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Synthesis of 5-Substituted 3-[5-(2,5-Dimethylphenyl)-1,2-oxazol-3-yl]-1,2,4-oxadiazoles

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Abstract—5-(2,5-Dimethylphenyl)-1,2-oxazole-3-carbaldehyde oxime reacted with acetic anhydride in pyridine to give 5-(2,5-dimethylphenyl)-1,2-oxazole-3-carbonitrile which was converted into the corresponding amide oxime by treatment with hydroxylamine. *O*-Acyl derivatives of *N*′-hydroxy-5-(2,5-dimethylphenyl)-1,2-oxazole-3-carboximidamide underwent heterocyclization into 5-substituted 3-[5-(2,5-dimethylphenyl)-1,2-oxazol-3-yl]-1,2,4-oxadiazoles on heating in acetic acid.

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Isoxazole and 1,2,4-oxadiazole rings are structural fragments of many biomolecules, and studies in field of synthesis of new derivatives containing isoxazole and 1,2,4-oxadiazole rings attract persistent interest [1–4]. Obviously, compounds containing both these heterocycles in a single molecule are very promising from the viewpoint of their biological activity.

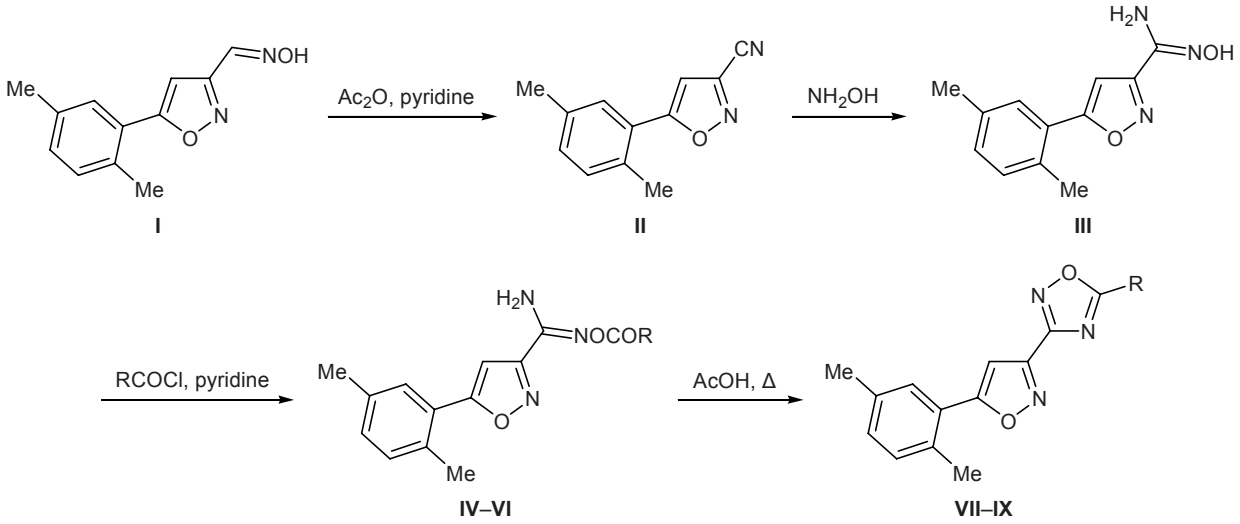
We previously developed a convenient procedure for the synthesis of 5-(2,5-dimethylphenyl)-1,2-oxazole-3-carbaldehyde oxime (**I**) from accessible 3,4,4-trichloro-1-(2,5-dimethylphenyl)but-3-en-1-one. The latter can be prepared as a result of successive transformations of trichloroethylene dimer [5]. The goal of the present work was to effect transformation of the hydroxyiminomethyl group in isoxazole derivative **I** into cyano group and to use 5-(2,5-dimethylphenyl)-1,2-oxazole-3-carbonitrile (**II**) thus obtained in the synthesis of 1,2,4-oxadiazole derivatives. Nitriles are versatile synthetic intermediates, and they are widely used for the preparation of various compounds, including heterocyclic ones [6]. We tried to construct 1,2,4-oxadiazole ring according to a scheme including initial synthesis of amide oxime [7].

Cyanoisoxazole **II** was synthesized in 82% yield by treatment of oxime **I** with acetic anhydride in pyridine at 90°C. The formation of **II** was confirmed by the presence of characteristic C≡N absorption band at 2253 cm^{-1} in the IR spectrum, as well as by disappearance from the ^1H and ^{13}C NMR spectra of signals from the exocyclic CH group, typical of initial oxime **I**. The mass spectrum of **II** contained the molecular ion peak with *m*/*z* 198. Addition of hydroxylamine at the triple C≡N bond of cyanoisoxazole **II** gave 97% of *N*′-hydroxy-5-(2,5-dimethylphenyl)-1,2-oxazole-3-carboximidamide (**III**). Acylation of **III** with acetyl, 3,4,4-trichlorobut-3-enoyl, and 4,5-dichloro-1,2-thiazole-3-carbonyl chlorides occurred exclusively at the *N*-hydroxy group (as reported previously for heteroaromatic amide oximes [6]) and resulted in the formation of the corresponding *N*′-acyloxy derivatives **IV**–**VI** in 80–87% yield (Scheme 1).

The structure of compounds **III**–**VI** was determined on the basis of their elemental compositions and IR, ^1H and ^{13}C NMR, and mass spectra. The IR spectra of **III**–**VI** lacked C≡N absorption in the region of 2253 cm^{-1}, but absorption bands appeared in the region 3302–3475 cm^{-1} due to stretching vibrations of N–H bonds (and also O–H bond in the spectrum of **III**). Stretching vibrations of the C=C and C=N bonds gave rise to absorption bands at 1503–1650 cm^{-1}. Acyloxy derivatives **IV**–**VI** displayed strong carbonyl absorption in the region 1736–1770 cm^{-1}; no analogous band was observed in the IR spectrum of amide oxime **III**.

The ^1H NMR spectra of **III**–**VI** contained broadened singlets at δ 5.59–5.83 ppm from the NH_2 protons, and the hydroxy proton in amide oxime **III** resonated as a singlet at δ 9.52 ppm; the latter was absent in the spectra of N-acyloxy derivatives **IV**–**VI**. In addition, a singlet from 4-H in the isoxazole ring was present at δ 6.74–6.98 ppm together with signals

Scheme 1.



IV, **VII**, R = Me; **V**, **VIII**, R = $Cl_2C{=}C(Cl)CH_2$; **VI**, **IX**, R = 4,5-dichloro-1,2-thiazol-3-yl.

from protons in the aromatic ring. Methyl protons in the acetyl group of **IV** gave a singlet at δ 2.27 ppm, and methylene protons in the acyl residue of **V** resonated at δ 3.89 ppm.

The ^{13}C NMR spectrum of amide oxime **III** contained 12 signals. Analysis of the signal multiplicities in the spectrum recorded using DEPT pulse sequence showed that six signals belong to carbon atoms attached to protons (two methyl groups, three aromatic CH atoms, and C^4H in the isoxazole ring) and that the remaining signals belong to six quaternary carbon atoms (C=NOH), $3C_{arom}$, C^3, and C^5). Apart from the above signals, compounds **IV**–**VI** showed in the ^{13}C NMR spectra carbonyl carbon signals (δ_C 171.5–171.8 ppm) and carbon signals of the acyl residue.

No molecular ion peaks were detected in the mass spectra of isoxazole derivatives **III**–**VI**. Instead, peaks from the fragment ions $[M - NH_2OH]^+$ (**III**) and $[M - H_2O]^+$ (**IV**–**VI**) were present. The intensity ratios of the $^{35}Cl/^{37}Cl$ isotope clusters for the $[M - H_2O]^+$ ions were equal to 100:98:32:3.5 and 100:65:1.1 for compounds **V** and **VI**, respectively, indicating that their molecules contain three and two chlorine atoms [8, 9].

Acylated amide oximes **IV**–**VI** underwent heterocyclization on heating in glacial acetic acid. The cyclization was accompanied by elimination of water, and the products were the corresponding 5-substituted 3-[5-(2,5-dimethylphenyl)-1,2-oxazol-3-yl]-1,2,4-oxadiazoles **VII**–**IX** which were isolated in 91–96% yields. Compounds **VII**–**IX** were identified on the basis of analytical and spectral data.

The IR spectra of isoxazolyl-1,2,4-oxadiazoles **VII**–**IX** lacked absorption bands assignable to carbonyl and amino groups typical of initial *N*′-acyloxyisoxazolecarboximidamides **IV**–**VI**. The C=C and C=N bond system was characterized by absorption in the region 1488–1607 cm^{-1}, and considerable shift of the high-frequency band toward lower frequencies should be noted (from 1632–1641 cm^{-1} in the spectra of **IV**–**VI** to 1589–1607 cm^{-1} in the spectra of **VII**–**IX**. The ^1H NMR spectra of **VII**–**IX** contained singlets from the 4-H proton in the isoxazole ring and signals from protons in the xylene fragment. Compounds **VII** and **VIII** also displayed signals from protons in the substituent on C^5 of the oxadiazole ring. The ^{13}C NMR spectra of compounds **VII**–**IX** were consistent with the assumed structures: the numbers of signals from protonated and quaternary carbon atoms were the same as in the spectra of initial amide oxime esters **IV**–**VI**.

In the mass spectra of **VII**–**IX** we observed the corresponding molecular ion peaks and peaks from fragment ions, which indicated that their fragmentation under electron impact involved elimination of substituents and heterocyclic residues and their subsequent decomposition. The isotope ratios in the molecular ion clusters of chlorine-containing compounds **VIII** and **IX** confirmed the presence of, respectively, three and two chlorine atoms in their molecules [8, 9].

EXPERIMENTAL

The IR spectra were recorded on a Nicolet Protégé-460 spectrometer with Fourier transform from samples prepared as KBr pellets. The ^1H and ^{13}C NMR spectra

were measured on a Bruker Avance-500 spectrometer from solutions in $CDCl_3$ (**II**, **IV**–**IX**) or acetone-d_6 (**III**). The chemical shifts were measured relative to tetramethylsilane (^1H) or solvent signals ($CDCl_3$, δ_C 77.0 ppm; acetone-d_6, δ_C 30.2 ppm). The mass spectra (electron impact, 70 eV) were obtained on a Hewlett–Packard HP 5972 mass-selective detector coupled with an HP 5890 gas chromatograph (HP-5MS capillary column, 30 m × 0.25 mm, film thickness 0.25 μm, 5% of phenylmethylsilicone; injector temperature 250°C).

Initial 5-(2,5-dimethylphenyl)-1,2-oxazole-3-carbaldehyde oxime (**I**) was synthesized according to the procedure described in [5].

5-(2,5-Dimethylphenyl)-1,2-oxazole-3-carbonitrile (II). Acetic anhydride, 7.66 g (75 mmol), was added under stirring to a solution of 10.81 g (50 mmol) of compound **I** in 20 ml of pyridine. The mixture was stirred for 6 h at 90°C, poured into water, acidified to pH 5 with hydrochloric acid, and extracted with chloroform. The extract was washed over calcium chloride and evaporated under reduced pressure, and the dry residue was recrystallized from hexane. Yield 10.04 g (82%), mp 74–76°C. IR spectrum, ν, cm^{-1}: 1505, 1567, 1633 (C=C, C=N); 2253 (C≡N). ^1H NMR spectrum, δ, ppm: 2.40 s (3H, Me), 2.47 s (3H, Me), 6.74 s (4-H), 7.25 br.s (2H, H_{arom}), 7.54 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.49 (Me), 21.52 (Me), 104.96 (C^4), 129.70 (CH_{arom}), 132.32 (CH_{arom}), 132.82 (CH_{arom}), 110.86, 125.34, 134.10, 136.96, 140.38, 173.56. Mass spectrum: *m*/*z* 198 $[M]^+$. Found, %: C 72.80; H 5.42; N 14.32. $C_{12}H_{10}N_2O$. Calculated, %: C 72.71; H 5.08; N 14.13. *M* 198.22.

***N′*-Hydroxy-5-(2,5-dimethylphenyl)-1,2-oxazole-3-carboximidamide (III).** Hydroxylamine hydrochloride, 0.36 g (5.2 mmol), was added to a solution of 0.29 g (5.2 mmol) of potassium hydroxide in 20 ml of methanol, the mixture was stirred for 0.5 h at 30°C, 1.0 g (5 mmol) of nitrile **II** was added in one portion, and the mixture was stirred for 1 h. It was then poured into water, and the precipitate was filtered off, washed with water, dried under reduced pressure, and recrystallized from chloroform–hexane (6:1). Yield 1.13 g (97%), mp 172–174°C. IR spectrum, ν, cm^{-1}: 3475, 3343 (OH, NH_2); 1650, 1579, 1504 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.35 s (3H, Me), 2.44 s (3H, Me), 5.60 br.s (2H, NH_2), 6.74 s (4-H), 7.21 d (1H, H_{arom}, ^3J = 8 Hz), 7.25 d (1H, H_{arom}, ^3J = 8 Hz), 7.55 s (1H, H_{arom}), 9.52 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 20.02 (Me), 20.16 (Me), 100.00 (C^4), 128.83 (CH_{arom}), 131.07 (CH_{arom}), 131.47 (CH_{arom}), 126.58, 133.20, 135.98, 144.52, 157.86, 170.02. Mass spectrum: *m*/*z* 198 $[M - NH_2OH]^+$. Found, %: C 62.76; H 6.11; N 18.02. $C_{12}H_{13}N_3O_2$. Calculated, %: C 62.32; H 5.67; N 18.17. *M* 231.54.

***N′*-Acetoxy-5-(2,5-dimethylphenyl)-1,2-oxazole-3-carboximidamide (IV).** Acetyl chloride, 0.39 g (5 mmol), was added in one portion to a suspension of 1.16 g (5 mmol) of amide oxime **III** in 50 ml of anhydrous diethyl ether, and a solution of 0.41 g (5.2 mmol) of pyridine in 5 ml of anhydrous diethyl ether was then added dropwise under stirring. The mixture was heated for 3 h under reflux, and the precipitate was filtered off, washed with water and diethyl ether, and dried under reduced pressure. Yield 1.16 g (85%), mp 140–141°C. IR spectrum, ν, cm^{-1}: 3320 (N–H); 1736 (C=O); 1503, 1637, 1599, 1577 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.27 s (3H, MeCO), 2.37 s (3H, Me), 2.48 s (3H, Me), 5.59 br.s (2H, NH_2), 6.90 s (1H, 4-H), 7.18 d (1H, H_{arom}, ^3J = 8 Hz), 7.20 d (1H, H_{arom}, ^3J = 8 Hz), 7.55 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 19.92 (**Me**CO), 21.01 (Me), 21.18 (Me), 100.48 (C^4), 129.06 (CH_{arom}), 131.42 (CH_{arom}), 131.55 (CH_{arom}), 126.10, 133.46, 136.06, 148.45, 156.02, 168.24, 171.54 (C=O). Mass spectrum: *m*/*z* 255 $[M - H_2O]^+$. Found, %: C 61.84; H 5.67; N 15.65. $C_{14}H_{15}N_3O_3$. Calculated, %: C 61.52; H 5.53; N 15.38. *M* 273.29.

Compounds **V** and **VI** were synthesized in a similar way by acylation of amide oxime **III** with the corresponding acid chlorides.

5-(2,5-Dimethylphenyl)-*N′*-(3,4,4-trichlorobut-3-enoyloxy)-1,2-oxazole-3-carboximidamide (V). Yield 80%, mp 138–139°C. IR spectrum, ν, cm^{-1}: 3325 (N–H); 1770 (C=O); 1641, 1595, 1570, 1505 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.38 s (3H, Me), 2.48 s (3H, Me), 3.89 s (2H, CH_2), 5.61 br.s (2H, NH_2), 6.90 s (1H, 4-H), 7.19 d (1H, H_{arom}, ^3J = 8 Hz), 7.21 d (1H, H_{arom}, ^3J = 8 Hz), 7.55 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.02 (Me), 21.18 (Me), 41.32 (CH_2), 100.42 (C^4), 129.07 (CH_{arom}), 131.50 (CH_{arom}), 131.58 (CH_{arom}), 122.25, 124.40, 126.01, 133.48, 136.12, 149.15, 155.63, 164.41, 171.73 (C=O). Mass spectrum: *m*/*z* 383 (^{35}Cl) $[M - H_2O]^+$. Found, %: C 48.18; H 3.77; Cl 26.61; N 10.15. $C_{16}H_{14}Cl_3N_3O_3$. Calculated, %: C 47.72; H 3.50; Cl 26.41; N 10.44. *M* 402.65.

***N′*-(4,5-Dichloro-1,2-thiazol-3-ylcarbonyloxy)-5-(2,5-dimethylphenyl)-1,2-oxazole-3-carboximidamide (VI).** Yield 87%, mp 159–160°C. IR spectrum,

ν, cm^{-1}: 3302 (N–H); 1760 (C=O); 1632, 1589, 1567, 1510 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.39 s (3H, Me), 2.50 s (3H, Me), 5.83 br.s (2H, NH_2), 6.98 s (1H, 4-H), 7.20 d (1H, H_{arom}, ^3J = 8 Hz), 7.23 d (1H, H_{arom}, ^3J = 8 Hz), 7.57 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.03 (Me), 21.23 (Me), 100.60 (C^4), 129.07 (CH_{arom}), 131.50 (CH_{arom}), 131.58 (CH_{arom}), 125.69, 126.02, 133.51, 136.10, 150.10, 151.10, 153.48, 155.61, 156.06, 171.76 (C=O). Mass spectrum: *m*/*z* 392 (^{35}Cl) $[M - H_2O]^+$. Found, %: C 46.52; H 3.17; Cl 17.56; N 13.88; S 8.07. $C_{16}H_{12}Cl_2N_4O_3S$. Calculated, %: C 46.73; H 2.94; Cl 17.24; N 13.63; S 7.80. *M* 411.26.

3-[5-(2,5-Dimethylphenyl)-1,2-oxazol-3-yl]-5-methyl-1,2,4-oxadiazole (VII). A solution of 1.37 g (5 mmol) of compound **IV** in 20 ml of glacial acetic acid was heated for 6 h under reflux. The mixture was then poured into 200 ml of water and neutralized to pH ~7 with a solution of potassium hydroxide. The precipitate was filtered off, washed with water, dried under reduced pressure, and recrystallized from ethanol. Yield 1.23 g (96%), mp 93–95°C. IR spectrum, ν, cm^{-1}: 1589, 1580, 1567, 1507 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.40 s (3H, Me), 2.52 s (3H, Me), 2.74 s (3H, Me), 6.95 s (1H, 4-H), 7.20 d (1H, H_{arom}, ^3J = 8 Hz), 7.22 d (1H, H_{arom}, ^3J = 8 Hz), 7.63 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.56 (Me), 21.03 (Me), 21.18 (Me), 101.48 (C^4), 129.15 (CH_{arom}), 131.50 (CH_{arom}), 131.57 (CH_{arom}), 126.05, 133.41, 136.15, 152.86, 161.76, 171.81, 177.91. Mass spectrum: *m*/*z* 255 $[M]^+$. Found, %: C 65.73; H 5.35; N 16.34. $C_{14}H_{13}N_3O_2$. Calculated, %: C 65.87; H 5.13; N 16.46. *M* 255.27.

Compounds **VIII** and **IX** were synthesized in a similar way.

3-[5-(2,5-Dimethylphenyl)-1,2-oxazol-3-yl]-5-(2,3,3-trichloroprop-2-en-1-yl)-1,2,4-oxadiazole (VIII). Yield 94%, mp 89–91°C. IR spectrum, ν, cm^{-1}: 1607, 1581, 1552, 1505 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.40 s (3H, Me), 2.52 s (3H, Me), 4.37 s (2H, CH_2), 6.97 s (1H, 4-H), 7.22 d (1H, H_{arom}, ^3J = 8 Hz), 7.23 d (1H, H_{arom}, ^3J = 8 Hz), 7.63 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.03 (Me), 21.19 (Me), 34.27 (Me), 101.57 (C^4), 129.17 (CH_{arom}), 131.60 ($2CH_{arom}$), 123.22, 123.59, 125.96, 133.47, 136.18, 152.53, 162.10, 172.05, 175.08. Mass spectrum: *m*/*z* 383 (^{35}Cl) $[M]^+$. Found, %: C 49.68; H 3.44; Cl 27.43; N 10.59. $C_{16}H_{12}Cl_3N_3O_2$. Calculated, %: C 49.96; H 3.14; Cl 27.65; N 10.93. *M* 384.62.

5-(4,5-Dichloro-1,2-thiazol-3-yl)-3-[5-(2,5-dimethylphenyl)-1,2-oxazol-3-yl]-1,2,4-oxadiazole (IX). Yield 91%, mp 177–179°C. IR spectrum, ν, cm^{-1}: 1593, 1587, 1573, 1545, 1488 (C=C, C=N). ^1H NMR spectrum, δ, ppm: 2.41 s (3H, Me), 2.54 s (3H, Me), 2.74 s (3H, Me), 6.95 s (1H, 4-H), 7.23 d (1H, H_{arom}, ^3J = 8 Hz), 7.24 d (1H, H_{arom}, ^3J = 8 Hz), 7.63 s (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.04 (Me), 21.21 (Me), 101.89 (CH), 129.18 (CH_{arom}), 131.62 ($2CH_{arom}$), 125.61, 125.94, 133.50, 136.20, 148.75, 151.93, 152.43, 162.37, 169.37, 172.16. Mass spectrum: *m*/*z* 392 (^{35}Cl) $[M]^+$. Found, %: C 48.98; H 2.77; Cl 18.27; N 14.57; S 8.25. $C_{16}H_{10}Cl_2N_4O_2S$. Calculated, %: C 48.87; H 2.56; Cl 18.03; N 14.25; S 8.15. *M* 393.24.

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