A convenient synthesis of 3-substituted 5-guanidino-1,2,4-oxadiazoles

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The reaction of amidoximes with cyanoguanidine in the presence of Lewis acids affords 3-substituted 5-guanidino-1,2,4-oxadiazoles. A study of the reaction of ^{15}N-labeled chloroacetamidoxime with cyanoguanidine showed that the formation of the oxadiazole ring occurs *via* the elimination of the amino group from the amidoxime fragment. 1,2,4-Oxadiazoles bearing the imidazole or pyrimidine moiety were synthesized.

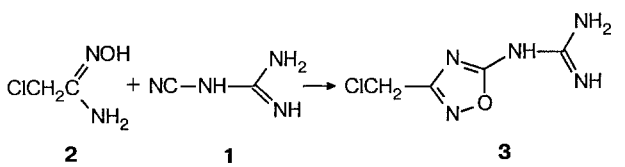
Key words: amidoximes, cyanoguanidine, 1,2,4-oxadiazoles.

It is known that 3-substituted 5-guanidino-1,2,4-oxadiazoles possess biological activity.[1,2] The guanidine moiety can also be transformed to various heterocycles such as pyrimidine,[3] 1,2,4-oxadiazole,[4] imidazole,[5] and others. However, the procedures reported for the preparation of 3-substituted 5-guanidino-1,2,4-oxadiazoles have several drawbacks. For example, the reaction of cyanoguanidine with nitrile oxides is thought to be a convenient approach[6] for synthesizing 5-guanidino-1,2,4-oxadiazoles, although nitrile oxides with the required functional groups are not always available. A method is also known which consists of the treatment of amidoximes with trichloroacetic anhydride or chloride followed by the replacement of the trichloromethyl group in 1,2,4-oxadiazole by a guanidine group.[7] However, this method is used rather rarely since the overall yield generally does not exceed 40 %.

The reaction of amidoximes with *N,N*-dialkylcyanamides under high pressure has also been reported.[8] The formation of 5-dialkylguanidino-1,2,4-oxadiazoles proceeds rather smoothly in this case. However, no information is provided in ref. 8 about whether 1,2,4-oxadiazoles with an unsubstituted guanidine moiety can be obtained by this method.

The possibility of synthesizing 3-substituted 5-guanidino-1,2,4-oxadiazoles by treatment of amidoximes with the available cyanoguanidine (**1**) was studied in the present paper.

The conditions of the reaction between amidoximes and cyanoguanidine (**1**) were studied using chloroacetamidoxime (**2**) as an example.



2 **1** **3**

This choice was made due to the fact that 3-chloromethyl-5-guanidino-1,2,4-oxadiazole (**3**) is the starting compound in the syntheses of a number of biologically active compounds.[1]

The only method known for obtaining compound **3** involves the treatment of the iminoester of cyanoguanidine with chloroacetamidoxime. However, the yield of compound **3** was not reported. When we reproduced the procedure, compound **3** was obtained in a yield not exceeding 10 %.

We found that 3-chloromethyl-5-guanidino-1,2,4-oxadiazole **3** is not formed even when cyanoguanidine **1** is refluxed for a long time with chloroacetamidoxime **2** in various solvents. We assumed on the basis of our previous studies[9] that this reaction could be accelerated with the use of Lewis acids ($ZnCl_2$, $AlCl_3$, $SnCl_4$), either in the pure form or in combination with hydrogen halides. It turned out that refluxing **1** and **2** in ethyl acetate in the presence of Lewis acids results in the formation of oxadiazole **3** in 35—62 % yield. Combining Lewis acids with HCl generally results in increased yields of **3** and decreased reaction time (see Table 1). The highest yield of **3** was achieved when a combination of $ZnCl_2$ with HCl in ethyl acetate was used. When the latter was

Table 1. Effect of the Lewis acid used and the presence of HCl on the yield of 3-chloromethyl-5-guanidino-1,2,4-oxadiazole (**3**)

Lewis acid	HCl	Reaction time/h	Yield **3** (%)
$ZnCl_2$	—	6	35
$ZnCl_2$	+	1.5	80
$AlCl_3$	—	6	45
$AlCl_3$	+	2.5	55
$SnCl_4$	—	5	62
$SnCl_4$	+	2.5	60

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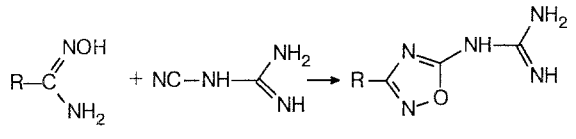
Table 2. Effect of the solvent on the yield of 3-chloromethyl-5-guanidino-1,2,4-oxadiazole (**3**)

Solvent	*T*/°C	Time/h	Yield of **3** (%)
EtOAc	77	1.5	80
BuOAc	60	0.5	60
BuOAc	120	0.5	65
O_2NPh	60	10	35
O_2NPh	120	10	40
DMSO	60	6	20
DMSO	120	6	—
Acetone	56	10	—
$CHCl_3$	61	10	—

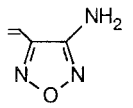
replaced by other solvents, the yield of **3** decreased (Table 2).

The selected catalytic system and solvent were successfully used in reactions of **1** with other amidoximes. The yields of the respective 5-guanidino-1,2,4-oxadiazoles (**5a—c**) were from 58 to 69 %.

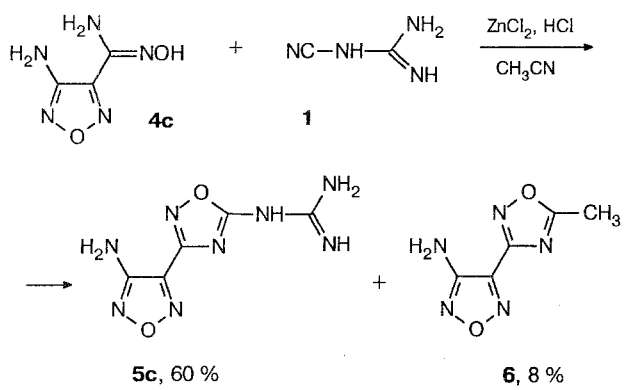


4a—c **1** **5a—c**

4a, 5a: R = Me; **4b, 5b:** R = CH_2CN; **4c, 5c:** R =

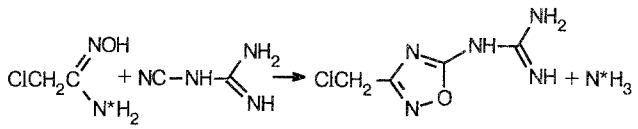


Cyanoguanidine undergoes the reaction with amidoximes more readily than organic nitriles used previously, which almost do not react with amidoximes in the presence of Lewis acids without HCl, and normally require higher temperatures.[9] Moreover, we found that the treatment of compound **1** with **4c** in acetonitrile affords mainly 5-guanidino-1,2,4-oxadiazole (**5c**, yield 60 %) rather than the product of the reaction of **1** with acetonitrile, *viz.*, 3-aminofurazanyl-5-methyl-1,2,4-oxadiazole (**6**, yield 8 %).



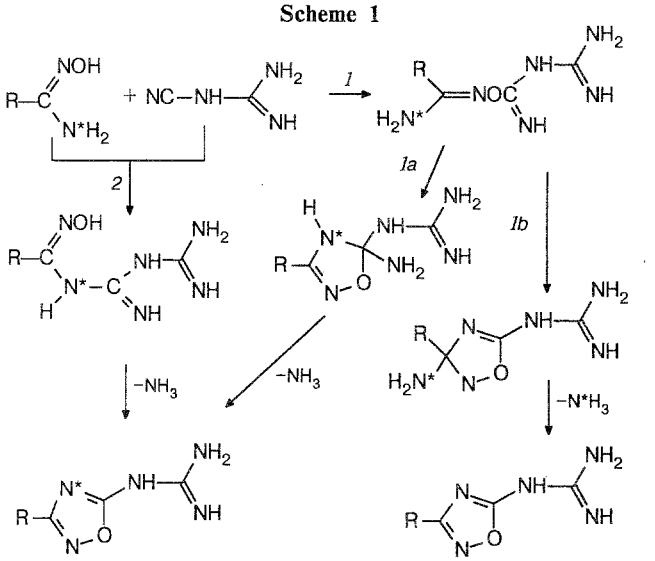
4c **1** **5c**, 60 % **6**, 8 %

The study of the reaction of compound **1** with ^{15}N-labeled chloroacetamidoxime **2** showed that the formation of the oxadiazolyl ring proceeds *via* abstraction of the amino group from the amidoxime moiety.



The content of the label in compound **3** was determined by mass spectrometry. It was found that oxadiazole **3** did not contain the ^{15}N isotope. The results obtained imply that of the three possible pathways of this reaction, *viz.*, *1a*, *1b*, and *2*, route *1b* is realized, *i.e.*, the only one involving the abstraction of the amino group from the amidoxime moiety during ring formation (Scheme 1) is the one that occurs.

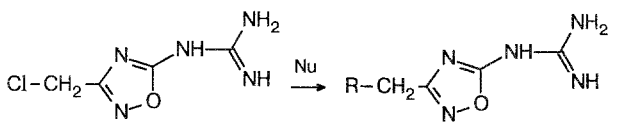
Scheme 1



We have reported previously[9] that the reaction of amidoximes with carbonitriles also involves the abstraction of the amino group from the amidoxime moiety.

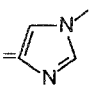
As was already mentioned above, 3-substituted 5-guanidino-1,2,4-oxadiazoles find use as biologically active compounds. Therefore, we studied different approaches to their synthesis.

It was shown that the chlorine atom in compound **3** is replaced through the action of some nucleophiles such as the cyanide anion or diethylamine. The reaction proceeds under the conditions of phase transfer catalysis. A heterocyclic moiety, *e.g.*, imidazolyl, can also be introduced this way into the molecule:

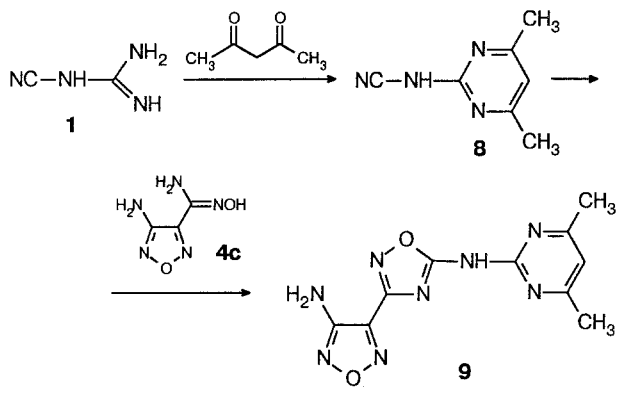


3 **5b, 7a,b**

5b: R = NC–; **7a:** R = Et_2N–; **7b:** R =



Scheme 2



The reaction of 2-cyanamino-4,6-dimethylpyrimidine (**8**), obtained from cyanoguanidine **1** and acetylacetone,[10] with compound **4c** in the presence of $ZnCl_2$ and HCl in ethyl acetate gives 3-aminofurazanyl-5-*N*-(4,6-dimethyl-2-pyrimidinyl)amino-1,2,4-oxadiazole (**9**) (Scheme 2).

Compound **9** was also obtained by an independent synthesis from compound **5c** and acetylacetone.

Experimental

IR spectra were obtained on a UR-20 spectrophotometer in thin layers or in KBr pellets. ^1H NMR spectra were recorded on a Tesla BS 467 spectrometer (60 MHz) in deuteroacetone relative to HMDS. Mass spectra were recorded on a Varian CH-6 instrument with direct sample introduction into the ionization cell; the ionization energy was 70 eV, and the controlling voltage was 1.75 kV. The solvents were dried and distilled. Anhydrous Lewis acids were used. Amidoximes were prepared by the known procedures.[11]

I. Reaction of cyanoguanidine 1 with chloracetamidoxime 2 (general procedure).

1. Reaction of 1 and 2 in the presence of Lewis acids. Cyanoguanidine **1** (3 mmol), chloracetamidoxime **2** (3 mmol), and a Lewis acid (3 mmol) were dissolved in ethyl acetate (10 mL). The mixture was refluxed and then cooled to ~20 °C. Water (3 mL) was added, the organic layer was separated, and the aqueous layer was neutralized with a $NaHCO_3$ solution to pH 7 and extracted with hot ethyl acetate (3 × 6 mL). The combined extract was dried with $MgSO_4$, the solvent was distilled off *in vacuo*, and the residue was crystallized from water.

a. $ZnCl_2$ was used as the Lewis acid, the reaction time was 6 h. The yield of 3-chloromethyl-5-guanidino-1,2,4-oxadiazole **3** was 0.184 g (35 %), m.p. 185—186 °C (ref. 1: 164—166 °C). Found (%): C, 27.46; H, 3.58; Cl, 20.42; N, 40.08. $C_4H_6ClN_5O$. Calculated (%): C, 27.35; H, 3.41; Cl, 20.22; N, 39.88. ^1H NMR, δ: 4.51 (s, 2 H); 7.11 (br.s, 4 H). MS, *m/z*: 175 (177) $[M]^+$.

b. $AlCl_3$ as the Lewis acid, reaction time 6 h. The yield of product **3** was 0.237 g (45 %).

c. $SnCl_4$ as the Lewis acid, reaction time 5 h. The yield of product **3** was 0.326 g (62 %).

2. The reaction of 1 with 2 in the presence of a Lewis acid and HCl. The reaction was carried out as described above, but gaseous HCl (3 mmol) was passed through the mixture before heating.

a. $ZnCl_2$ as the Lewis acid, reaction time 1.5 h. The yield of **3** was 0.421 g (80 %).

b. $AlCl_3$ as the Lewis acid, reaction time 2.5 h. The yield of **3** was 0.289 g (55 %).

c. $SnCl_4$ as the Lewis acid, reaction time 2.5 h. The yield of **3** was 0.315 g (60 %).

II. Synthesis of 3-substituted 5-guanidino-1,2,4-oxadiazoles by treatment of amidoximes with cyanoguanidine

These compounds were obtained by procedure I.2.*a* in ethyl acetate.

3-Methyl-5-guanidino-1,2,4-oxadiazole (5a). Reagents: acetamidoxime **4a** and cyanoguanidine **1**, reaction time 4 h. The yield of compound **5a** was 0.245 g (58 %), m.p. 260 °C (from CH_3CN) (ref. 12: 260 °C). ^1H NMR, δ: 2.28 (s, 3 H); 7.22 (br.s, 4 H). MS, *m/z*: 141 $[M]^+$.

3-Cyanomethyl-5-guanidino-1,2,4-oxadiazole (5b). Reagents: **4b** and **1**, reaction time 1.5 h. The yield of compound **5b** was 0.344 g (69 %), m.p. 203—205 °C (from water). Found (%): C, 36.4; H, 3.7; N, 50.9. $C_5H_6N_6O$. Calculated (%): C, 36.2; H, 3.6; N, 50.6. ^1H NMR, δ: 4.11 (s, 2 H); 7.25 (br.s, 4 H). MS, *m/z*: 166 $[M]^+$.

3-Aminofurazanyl-5-guanidino-1,2,4-oxadiazole (5c).

a. Reagents: **4c** and **1**, reaction time 3 h. The yield of **5c** was 0.41 g (65 %), m.p. 271—272 °C (from CH_3COOH). Found (%): C, 28.7; H, 2.9; N, 53.8. $C_5H_6N_8O_2$. Calculated (%): C, 28.6; H, 2.9; N, 53.3. ^1H NMR, δ: 6.36 (s, 2 H); 7.20 (br.s, 4 H). MS, *m/z*: 210 $[M]^+$.

b. The procedure was similar to that described above, but acetonitrile in the molar ratio **1** : CH_3CN = 1 : 50 was used as the solvent. After the solvent was removed, the residue was purified by TLC (silica gel, ethyl acetate : chloroform = 5 : 1). The yield of compound **5c** was 0.378 g (60 %), and that of 3-aminofurazanyl-5-methyl-1,2,4-oxadiazole **6** (m.p. 166 °C from benzene) was 0.04 g (8 %). Found (%): C, 35.8; H, 2.9; N, 41.9. $C_5H_5N_5O_2$. Calculated (%): C, 35.9; H, 3.0; N, 41.9.

III. Reaction of 3-chloromethyl-5-guanidino-1,2,4-oxadiazole (3) with nucleophiles under the conditions of phase transfer catalysis (general procedure)

$NaHCO_3$ (0.168 g, 2 mmol), Et_4NBr (0.005 g), BuOAc (10 mL), and the respective nucleophile (2 mmol) were added to a suspension of chloromethyloxadiazole **3** (0.351 g, 2 mmol) in water (10 mL). The mixture was boiled and cooled, the solvent was distilled off, and the precipitate was recrystallized from water.

3-Cyanomethyl-5-guanidino-1,2,4-oxadiazole (5b). KCN was used as the nucleophile, reaction time 1.5 h. The yield of compound **5b** was 0.24 g (72 %), m.p. 203—205 °C.

3-Diethylaminomethyl-5-guanidino-1,2,4-oxadiazole (7a). Diethylamine was used as the nucleophile, reaction time 1 h. The yield of compound **7a** was 0.32 g (76 %), m.p. 251—252 °C (from water). Found (%): C, 44.5; H, 7.5; N, 39.5. $C_8H_{16}N_6O$. Calculated (%): C, 45.3; H, 7.5; N, 39.6. MS, *m/z*: 212 $[M]^+$.

1-Imidazolyl-(5-guanidino-1,2,4-oxadiazolyl-3)methane (7b). Imidazole was used as the nucleophile, reaction time 5 h. The yield of compound **7b** was 0.294 g (71 %), m.p. 230—231 °C (from water). Found (%): C, 40.2; H, 4.4;

N, 47.0. $C_7H_9N_7O$. Calculated (%): C, 40.6; H, 4.3; N, 47.3. MS, *m/z*: 207 $[M]^+$.

IV. Synthesis of 3-aminofurazanyl-5-(4,6-dimethylpyrimidinyl-2-amino)-1,2,4-oxadiazole (9)

a. Acetylacetone (0.5 g, 5 mmol) and 10 % aqueous NaOH (2 mL) were added to a suspension of compound **5c** (1.05 g, 5 mmol) in water (10 mL). The mixture was refluxed for 6 h and then cooled. The resulting precipitate was filtered off and recrystallized from DMF to give 1 g of compound **9** (74 %), m.p. 274—275 °C. Found (%): C, 43.7; H, 3.8; N, 40.8. $C_{10}H_{10}N_8O$. Calculated (%): C, 43.8; H, 3.7; N, 40.9. ^{1}H NMR, δ: 2.32 (s, 7 H); 6.38 (s, 2 H); 6.91 (s, 1 H).

b. 2-Cyanamino-4,6-dimethylpyrimidine **8** (0.45 g, 3 mmol) and $ZnCl_2$ (0.8 g, 6 mmol) were added to a suspension of compound **4c** (0.43 g, 3 mmol) in ethyl acetate (10 mL), and the mixture was saturated with HCl (3 mmol). The reaction mixture was refluxed for 3 h and cooled. The resulting precipitate was filtered off, washed with water, and recrystallized from DMF to give 0.55 g of compound **9** (67 %), m.p. 274—275 °C.

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