COOEt}\}\cdot\text{CH}_{3}\text{CN}\}^{-}\) at 285.2 amu for \((\text{Ph}_4\text{P})[\text{B}_{12}\text{H}_{11}\text{NH}_{2}\text{CH}(\text{CH}_2\text{C}_6\text{H}_5)\text{COOEt}]\) and ions \([\text{B}_{12}\text{H}_{11}\text{NH}_{2}\text{CHCH}_2\text{C}_6\text{H}_5\text{COOEt}]^{-}\) at 334.1 amu for compound \((\text{Ph}_4\text{P})[\text{B}_{12}\text{H}_{11}\text{NH}_{2}\text{CH}_2\text{COOtBu}]\).

**CONCLUSIONS**

A method for the synthesis of the \([\text{B}_{12}\text{H}_{11}\text{IPh}]^{-}\) anion in an anhydrous medium has been proposed. New substituted ammonium-type closo-dodecaborates \([\text{B}_{12}\text{H}_{11}\text{NH}_{2}\text{CHRCOOEt}]^{-}\) (R = H, CH2Ph) were obtained based on the processes of nucleophilic substitution of the phenyliodonium substituent under the action of ethyl esters of amino acids.

**ACKNOWLEDGMENTS**

The NMR spectra of the obtained samples were recorded using the equipment of the Center for Collective Use of the Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, which functions with the support of the State Assignment of the Kurnakov Institute, Russian Academy of Sciences in the field of fundamental scientific research.

**FUNDING**

This work was supported by the Russian Science Foundation (grant no. 18-73-10092).

**CONFLICT OF INTEREST**

The authors declare that they have no conflicts of interest.

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Translated by V. Avdeeva