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# SYNTHESIS AND CYTOTOXICITY OF SILYL- AND CARBONYL-SUBSTITUTED ISOXAZOLES

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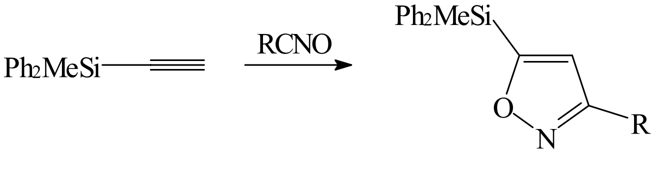
*We have obtained various diphenylmethylsilyl- and carbonyl-substituted isoxazoles by [2+3]-dipolar cycloaddition of nitrile oxides to diphenylmethylsilyl-, hydroxymethyl-, methoxymethyl-, and ethoxycarbonylacetylenes. We have observed that the isoxazoles obtained exhibit moderate cytotoxicity relative to the HT-1080 and MG-22A cell lines. The highest activity level is displayed by 3-methyl-5-diphenylmethylsilylisoxazole.*

**Keywords:** isoxazole, silicon, silyl group, cycloaddition, cytotoxicity.

Isoxazole derivatives have aroused interest as valuable synthons in organic synthesis and potentially biologically active substances [1-3]. Silyl- and germyl-substituted isoxazoles exhibit a broad spectrum of biological activity. Triethylsilyl-, triethylgermyl-, triethylgermylmethyl-, phenyldimethylsilyl-, and silatranylisoxazolines have displayed a high level of vasodilating, antithrombotic, and cardioprotective activity. 3-(5'-Triethylgermyl-3'-isoxazolinyl)pyridine hydrochloride prevents disruption of cardiac rhythm during ischemia [4, 5]. Silyl- and germylisoxazolines have moderate toxicity and low cytotoxicity, and also rather high psychotropic activity [6]. On the other hand, silyl derivatives of 4,4-dioxo-3a,6a-dihydrothieno[2,3-*d*]-2-isoxazolines have pronounced cytotoxicity, especially relative to MG-22A (mouse hepatoma) and HT-1080 (human fibrosarcoma) lines [7].

The goal of this work was to synthesize and study the cytotoxicity of diphenylmethylsilyl- and carbonylisoxazoles.

[2+3]-Dipolar cycloaddition of nitrile oxides to diphenylmethylethynylsilane proceeds with formation of diphenylmethylsilyl-substituted isoxazoles (Table 1). According to GLC, HPLC, and mass spectrometric analysis data, only one product is formed in the cycloaddition reactions. According to $^1$H NMR data, 5-diphenylmethylsilyl-substituted isoxazoles are formed regiospecifically.



**1-6**

To obtain 5-diphenylmethyl-3-methylsilylisoxazole **1**, we used the Mukaiyama method [8]. The reaction was carried out in benzene, adding dropwise nitroethane with a catalytic amount of triethylamine to a mixture of ethynylsilane and a double equivalent of phenylisocyanate. Evidence that the reaction was occurring came from evolution of $CO_2$ and precipitation of diphenylurea.

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TABLE 1. Synthesis of Diphenylmethylsilyl-substituted Isoxazoles **1-6**

| Compound | R | Reaction time, h | Temperature, °C | Yield, % |
|---|---|---|---|---|
| **1** | Me | 4 | 80 | 71 |
| **2** | Ph | 2 | 20 | 80 |
| **3** | 4-($F_3C$)$C_6H_4$ | 2 | 20 | 75 |
| **4** | 2-Py | 5 | 20 | 58 |
| **5** | 3-Py | 5 | 20 | 55 |
| **6** | 4-Py | 5 | 20 | 64 |

Isoxazoles containing an aryl group in the 3 position (**2-6**) were obtained by adding arylhydroxamic acid chloride dropwise to a solution of silylacetylene and an equimolar amount of triethylamine in ether. Evidence for occurrence of the reaction came from precipitation of triethylamine hydrochloride. Cycloaddition of substituted benzhydroxamic acid chlorides to diphenylmethylethynylsilane occurs in higher yields than for the pyridine analogs, due to the lower solubility of the latter in benzene.

A signal from the aromatic proton of the isoxazole ring H(4) in the $^1$H NMR spectrum is found within the range 6.26-6.84 ppm. The methyl group of the silyl substituent gives a signal in the 0.80-0.91 ppm region. The downfield shift of the signal is caused by introducing an aromatic substituent into the 3 position (Table 3).

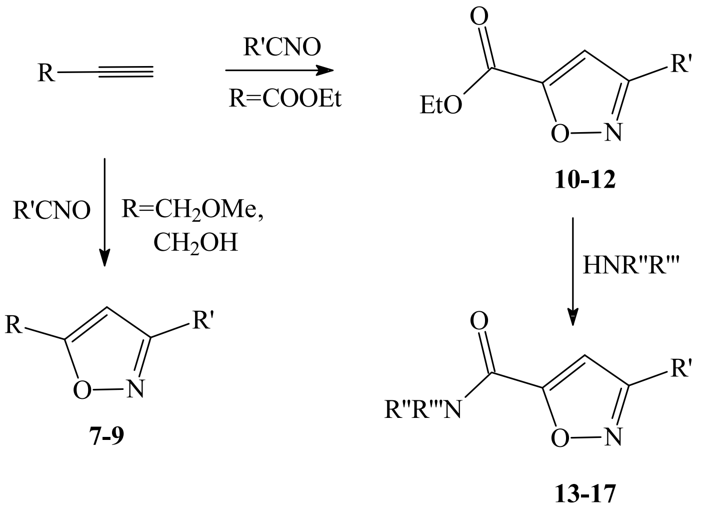


TABLE 2. Data on Synthesis of Carbonyl-substituted Isoxazoles **7-17**

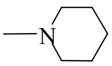
| Compound | R | R' | R" | R'" | Yield, % |
|---|---|---|---|---|---|
| **7** | $CH_2OMe$ | 2-$MeOC_6H_4$ | | | 90 |
| **8** | $CH_2OH$ | 2-$MeOC_6H_4$ | | | 80 |
| **9** | $CH_2OMe$ | 3-Py | | | 67 |
| **10** | COOMe | 2-$MeOC_6H_4$ | | | 86 |
| **11** | COOEt | 2-$CHF_2OC_6H_4$ | | | 80 |
| **12** | COOEt | 3-Py | | | 55 |
| **13** | | 2-$MeOC_6H_4$ | Me | Me | 65 |
| **14** | | 2-$CHF_2OC_6H_4$ | Me | Me | 65 |
| **15** | | 3-Py | Me | Me | 62 |
| **16** | | 3-Py |  | | 50 |
| **17** | | 3-Py | H | $CH_2Ph$ | 42 |

TABLE 3. $^1$H NMR Spectra of Compounds **1-17**

| Compound | Chemical shift, ppm |
|---|---|
| **1** | 0.80 (3H, s, MeSi); 2.24 (3H, s, Me); 6.26 (1H, s, CH); 7.31-7.50 (10H, m, arom.) |
| **2** | 0.87 (3H, s, MeSi); 6.73 (1H, s, CH); 7.31-7.86 (15H, m, arom.) |
| **3** | 0.89 (3H, s, MeSi); 6.76 (1H, s, CH); 7.32-7.71 (14H, m, arom.) |
| **4** | 0.90 (3H, s, MeSi); 6.84 (1H, s, CH); 7.34-7.52 (12H, m, arom.); 7.91 (1H, td, $J = 2$, $J = 8$ Hz, CH); 8.56 (1H, dd, $J = 2$, $J = 6$ Hz, CH) |
| **5** | 0.91 (3H, s, MeSi); 6.80 (1H, s, CH); 7.30-7.50 (11H, m, arom.); 8.13 (1H, td, $J = 2$, $J = 8$ Hz, CH); 8.64 (1H, dd, $J = 2$, $J = 6$ Hz, CH); 8.99 (1H, d, $J = 2$ Hz, CH) |
| **6** | 0.90 (3H, s, MeSi); 6.83 (1H, s, CH); 7.30-7.50 (10H, m, arom.); 8.64 (2H, dd, $J = 6.8$ Hz, 2CH); 9.05 (2H, dd, $J = 6.8$ Hz, 2CH) |
| **7** | 3.45 (3H, s, MeO); 3.88 (3H, s, MeO); 4.58 (2H, s, $CH_2$); 6.76 (1H, s, CH); 6.96-7.06 (2H, m, arom.); 7.35-7.45 (2H, m, arom.); 7.85-7.90 (1H, m, arom.) |
| **8** | 2.45 (1H, s, HO); 3.88 (3H, s, MeO); 4.60 (2H, s, $CH_2$); 6.56 (1H s, CH); 6.96-7.06 (2H, m, arom.); 7.35-7.45 (2H, m, arom); 7.85-7.90 (1H, m, arom.) |
| **9** | 3.46 (3H, s, $CH_3$); 4.62 (2H, s, $CH_2$); 6.62 (1H s, CH); 7.33-7.55 (1H, m, arom.); 8.14 (1H, td, $J = 2$, $J = 8.2$ Hz, arom.); 8.70 (1H, dd, $J = 2$, $J = 4.6$ Hz, arom.); 9.00 (1H, d, $J = 2$ Hz, arom.) |
| **10** | 3.73 (1H, d, $J = 0.5$ Hz, CH); 3.89 (3H, s, MeO); 3.96 (3H s, MeO); 6.85-7.06 (2H, m, arom.); 7.32-7.54 (2H, m, arom.); 7.84-7.96 (1H, m, arom.) |
| **11** | 1.44 (3H, t, $J = 8$ Hz, $CH_3$); 3.46 (2H, q, $J = 8$ Hz); 4.22 (1H, s, CH); 6.60 (1H s, CH); 6.62 (1H, s, $F_2CHO$); 7.17-7.46 (3H, m, arom.); 7.94-8.04 (1H, m, arom.) |
| **12** | 1.42 (3H, t, $J = 7.2$ Hz, $CH_3$); 3.52 (2H, quartet, $J = 7.2$ Hz, $CH_2$); 7.29 (1H, s, CH); 7.36-7.51 (1H, m, arom.); 8.17 (1H, td, $J = 2$ Hz, $J =$ Hz, arom.); 8.75 (1H, dd, $J = 2$, $J = 4.6$ Hz, arom.); 9.08 (1H, d, $J = 2$ Hz, arom.) |
| **13** | 3.13 (3H, s, $Me_2N$); 3.32 (1H, s, CH); 3.91 (3H, s, MeO); 6.88-7.05 (1H, m, arom.); 7.35-7.54 (2H, m, arom.); 7.88-7.98 (1H, m, arom.) |
| **14** | 3.17 (6H, s, $Me_2N$); 3.75 (1H, s, CH); 6.44 (1H, s, $CHF_2O$); 7.38-7.60 (4H, m, arom.) |
| **15** | 3.17 (3H, s, $Me_2N$); 3.28 (1H, s, CH); 7.11 (1H, s, CH); 7.33-7.51 (1H, m, arom.); 8.11 (1H, td, $J = 2.1$, $J = 8.2$ Hz, arom.); 8.71 (1H, dd, $J = 2.1$, $J = 4.6$ Hz, arom.); 8.93 (1H, d, $J = 2.1$ Hz, arom.) |
| **16** | 2.57-2.63 (4 H, m, $CH_2N$), 1.45-1.57 (6 H, m, $CH_2$); 3.28 (1H, s, CH); 7.11 (1H, m, CH); 7.33-7.51 (1H, m, arom.); 8.11 (1H, m, $J = 2.1$, $J = 8.2$ Hz, arom.); 8.71 (1H, dd, $J = 2.1$, $J = 4.6$ Hz, arom.); 8.93 (1H, $J = 2.1$ Hz, arom.) |
| **17** | 4.66 (2H, s, $CH_2$); 6.89 (1H, s, NH); 7.11 (1H, s, CH); 7.25-7.51 (6H, m, arom.); 8.11 (1H, td, $J = 2.1$, $J = 8.2$ Hz, arom.); 8.71 (1H, dd, $J = 2.1$, $J = 4.6$ Hz, arom.); 8.93 (1H, d, $J = 2.1$ Hz, arom.) |

Dipolar addition of nitrile oxides to propargyl alcohol, methylpropargyl ester, and ethyl ester of propiolic acid occurs with formation of 5-substituted isoxazoles **7-17** in good yields (55-90%).

The reaction is carried out at room temperature in benzene, adding a solution of triethylamine dropwise to a mixture of arylhydroxamic acid chloride and an equimolar amount of the acetylene derivative. The obtained ethyl esters of isoxazolecarboxylic acids **10-12** are converted to the corresponding amides by the conventional method, by dissolving in ethanol with a five-fold excess of amine and allowing to stand for 3-4 days. As a result, we obtained amides of isoxazolecarboxylic acids **13-17** in satisfactory yields (Table 2). The $^1$H NMR spectra of the products obtained are represented in Table 3.

For some of the synthesized compounds, we studied the cytotoxic properties *in vitro* relative to two lines of tumor cells: HT-1080 (human fibrosarcoma) and MG-22A (mouse hepatoma). The concentrations of the compounds resulting in 50% cell death *in vitro* (TD50) (Table 4) were determined using the standard procedure, from the intensity of staining of the cell membranes by crystal violet and the mitochondrial enzymes by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide [9-11].

In the series of 5-diphenylmethylsilylisoxazoles **1-6**, the greatest cytotoxic effect was observed for the 3-methyl-substituted isoxazole **1**. The phenyl-substituted analogs **2** and **3** do not exhibit cytotoxicity, while the 3- and 4-pyridyl derivatives **5** and **6** displayed moderate activity. When the methoxymethyl group in the 5 position in compound **7** was substituted by an ethoxycarbonyl and an aminocarbonyl group, the cytotoxicity decreased even to complete lack of cytotoxicity in the case of 5-piperidinocarbonyl-3-(3'-pyridyl)isoxazole (**16**).

TABLE 4. *In vitro* Cytotoxic Activity of Silyl- and Carbonyl-substituted Isoxazoles

| Com-pound | Cell lines | | | | | |
|---|---|---|---|---|---|---|
| | HT-1080 | | | MG-22A | | |
| | $TD_{50}$* CV*[2] | $TD_{50}$* MTT*[3] | NO %, CV*[4] | $TD_{50}$* CV | $TD_{50}$* MTT | NO %, CV |
| **1** | 7 | 3 | 75 | 8 | 12 | 88 |
| **2** | *[5] | *[5] | 9 | *[5] | 100 | 13 |
| **3** | *[5] | *[5] | 17 | 17 | 39 | 22 |
| **4** | 44 | *[5] | 20 | *[5] | *[5] | 13 |
| **5** | 40 | 47 | 254 | 33 | 41 | 350 |
| **6** | 33 | 45 | 104 | 41 | 36 | 54 |
| **7** | 13 | 28 | 43 | 10 | 17 | 250 |
| **8** | 20 | 46 | 192 | 14 | 23 | 400 |
| **11** | 36 | *[5] | 13 | 43 | 74 | 30 |
| **13** | 42 | 35 | 25 | 22 | 32 | 155 |
| **14** | *[5] | *[5] | 9 | 100 | 100 | 15 |
| **15** | *[5] | 71 | 12 | *[5] | *[5] | 8 |
| **16** | *[5] | *[5] | 5 | *[5] | *[5] | 8 |

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* Concentration resulting in 50% cell death, μg/ml.

*[2] Staining with crystal violet.

*[3] Staining with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.

*[4] NO concentration (%) (staining with crystal violet).

*[5] No cytotoxic activity.

The level of NO generation is especially high for the 3-pyridyl-substituted silylisoxazole (**5**) (up to 350% in the MG-22A line) and the methoxymethyl and hydroxymethyl derivatives **7** and **8**, especially in the MG-22A line (up to 400%).

3-Methyl-5-diphenylmethylsilylisoxazole (**1**) is distinguished by the highest activity of all the investigated compounds, which suggests the possibility of discovering new cytotoxically active compounds in the series of 3-alkyl-substituted silyl derivatives of isoxazole.

## EXPERIMENTAL

The $^1$H NMR spectra were taken on a Bruker WH-90/DS (90 MHz) spectrometer in $CDCl_3$, internal standard TMS. The elemental analyses were performed using a Carlo Erba 1108 analyzer. The isoxazolines were purified using a chromatographic column (support: silica gel 0.060-0.0200 mm, pore diameter 6 nm, from Acros; eluent ethyl acetate–petroleum ether). The optical density in the biological tests, conducted on 96-well plates, was determined by a Tetertek Multiscan MCC/340 horizontal spectrophotometer.

**5-Diphenylmethylsilyl-3-methylisoxazole (1).** A solution of nitroethane (0.4 g, 5.4 mmol) and triethylamine (1 drop) in dry benzene was added dropwise over a 4 h period to a mixture of diphenylmethylethynylsilane (1.2 g, 5.4 mmol) and two equivalents of phenylisocyanate (1.28 g, 0.0108 mol) at room temperature. After a few minutes, evolution of carbon dioxide began and diphenylurea began to precipitate. The reaction mixture was heated for 2 h at 70-80°C. After cooling down to room temperature, diphenylurea was filtered off and the solution was evaporated. The target product was separated on a chromatographic column. Yield 71%. Content of the primary substance 98.2% according to HPLC data (Zorbax $C_{18}$, 4.6×150 mm; system: 70% acetonitrile + 30% $H_2O$). UV detector ($\lambda$ = 220 nm). Found, %: C 73.15; H 6.15; N 4.96. $C_{17}H_{17}NOSi$. Calculated, %: C 73.08; H 6.13; N 5.01.

**5-Diphenylmethylsilyl-3-phenylisoxazole (2).** A solution of arylhydroxamic acid chloride (0.01 mol) in dry ether was added dropwise over a 2 h period to a mixture of diphenylmethylethynylsilane (0.01 mol) and triethylamine (0.01 mol) in dry ether at room temperature. After a few minutes, triethylamine hydrochloride began to precipitate. The reaction mixture was stirred for 2 h. Then the precipitate was filtered off and the solvent was evaporated. The target product was separated on a chromatographic column. Yield 80%. Content of the primary substance 98.2% according to HPLC data (Zorbax $C_{18}$, 4.6×150 mm; system: 70% acetonitrile + 30% $H_2O$). UV detector ($\lambda$ = 220 nm). Found, %: C 77.15; H 5.67; N 4.06. $C_{22}H_{19}NOSi$. Calculated, %: C 77.38; H 5.61; N 4.10.

**5-Diphenylmethylsilyl-3-(4'-trifluoromethylphenyl)isoxazole (3).** Obtained similarly to **2**. The target product was separated on a chromatographic column. Yield 75%. Content of primary substance 98.5% according to HPLC data (Ultrasphere, 4.6×250 mm; system: 10% acetonitrile + 90% hexane). UV detector ($\lambda$ = 254 nm). Found, %: C 67.56; H 4.51; N 3.25. $C_{23}H_{18}F_3NOSi$. Calculated, %: C 67.47; H 4.43; N 3.42.

**5-Diphenylmethylsilyl-3-(2'-pyridyl)isoxazole (4).** Diphenylmethylethynylsilane (0.01 mol), triethylamine (0.01 mol) and pyridinehydroxamic acid chloride were dissolved in 50 ml dry benzene and vigorously stirred at room temperature. Then the precipitate (triethylamine hydrochloride) was filtered off and the solvent was evaporated. The target product was separated on a chromatographic column. Yield 58%. Content of primary substance 98.3% according to HPLC data (Zorbax $C_{18}$, 4.6×150 mm; system: 70% acetonitrile + 30% $H_2O$). UV detector ($\lambda$ = 254 nm). Found, %: C 73.56; H 6.31; N 3.92. $C_{21}H_{18}N_2OSi$. Calculated, %: C 73.65; H 5.30; N 4.09. The compound is light sensitive.

**5-Diphenylmethylsilyl-3-(3'-pyridyl)isoxazole (5).** Obtained similarly to **4**. The target product was separated on a chromatographic column. Yield 55%. Content of primary substance 98.2% according to HPLC data (Zorbax $C_{18}$, 4.6×150 mm; system: 70% acetonitrile + 30% $H_2O$). UV detector ($\lambda$ = 254 nm). Found, %: C 73.65; H 6.33; N 4.06. $C_{21}H_{18}N_2OSi$. Calculated, %: C 73.65; H 5.30; N 4.09.

**5-Diphenylmethylsilyl-3-(4'-pyridyl)isoxazole (6).** Obtained similarly to **4**. The target product was separated on a chromatographic column. Yield 64%. Content of primary substance 98.4% according to HPLC data (Zorbax $C_{18}$, 4.6×150 mm; system: 70% acetonitrile + 30% $H_2O$). UV detector ($\lambda$ = 254 nm). Found, %: C 73.62; H 6.36; N 4.14. $C_{21}H_{18}N_2OSi$. Calculated, %: C 73.65; H 5.30; N 4.09.

**5-Methoxymethyl-3-(*o*-methoxyphenyl)isoxazole (7).** A solution of triethylamine (0.01 mol) in dry benzene was added dropwise over a 2 h period to a mixture of methylpropargyl ester (0.01 mol) and arylhydroxamic acid chloride (0.01 mol) in dry benzene and at room temperature. After a few minutes, triethylamine hydrochloride began to precipitate. The reaction mixture was stirred for 2 h. Then the precipitate was filtered off and the solvent was evaporated. The target product was separated on a chromatographic column. Yield 90%. Content of primary substance 98.4% according to HPLC data (Symmetry $C_{18}$, 3.9×150 mm; system: 50% acetonitrile + 50% $H_2O$). UV detector ($\lambda$ = 254 nm). Found, %: C 65.83; H 6.03; N 6.43. $C_{12}H_{13}NO_3$. Calculated, %: C 65.74; H 5.98; N 6.39.

**5-Hydroxymethyl-3-(*o*-methoxyphenyl)isoxazole (8).** Obtained similarly to **7**. The target product was separated on a chromatographic column. Yield 80%. Content of primary substance 98.4% according to HPLC data (Symmetry $C_{18}$, 3.9×150 mm; system: 50% acetonitrile + 50% $H_2O$). UV detector ($\lambda$ = 254 nm). Found, %: C 64.33; H 5.45; N 6.70. $C_{11}H_{11}NO_3$. Calculated, %: C 64.38; H 5.40; N 6.83.

**5-Methoxymethyl-3-(3'-pyridyl)isoxazole (9).** Obtained similarly to **7**. The target product was separated on a chromatographic column. Yield 67%. Content of primary substance 98.4% according to HPLC data (Symmetry $C^{18}$, 3.9×150 mm; system: 30% acetonitrile + 70% $H_2O$). UV detector ($\lambda$ = 220 nm). Found, %: C 63.24; H 5.38; N 14.85. $C_{10}H_{10}N_2O_2$. Calculated, %: C 63.15; H 5.30; N 14.73.

**5-Ethoxycarbonyl-3-(*o*-methoxyphenyl)isoxazole (10).** Obtained similarly to **7**. The target product was separated on a chromatographic column. Yield 86%. Content of primary substance 98.5% according to HPLC data (Ultrasphere, 4.6×250 mm; system: 10% ethylacetate + 90% hexane). UV detector ($\lambda$ = 254 nm). Found, %: C 66.35; H 5.10; N 6.65. $C_{12}H_{11}NO_4$. Calculated, %: C 66.43; H 5.17; N 6.55.

**3-(*o*-Difluoromethoxyphenyl)-5-ethoxycarbonylisoxazole (11).** Obtained similarly to **7**. The target product was separated on a chromatographic column. Yield 80%. Content of primary substance 98.5% according to HPLC data (Zorbax $C_{18}$, 4.6× 250 mm; system: 60% acetonitrile + 40% $H_2O$). UV detector ($\lambda$ = 220 nm). Found, %: C 55.25; H 4.08; N 4.85. $C_{13}H_{11}F_2NO_4$. Calculated, %: C 55.13; H 3.92; N 4.95.

**5-Ethoxycarbonyl-3-(3'-pyridyl)isoxazole (12).** Obtained similarly to **7**. The target product was separated on a chromatographic column. Yield 80%. Content of primary substance 99% according to HPLC data (Kromasil 100-$C_{18}$, 4.6×150 mm; system: acetonitrile + [0.1% $H_3PO_4$ + $H_2O$]). UV detector ($\lambda$ = 330 nm). Found, %: C 60.45; H 4.68; N 12.75. $C_{11}H_{10}N_2O_3$. Calculated, %: C 60.55; H 4.62; N 12.84.

**5-Dimethylaminocarbonyl-3-(*o*-methoxyphenyl)isoxazole (13).** A solution of ethoxycarbonyl derivative **10** (0.01 mol) in ethanol was poured into a 30% solution of dimethylamine in water (0.05 mol) and allowed to stand at room temperature for several days. Then the solvent was evaporated. The target product was separated on a chromatographic column. Yield 65%. Content of primary substance 98.5% according to HPLC data (Zorbax $C_{18}$, 3.9×150 mm; system: 10% ethylacetate + 90% hexane). UV detector ($\lambda$ = 254 nm). Found, %: C 63.33; H 5.68; N 11.39. $C_{13}H_{14}N_2O_3$. Calculated, %: C 63.40; H 5.73; N 11.37.

**3-(*o*-Difluoromethoxyphenyl)-5-dimethylaminocarbonylisoxazole (14).** Obtained similarly to **13**. The target product was separated on a chromatographic column. Yield 65%. Content of primary substance 98.5% according to HPLC data (Zorbax $C_{18}$, 3.9×150 mm; system: 60% acetonitrile + 40% $H_2O$). UV detector ($\lambda$ = 254 nm). Found, %: C 55.21; H 4.33; N 10.04. $C_{13}H_{12}F_2N_2O_3$. Calculated, %: C 55.32; H 4.29; N 9.92.

**5-Dimethylaminocarbonyl-3-(3'-pyridyl)isoxazole (15).** Obtained similarly to **13**. The target product was separated on a chromatographic column. Yield 62%. Content of primary substance 99% according to HPLC data (Symmetry $C_{18}$, 3.9×150 mm; system: 20% acetonitrile + 80% $H_2O$). UV detector ($\lambda$ = 220 nm). Found, %: C 60.77; H 5.08; N 19.51. $C_{11}H_{11}N_3O_2$. Calculated, %: C 60.82; H 5.10; N 19.34.

**5-Piperidinocarbonyl-3-(3'-pyridyl)isoxazole (16).** Obtained similarly to **13** in alcoholic solution. The target product was separated on a chromatographic column. Yield 50%. Content of primary substance 98.5% according to HPLC data (Symmetry $C_{18}$, 3.9×150 mm; system: 30% acetonitrile + 70% $H_2O$). UV detector ($\lambda$ = 254 nm). Found, %: C 65.33; H 5.79; N 16.39. $C_{14}H_{15}N_3O_2$. Calculated, %: C 65.36; H 5.88; N 16.33.

**5-Benzylaminocarbonyl-3-(3'-pyridyl)isoxazole) (17).** Obtained similarly to **13** in alcoholic solution. The target product was separated on a chromatographic column. Yield 42%. Content of primary substance 98.3% according to HPLC data (Symmetry $C_{18}$, 3.9×150 mm; system: 20% acetonitrile + 80% $H_2O$). UV detector ($\lambda$ = 220 nm). Found, %: C 68.72; H 4.58; N 15.01. $C_{16}H_{13}N_3O_2$. Calculated, %: C 68.81; H 4.69; N 15.04.

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