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Synthesis of *N*-Arylcarbamates with Tetrazole Fragment and Some Their Derivatives

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Abstract—Reactions of methyl(ethyl) *N*-(2-cyanophenyl)carbamates with sodium azide in dimethylformamide at 80–90°C in the presence of anhydrous $CdCl_2$ afforded the corresponding *N*-arylcarbamates with a 1,2,3,4-tetrazole fragment. The acylation of methyl *N*-[2-(1*H*-1,2,3,4-tetrazol-5-yl)phenyl]carbamate with acetic anhydride followed by the condensation of the obtained *N*-acyl derivative with thiophene-2-carbaldehyde in the KOH methanol solution led to the formation of methyl *N*-(2-{1-[3-(2-thienyl)-2-propenoyl]-1*H*-1,2,3,4-tetrazol-5-yl}phenyl)carbamate. The reaction of cyclohexyl N-(4-aminophenyl)carbamate with a triethyl orthoformate and sodium azide in glacial AcOH yielded cyclohexyl *N*-[4-(1*H*-1,2,3,4-tetrazol-1-yl)phenyl]carbamate.

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Specific properties of the tetrazole ring consisting in its partial aromaticity and relatively high stability regardless the presence of four heteroatoms attract the interest to tetrazoles as objects of fundamental research [1]. They serve as semiproducts in the synthesis of versatile condensed, linearly connected, and spiro fused heterocycles.

The tetrazole chemistry over the course of a century of its development is encompassed in several general reviews [2–8] and in a number of specialty surveys on 2-aryltetrazoles [9], tetrazolium salts [10], energetic tetrazoles [11], synthesis and reactions of lithium tetrazoles [12], acid-base properties [13], complex formation [14, 15], phase transfer catalysis [16], thermal transformations [17], analogy of thermal and mass spectrometric fragmentation [18], medical applications [19,20], and also on various kinds of tautomerism, some synthetic problems, and other issues.

The growing world-wide interest in tetrazoles originates above all from the considerable success in manufacturing proceeding from 1-mono-, 1,5- and 2,5-disubstituted tetrazoles of a number of highly efficient drugs: antibiotics of cephalosporin series, cholesterol reducing, antihypertensive and antiviral medications, in particular, enzymes inhibitors of HIV/AIDS.

Tetrazoles are also promising as analytical reagents, radioprotectors, herbicides, components of mixed fuels, pyrotechnic, explosive, and gas-generating compositions, they are exclusively important for synthetic chemistry in the preparation of various classes of compounds.

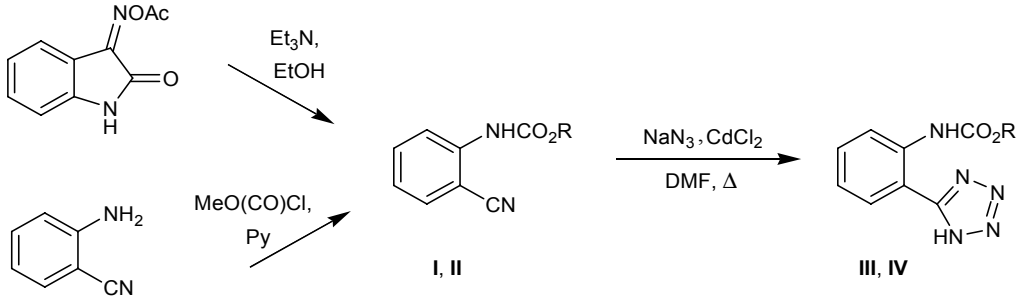
We studied the possibility of the synthesis of 1*H*-tetrazoles with phenylcarbamate fragment proceeding from ethyl(methyl) (2-cyanophenyl)carbamates **I** and **II**. Carbamate **I** in its turn was obtained by acylation of 2-aminobenzonitrile with methyl chloroformate in pyridine solution and compound **II** was prepared by the cleavage of O-acyl derivative of isatin oxime in the presence of ethanol [21]. The synthesis of 1*H*-tetrazole derivatives **III** and **IV** was performed by heating a mixture of 1 equiv of carbamates cyano derivatives **I** and **II** with 2 equiv of sodium azide in DMF in the presence of anhydrous cadmium chloride at 80–90°C for 8 h [22] (Scheme 1).

The structure of compounds **III** and **IV** was confirmed by IR, ^{1}H NMR, and mass spectra, and of tetrazole **III**, additionally by ^{13}C NMR spectrum.

The formation of compounds **III** and **IV** occurs as a result of the [3+2]-cycloaddition of the hydrogen azide formed in the course of the reaction to the cyano group of carbamates.

The acylation of tetrazole **III** with acetic anhydride afforded the corresponding *N*-acyl derivative **V** whose structure was confirmed by IR, ^{1}H NMR spectra and by elemental analysis.

Scheme 1.



The obtained *N*-acyl derivative **V** we further brought into the aldol-crotonic condensation with thiophene-2-carbaldehyde catalyzed by a base. The study of the product structure by IR, ^{1}H NMR spectroscopy and mass spectrometry showed that the reaction as expected led to the formation of methyl *N*-(2-{1-[3-(2-thienyl)-2-propenoyl]-1*H*-1,2,3,4-tetrazol-5-yl}phenyl)carbamate (**VI**) in 89% yield (Scheme 2).

IR spectrum of compound **VI** along with the other absorption bands contains the band at 1285 cm^{-1} generated by the stretching vibrations of N–N=N– bonds, and also absorption bands at 1108 and 1138 cm^{-1} belonging to the stretching vibrations of the tetrazole ring that does not contradict the spectral data on the other 5-phenyl-1*H*-tetrazoles [23].

In the ^{1}H NMR spectrum of chalcone **VI** along with the signals of the other protons a doublet is present of H$^{\beta}$ from the fragment Ht–H$^{\beta}$C=CH$^{\alpha}$–CO at 7.81 ppm (*J* 15.5 Hz), and the signal of H$^{\alpha}$ is overlapped with the signal of the thiophene ring proton that appears as a multiplet in the region 6.95–6.97 ppm. The large value of the spin-spin coupling constant indicates the *E*-configuration of the chalcone [24].

One among the general methods of 1-substituted tetrazoles synthesis is the reaction of amines with ethyl orthoformate and sodium azide [6]. We tested the possibility to synthesize 1-substituted tetrazole by the heterocyclization of cyclohexyl *N*-(4-aminophenyl)-carbamate (**VII**) [25], ethyl orthoformate, and sodium azide [26, 27]. The reaction was performed by refluxing the reaction mixture at TLC monitoring.

The study of the product structure by IR, ^{1}H,^{13}C NMR spectroscopy showed that as expected the reaction product was cyclohexyl *N*-[4-(1*H*-1,2,3,4-tetrazol-1-yl)phenyl]carbamate (**VIII**) (Scheme 3).

In the ^{1}H NMR spectrum of compound **VIII** the proton of the tetrazole ring appears in the weak field at 8.30 ppm, and in the ^{13}C NMR spectrum the atom C^5 gives rise to the signal at δ 147.90 ppm in agreement with the spectral parameters of the other 1-aryl-substituted 1*H*-1,2,3,4-tetrazoles [28, 29].

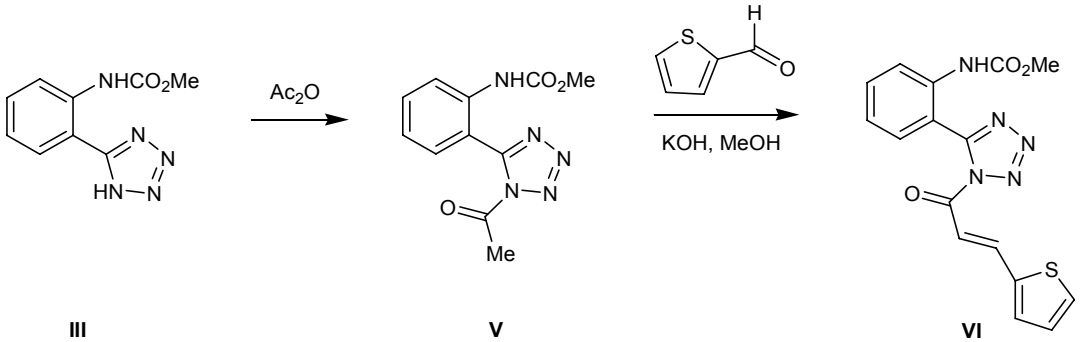
The formation of 1-aryl-substituted 1*H*-1,2,3,4-tetrazoles proceeds apparently along Scheme 4.

Hence in this study the application of cyano and amino derivatives of *N*-arylcarbamates to the synthesis of 1- and 5-aryl substituted 1*H*-1,2,3,4-tetrazoles possessing a considerable potential of biologic action was demonstrated.

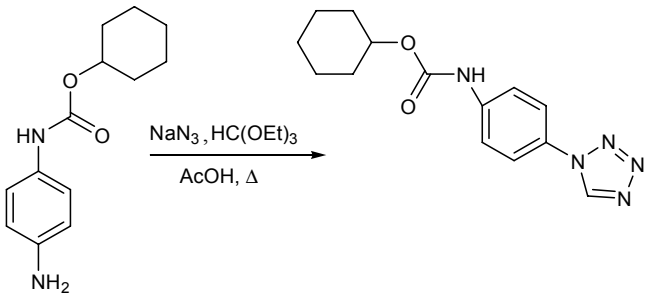
EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Bruker DRX-500 (500.13 MHz). ^{13}C NMR spectra were

Scheme 2.



Scheme 3.

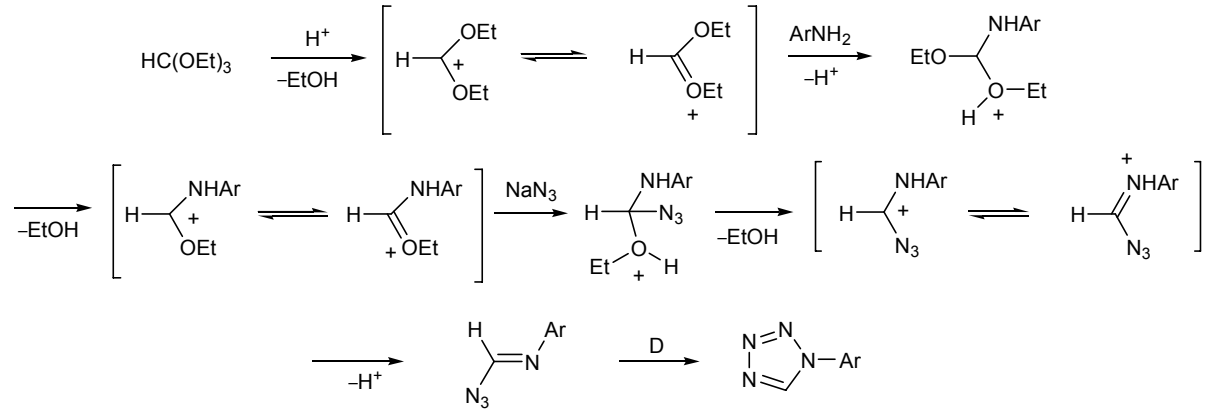


recorded on a spectrometer Bruker WM-400 (100 MHz) with a wide-band decoupling from protons, solvent DMSO-d_6. IR spectra were obtained on an IR Fourier spectrophotometer Infra-LUM FT-02 in the range 4000–400 cm^{-1} from pellets with KBr. The purity of compounds obtained was tested by TLC on Silufol UV-254 plates, development in iodine vapor. Ethyl N-(2-cyanophenyl)carbamate **II** was obtained by procedure described in [2], mp 106–107°C (mp 107°C [30]).

Methyl *N*-(2-cyanophenyl)carbamate (I). To a slurry of 11.8 g (0.1 mol) of 2-aminobenzonitrile in 46 mL of anhydrous pyridine was added dropwise at cooling to –1°C under vigorous stirring within 1 h 7.8 mL (0.1 mol) of methyl chloroformate. The reaction mixture was left standing for 8 h at room temperature, poured in 150 mL of water, and cautiously acidified with conc. hydrochloric acid (against Congo red). The separated precipitate was filtered off, thoroughly washed with water on the filter, dried in air, and recrystallized from hexane. Yield 17.3 g (98%), colorless crystals, mp 90–92°C. IR spectrum, ν, cm^{-1}: 3320 (NH), 2220 (C≡N), 1710 (C=O), 1610, 1585, 1565 (C=C, C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, $NHCO_2\underline{Me}$), 6.80 t (1H_{arom}, *J* 7.4 Hz),7.65 t (1H_{arom}, *J* 7.4 Hz), 7.93 d (1H_{arom}, *J* 7.4 Hz), 8.03 d (1H_{arom}, *J* 7.4 Hz), 10.12 br.s (1H, NH). Found, %: C 61.25; H 4.5; N 15. 85. $C_9H_8N_2O_2$. Calculated, %: C 61.36; H 4.55; N 15.91.

Methyl N-[2-(1*H*-1,2,3,4-tetrazol-5-yl)phenyl] carbamate (III). A mixture of 0.176 g (1 mmol) of methyl N-(2-cyanophenyl)carbamate (**I**), 0.13 g (2 mmol) of sodium azide, and 0.018 g (0.1 mmol) of anhydrous cadmium chloride in 5 mL of DMF was heated at 80–90°C for 8 h, cooled, diluted with 10 mL of water, and treated with ethyl acetate (2 × 15 mL). The combined organic solutions were washed with 5 N hydrochloric acid solution (20 mL), dried with anhydrous magnesium sulfate, the solvent was removed in a vacuum, the obtained crystals were subjected to chromatography on a down-tending glass column packed with activated Silicagel 100/400 μm, eluent ethyl acetate–petroleum ether, 4 : 1 (v/v). Yield 0.19 g (86%), colorless crystals, mp 201–202°C. IR spectrum, ν, cm^{-1}: 3380, 3330 (NH), 1710, 1615, 1575, 1565 (C=C, C=C_{arom}), 1285 (N–N=N–), 1108, 1138 (tetrazole ring). H NMR spectrum, δ, ppm: 3.73 s (3H, $NHCO_2\underline{Me}$), 6.48 s (1$H_{tetrazole}$), 7.28 t (1H_{arom}, *J* 7 Hz), 7.59 d (1H_{arom}, *J* 7 Hz), 7.95 d (1H_{arom}, *J* 7 Hz), 8.24 d (1H_{arom}, *J* 7 Hz), 10.42 br.s (1H, $N\underline{H}CO_2Me$). ^{13}C NMR spectrum, δ, ppm: 52.24, 120.03, 121.11, 122.32, 123.15, 128.64, 133.29, 137.27, 153.64. Mass spectrum, *m*/*z* (I_{rel}, %): 220 (8) $[M + 1]^+$, 219 (27) $[M]^+$, 191 (7), 159 (16), 148 (31), 131 (29), 118 (100), 104 (20), 90 (12), 77 (17). Found, %: C 49.51; H 4.12; N 31.86. $C_9H_9N_5O_2$. Calculated, %: C 49.32; H 4.11; N 31.96. *M* 219.

Scheme 4.



Ethyl N-[2-(1*H*-1,2,3,4-tetrazol-5-yl)phenyl]-carbamate (IV) was obtained similarly. Yield 0.19 g (83%), colorless crystals, mp 145–147°C. IR spectrum, ν, cm^{-1}: 3380, 3330 (NH), 1710, 1610, 1575, 1565 (C=C, C=C_{arom}), 1285 (N–N=N–), 1108, 1138 (tetrazole ring). ^{1}H NMR spectrum, δ, ppm: 1.27 t (3H, CH_3CH_2O, *J* 7 Hz), 4.17 q (2H, CH_3CH_2O, *J* 7 Hz), 6.47 s (1$H_{tetrazole}$), 7.27 t (1H_{arom}, *J* 7 Hz), 7.58 t (1H_{arom}, *J* 7 Hz), 7.95 d (1H_{arom}, *J* 7 Hz), 8.06 d (1H_{arom}, *J* 7 Hz), 10.40 br.s (1H, $NHCO_2Et$). Mass spectrum, *m/z* (I_{rel}, %): 234 (6) $[M + 1]^+$, 233 (38) $[M]^+$, 189 (12), 161 (21), 133 (18), 118 (100), 104 (18), 91 (27), 77 (12). Found, %: C 51.44; H 4.84; N 29.83. $C_{10}H_{11}N_5O_2$. Calculated, %: C 51.50; H 4.72; N 30.04. *M* 233.

Methyl 2-(1-acetyl-1*H*-tetrazol-5-yl)phenylcarbamate (V). A mixture of 1.1 g (5 mmol) of tetrazole **III** and 0.5mL (5.1 mmol) of acetic anhydride was heated on a boiling water bath for 20 min, cooled, and diluted with 10 mL of ice water. The separated precipitate was filtered off, washed with water on the filter (10 mL), dried in air, and recrystallized from ethanol. Yield 1.27 g (97%), colorless crystals, mp 150–152°C. IR spectrum, ν, cm^{-1}: 3310 (NH), 1710, 1695 (C=O), 1610, 1570, 1565 (C=C, C=C_{arom}), 1285 (N–N=N–), 1108, 1138 (tetrazole ring). ^{1}H NMR spectrum, δ, ppm: 2.78 s (3H, $COCH_3$), 3.71 s (3H, $NHCO_2Me$), 7.60 t (1H_{arom}, *J* 7.3 Hz), 7.80 t (1H_{arom}, *J* 7.3 Hz), 8.28 d (1H_{arom}, *J* 7.3 Hz), 8.59 d (1H_{arom}, *J* 7.3 Hz), 9.58 br.s (1H, NH). Found, %: C 50.60; H 4.13; N 26.71. $C_{11}H_{11}N_5O_3$. Calculated, %: C 50.58; H 4.22; N 26.82.

Methyl N-(2-{1-[3-(2-thienyl)-2-propenoyl]-1*H*-1,2,3,4-tetrazol-5-yl}phenyl)carbamate (VI). To a mixture of 1.31 g (5 mmol) of N-acyl derivative **V**, 0.46 mL (5 mmol) of freshly distilled thiophene-2-carbaldehyde in 15 mL of methanol was added at 35°C within 0.5 h at stirring 1.5 mL of 10% methanol solution of potassium hydroxide. The reaction mixture was stirred for 4 h at 35°C, left standing for 24 h at room temperature, poured into 100 mL of ice water, and cautiously acidified with dilute hydrochloric acid (1 : 1). The separated precipitate was filtered off, dried in air, and recrystallized from ethanol. Yield 1.7 g (96%), light yellow crystals, mp 213–214°C. IR spectrum, ν, cm^{-1}: 3310 (NH), 1710, 1680 (C=O), 1630 (C=C), 1610, 1585, 1565 (C=C, C=C_{arom}), 1285 (N–N=N–), 1108, 1138 (tetrazole ring). ^{1}H NMR spectrum, δ, ppm: 3.71 s (3H, $NHCO_2Me$), 6.74 d (1$H_{thienyl}$, *J* 5.1 Hz), 6.95–6.97 m (2H, 1$H_{thienyl}$, 1H, HC=CH), 7.19 d (1$H_{thienyl}$, *J* 5.0 Hz), 7.56 t (1H_{arom}, *J* 7.3 Hz), 7.81 d (1H, HC=CH, *J* 15.5 Hz), 7.95 t (1H_{arom}, *J* 7.3 Hz), 8.45 d (1H_{arom}, *J* 7.3 Hz), 8.79 d (1H_{arom}, *J* 7.3 Hz), 9.58 br.s (1H, NH). Found, %: C 54.15; H 3.70; N 19.54. $C_{16}H_{13}N_5O_3S$. Calculated, %: C 54.09; H 3.66; N 19.72.

Cyclohexyl N-[4-(1*H*-1,2,3,4-tetrazol-1-yl)phenyl] carbamate (VIII). To a slurry of 1.17 g (5 mmol) of cyclohexyl N-(4-aminophenyl)carbamate (**VII**) and 0.33 g (5.04 mmol) of sodium azide in 2.5 mL (15 mmol) of ethyl orthoformate was added 2.3 mL (40 mmol) of glacial acetic acid. The reaction mixture was refluxed for 4 h at stirring, then it was cooled, diluted with 10 mL of water, the mixture was extracted with ethyl acetate (2 × 15 mL), the organic solutions were washed with water, dried with anhydrous sodium sulfate, and the solvent was removed. The obtained crystals were recrystallized from a mixture ethyl acetate–hexane, 1 : 3 (v/v). Yield 1.21 g (84%), colorless crystals, mp 130–132°C. IR spectrum, ν, cm^{-1}: 3320 (NH), 1710 (C=O), 1665 (C=N), 1610, 1585, 1565 (C=C, C=C_{arom}). ^{1}H NMR spectrum, δ, ppm: 1.17–1.47 m (6$H_{cyclohexyl}$), 2.18–2.21 m (2$H_{cyclohexyl}$), 2.39–2.42 m (2$H_{cyclohexyl}$), 4.90–4.93 m (1H, OCH), 7.72 d (2H_{arom}, *J* 8.7 Hz), 8.50 d (2H_{arom}, *J* 8.7 Hz), 8.30 s (1$H_{tetrazole}$), 9.64 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 23.36, 25.32, 31.75 (5C, $CH_{2cyclohexyl}$), 69.30 (C, $CH_{cyclohexyl}$), 121.26, 126.07, 127.89, 135.16 (C_{Ar}), 147.90 ($C^5_{tetrazole}$), 154.10 (C=O). Found, %: C 58.47; H 5.90; N 24.28. $C_{14}H_{17}N_5O_2$. Calculated, %: C 58.54; H 5.92; N 24.39.

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