Synthesis of 3-carbamoyl-1,2,4-oxadiazoles

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A convenient method for the synthesis of 3-carbamoyl-1,2,4-oxadiazoles from carbamoylamidoximes and chlorides or anhydrides of haloacetic acids was developed. The reactions of 3-carbamoyl-5-trichloromethyl-1,2,4-oxadiazoles with amines and *N*,*N*-dimethylhydrazine were studied.

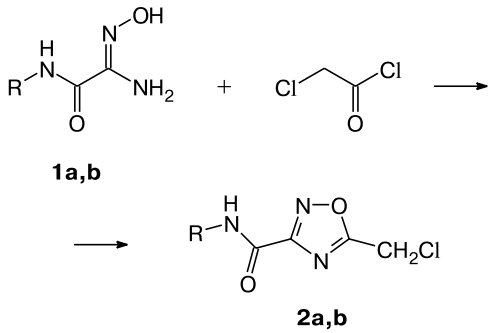
Key words: amidoximes, 1,2,4-oxadiazoles, acid chlorides, trifluoroacetic anhydride.

1,2,4-Oxadiazole derivatives manifest a wide spectrum of biological activity.[1] The synthesis of 3-carbamoyl-1,2,4-oxadiazoles, which are of interest as herbicides,[2,3] has attracted considerable attention in the recent time. However, the available methods for the synthesis of these heterocycles are multistep, based on the use of unavailable compounds, and have several other disadvantages.[1—3]

In this work we studied the reactions of presently available carbamoylamidoximes[4] with chloroacetyl chlorides to develop a simple method for the synthesis of 3-carbomoyl-1,2,4-oxadiazoles.

The reactions of carbamoylamidoximes **1a,b** with monochloroacetyl chloride were primarily studied (Scheme 1).

Scheme 1

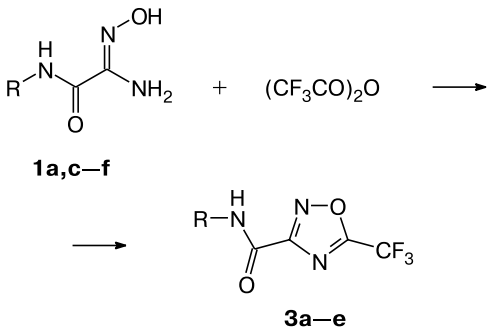


R = Ph (**a**), Bn (**b**)

The solvent and temperature effects on heterocyclization were studied. It turned out that 1,2,4-oxadiazoles were not formed on boiling of the corresponding amidoximes with chloroacetyl chloride in ethyl acetate or butyl acetate. Oxadiazoles **2a,b** were isolated in satisfactory yields only upon many-hour boiling in amyl acetate. Oily products were formed along with target oxadiazoles and hampered to isolate the latter. The drastic conditions of the reaction are likely related to the deactivation of the amidoxime fragment by the electron-withdrawing carbamoyl group. It could be expected that the introduction of strong electron-withdrawing substituents into acid chloride or acid anhydride would favor heterocyclization enhancing the electrophilicity of the carbon atom of the C=O group.[5]

Indeed, the reaction of carbamoylamidoximes **1a,c—f** with trifluoroacetic anhydride affords successively 5-trifluoromethyl-1,2,4-oxadiazole-3-carbamides **3a—e** (Scheme 2).

Scheme 2



R = Ph (**1a**, **3a**); *p*-ClC_6H_4 (**1c**, **3b**); *p*-$MeOC_6H_4$ (**1d**, **3c**); *p*-$O_2NC_6H_4$ (**1e**, **3d**); *p*-$H_2NSO_2C_6H_4$ (**1f**, **3e**)

When carbamoylamidoximes **1** are treated with dichloro- and trichloroacetyl chlorides, the corresponding 1,2,4-oxadiazoles **4** and **5** are smoothly formed (Scheme 3).

The 5-trichloromethyl group in the series of 1,2,4-oxadiazoles is known[6] to be substituted under the action of

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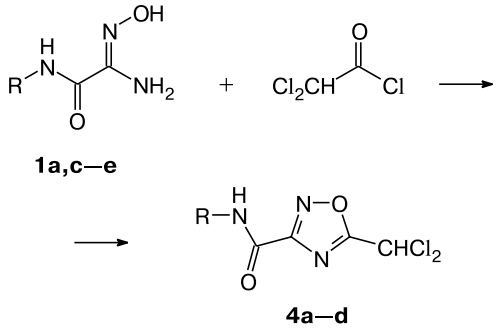
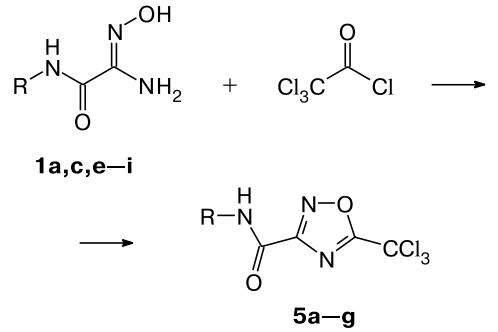
Scheme 3



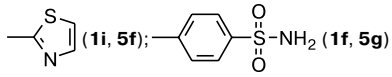
1a,c—e **4a—d**

4: R = Ph (**a**); 4-ClC_6H_4 (**b**); 4-$MeOC_6H_4$ (**c**); 4-$NO_2C_6H_4$ (**d**)



1a,c,e—i **5a—g**

R = Ph (**1a**, **5a**); 3,4-$Cl_2C_6H_3$ (**1g**, **5b**); 4-ClC_6H_4 (**1c**, **5c**); 4-$NO_2C_6H_4$ (**1e**, **5d**); 2,3-$Me_2C_6H_3$ (**1h**, **5e**);


(**1i**, **5f**); —SO_2NH_2 (**1f**, **5g**)

various nucleophiles. The reactions of oxadiazoles **5** with amines also afford the corresponding amino derivatives **6** in high yields (Scheme 4).

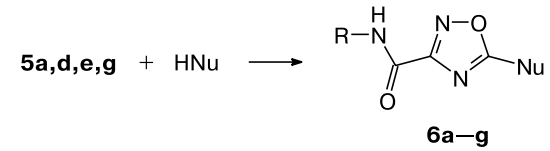
We have also found that the reaction of dimethylhydrazine with compounds **5** involves reductive condensation to form hydrazones **7**. Product **7a** is also formed in the reaction of dichloride **4a** with dimethylhydrazine (Scheme 5).

Thus, we proposed the convenient method for the synthesis of carbamoyl-1,2,4-oxadiazoles from available compounds.

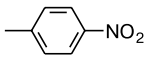
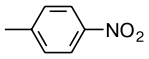
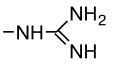
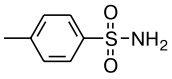
Experimental

IR spectra were obtained on a Specord IR-80 spectrophotometer in pellets with KBr. ^{1}H NMR spectra were recorded on a Bruker WM-250 instrument (250 MHz) in $(CD_3)_2SO$. Mass spectra (EI) were recorded on Varian MAT CH-6 and Kratos MS-30 instruments with the direct injection of a sample into an ion source, an ionizing voltage of 70 eV, and an emission current of 0.1 mA. Melting points (were not corrected) were determined on a Boetius heating stage. All reaction mixtures were analyzed and purity of isolated products was monitored by TLC on Silufol

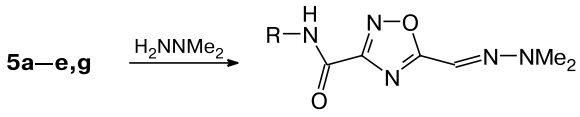
Scheme 4



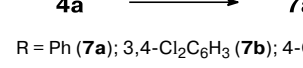
6a—g

6	—R	—Nu
a	—Ph	
b		
c		
d		
e		
f	—Ph	
g		

Scheme 5



7a—f



7a

R = Ph (**7a**); 3,4-$Cl_2C_6H_3$ (**7b**); 4-ClC_6H_4 (**7c**); 4-$NO_2C_6H_4$ (**7d**);

2,3-$Me_2C_6H_3$ (**7e**); —SO_2NH_2 (**7f**)

UV-254 plates using an EtOAc—hexane (1 : 1 vol/vol) mixture as the eluent. Before use, amyl acetate was dried above $MgSO_4$ and distilled.

Synthesis of 3-carbamoyl-1,2,4-oxadiazoles by the reaction of carbamoylamidoximes with acid chlorides (general procedure). Anhydrous Na_2CO_3 (1 mmol) and the corresponding acid chloride ($Cl_{3-n}H_nCOCl$) (2 mmol) or $(CF_3CO)_2O$ (for the synthesis of oxadiazoles **3**) (2 mmol) were added to a solution of amidoxime[4] (1 mmol) in amyl acetate (5 mL). The mixture was boiled with a reflux condenser equipped with a calcium chloride tube (TLC monitoring). The solution cooled to ~20 °C was washed with water (3×30 mL), the organic layer was dried above $MgSO_4$, the solvent was evaporated in a vacuum of a rotary evaporator, and the residue was recrystallized. Compounds **2a,b**, **3a—e**, **4a—d**, and **5a—g** were obtained by this method.

***N*-Phenyl-5-chloromethyl-1,2,4-oxadiazolyl-3-carboxamide (2a)** was obtained from amidoxime **1a** and $ClCH_2COCl$ by refluxing for 7 h in 60% yield (0.14 g), m.p. 89—91 °C (from

toluene). Found (%): C, 50.85; H, 3.53; Cl, 14.83; N, 17.49. $C_{10}H_8ClN_3O_2$. Calculated (%): C, 50.63; H, 3.39; Cl, 14.75; N, 17.68. ^{1}H NMR, δ: 5.20 (s, 2 H, CH_2Cl); 7.20 (t, 1 H, H_{arom}, J = 7.3 Hz); 7.35 (m, 2 H, H_{arom}); 7.75 (d, 2 H, H_{arom}, J = 8.0 Hz); 10.85 (s, 1 H, NH). MS, m/z: 237, 239 $[M]^+$.

***N*-Benzyl-5-chloromethyl-1,2,4-oxadiazolyl-3-carboxamide (2b)** was synthesized from amidoxime **1b** and $ClCH_2COCl$, the duration of refluxing was 7 h, 67% yield (0.16 g), m.p. 73—75 °C (from toluene). Found (%): C, 52.43; H, 3.75; Cl, 14.15; N, 16.70. $C_{11}H_{10}ClN_3O_2$. Calculated (%): C, 52.49; H, 3.98; Cl, 14.12; N, 16.69. ^{1}H NMR, δ: 4.40 (m, 2 H, CH_2Ph); 5.15 (s, 2 H, CH_2Cl); 7.20—7.40 (m, 5 H, H_{arom}); 9.50 (s, 1 H, NH). MS, m/z: 251, 253 $[M]^+$.

***N*-Phenyl-5-trifluoromethyl-1,2,4-oxadiazolyl-3-carboxamide (3a)** was synthesized from amidoxime **1a** and trifluoroacetic anhydride, the duration of refluxing was 90 min, 62% yield (0.18 g), m.p. 155—157 °C (from toluene). Found (%): C, 46.57; H, 2.28; N, 16.45. $C_{10}H_6F_3N_3O_2$. Calculated (%): C, 46.69; H, 2.33; N, 16.34. ^{1}H NMR, δ: 7.20 (t, 1 H, H_{arom}, J = 7.2 Hz); 7.40 (m, 2 H, H_{arom}); 7.80 (d, 2 H, H_{arom}, J = 8.1 Hz); 11.10 (s, 1 H, NH). MS, m/z: 257 $[M]^+$.

***N*-(4-Chlorophenyl)-5-trifluoromethyl-1,2,4-oxadiazolyl-3-carboxamide (3b)** was synthesized from amidoxime **1c** and trifluoroacetic anhydride by refluxing for 90 min in 52% yield (0.15 g), m.p. 164—166 °C (from toluene). Found (%): C, 41.20; H, 1.75; N, 14.35. $C_{10}H_5ClF_3N_3O_2$. Calculated (%): C, 41.16; H, 1.71; N, 14.41. ^{1}H NMR, δ: 7.85 (d, 2 H, H_{arom}, J = 8.7 Hz); 8.35 (d, 2 H, H_{arom}, J = 8.7 Hz); 10.55 (s, 1 H, NH). MS, m/z: 291, 293 $[M]^+$.

***N*-(4-Methoxyphenyl)-5-trifluoromethyl-1,2,4-oxadiazolyl-3-carboxamide (3c)** was synthesized from amidoxime **1d** and trifluoroacetic anhydride by refluxing for 60 min in 78% yield (0.11 g), m.p. 168—171 °C (from toluene). Found (%): C, 46.17; H, 2.78; N, 14.45. $C_{11}H_8F_3N_3O_3$. Calculated (%): C, 46.00; H, 2.81; N, 14.63. ^{1}H NMR, δ: 3.80 (s, 3 H, OMe); 6.55 (dd, 2 H, H_{arom}); 7.70 (dd, 2 H, H_{arom}); 10.95 (s, 1 H, NH). MS, m/z: 287 $[M]^+$.

***N*-(4-Nitrophenyl)-5-trifluoromethyl-1,2,4-oxadiazolyl-3-carboxamide (3d)** was synthesized from amidoxime **1e** and trifluoroacetic anhydride by refluxing for 90 min in 47% yield (0.14 g), m.p. 142—144 °C (from toluene). Found (%): C, 39.87; H, 1.69; N, 18.45. $C_{10}H_5F_3N_4O_4$. Calculated (%): C, 39.74; H, 1.66; N, 18.54. ^{1}H NMR, δ: 8.05 (d, 2 H, H_{arom}, J = 9.0 Hz); 8.30 (d, 2 H, H_{arom}, J = 9.0 Hz); 11.55 (s, 1 H, NH). MS, m/z: 302 $[M]^+$.

***N*-(4-Aminosulfonylphenyl)-5-trifluoromethyl-1,2,4-oxadiazolyl-3-carboxamide (3e)** was synthesized from amidoxime **1f** and trifluoroacetic anhydride by refluxing for 90 min in 30% yield (0.04 g), m.p. 203—205 °C (from toluene). Found (%): C, 35.83; H, 2.16; N, 16.45. $C_{10}H_7F_3N_4O_4S$. Calculated (%): C, 35.72; H, 2.09; N, 16.66. ^{1}H NMR, δ: 8.05 (t, 2 H, H_{arom}); 8.30 (t, 2 H, H_{arom}); 11.55 (s, 1 H, NH). MS, m/z: 336 $[M]^+$.

***N*-Phenyl-5-dichloromethyl-1,2,4-oxadiazolyl-3-carboxamide (4a)** was synthesized from amidoxime **1a** and $Cl_2CHCOCl$ by refluxing for 5 h in 53% yield (0.14 g), m.p. 111—113 °C (from chloroform). Found (%): C, 44.19; H, 2.69; Cl, 26.14; N, 15.40. $C_{10}H_7Cl_2N_3O_2$. Calculated (%): C, 44.12; H, 2.57; Cl, 26.10; N, 15.44. ^{1}H NMR, δ: 7.20 (t, 1 H, H_{arom}, J = 7.3 Hz); 7.40 (m, 2 H, H_{arom}); 7.75 (d, 2 H, H_{arom}, J = 8.0 Hz); 8.00 (s, 1 H, $CHCl_2$); 10.90 (s, 1 H, NH). MS, m/z: 271, 273, 275 $[M]^+$.

***N*-(4-Chlorophenyl)-5-dichloromethyl-1,2,4-oxadiazolyl-3-carboxamide (4b)** was synthesized from amidoxime **1c** and $Cl_2CHCOCl$ by refluxing for 3.5 h in 62% yield (0.13 g), m.p. 159—162 °C (from toluene). Found (%): C, 39.12; H, 1.90; Cl, 34.70; N, 13.75. $C_{10}H_6Cl_3N_3O_2$. Calculated (%): C, 39.15; H, 1.96; Cl, 34.75; N, 13.70. ^{1}H NMR, δ: 7.45 (d, 2 H, H_{arom}, J = 8.7 Hz); 7.80 (d, 2 H, H_{arom}, J = 8.7 Hz); 8.05 (s, 1 H, $CHCl_2$); 11.10 (s, 1 H, NH). MS, m/z (for ^{35}Cl): 305 $[M]^+$.

***N*-(4-Methoxyphenyl)-5-dichloromethyl-1,2,4-oxadiazolyl-3-carboxamide (4c)** was synthesized from amidoxime **1d** and $Cl_2CHCOCl$ by refluxing for 3.5 h in 60% yield (0.18 g), m.p. 144—146 °C (from toluene). Found (%): C, 43.63; H, 2.90; Cl, 23.53; N, 13.95. $C_{11}H_9Cl_2N_3O_3$. Calculated (%): C, 43.71; H, 2.98; Cl, 23.51; N, 13.91. ^{1}H NMR, δ: 3.75 (s, 3 H, OMe); 6.95 (d, 2 H, H_{arom}, J = 8.8 Hz); 7.70 (d, 2 H, H_{arom}, J = 8.8 Hz); 8.05 (s, 1 H, $CHCl_2$); 10.85 (s, 1 H, NH). MS, m/z: 301, 303, 305 $[M]^+$.

***N*-(4-Nitrophenyl)-5-dichloromethyl-1,2,4-oxadiazolyl-3-carboxamide (4d)** was synthesized from amidoxime **1e** and $Cl_2CHCOCl$ by refluxing for 3.5 h in 49% yield (0.11 g), m.p. 164—166 °C (from toluene). Found (%): C, 37.87; H, 1.86; Cl, 22.38; N, 17.55. $C_{10}H_6Cl_2N_4O_4$. Calculated (%): C, 37.85; H, 1.89; Cl, 22.40; N, 17.67. ^{1}H NMR, δ: 8.05 (s, 1 H, $CHCl_2$); 8.10 (d, 2 H, H_{arom}, J = 8.9 Hz); 8.30 (d, 2 H, H_{arom}, J = 8.9 Hz); 11.50 (s, 1 H, NH). MS, m/z: 316, 318, 320 $[M]^+$.

***N*-Phenyl-5-trichloromethyl-1,2,4-oxadiazolyl-3-carboxamide (5a)** was synthesized from amidoxime **1a** and CCl_3COCl by refluxing for 90 min in 70% yield (0.24 g), m.p. 108—111 °C (from toluene). Found (%): C, 39.25; H, 1.88; Cl, 34.60; N, 13.83. $C_{10}H_6Cl_3N_3O_2$. Calculated (%): C, 39.15; H, 1.97; Cl, 34.75; N, 13.70. ^{1}H NMR, δ: 7.20 (t, 1 H, H_{arom}, J = 7.3 Hz); 7.35 (m, 2 H, H_{arom}); 7.80 (d, 2 H, H_{arom}, J = 8.0 Hz); 11.10 (s, 1 H, NH). MS, m/z (for ^{35}Cl): 305 $[M]^+$.

***N*-(3,4-Dichlorophenyl)-5-trichloromethyl-1,2,4-oxadiazolyl-3-carboxamide (5b)** was synthesized from amidoxime **1g** and CCl_3COCl by refluxing for 90 min in 65% yield (0.24 g), m.p. 163—165 °C (from toluene). Found (%): C, 31.90; H, 1.00; Cl, 47.30; N, 11.23. $C_{10}H_4Cl_5N_3O_2$. Calculated (%): C, 31.96; H, 1.07; Cl, 47.27; N, 11.19. ^{1}H NMR, δ: 7.65 (m, 1 H, H_{arom}); 7.75 (m, 1 H, H_{arom}); 8.10 (s, 1 H, H_{arom}); 11.25 (s, 1 H, NH). MS, m/z (for ^{35}Cl): 373 $[M]^+$.

***N*-(4-Chlorophenyl)-5-trichloromethyl-1,2,4-oxadiazolyl-3-carboxamide (5c)** was synthesized from amidoxime **1c** and CCl_3COCl by refluxing for 90 min in 70% yield (0.24 g), m.p. 253—255 °C (from toluene). Found (%): C, 35.39; H, 1.49; Cl, 41.32; N, 12.78. $C_{10}H_5Cl_4N_3O_2$. Calculated (%): C, 35.19; H, 1.47; Cl, 41.64; N, 12.32. ^{1}H NMR, δ: 7.85 (d, 2 H, H_{arom}, J = 8.7 Hz); 7.35 (d, 2 H, H_{arom}, J = 8.7 Hz); 11.25 (s, 1 H, NH). MS, m/z (for ^{35}Cl): 339 $[M]^+$.

***N*-(4-Nitrophenyl)-5-trichloromethyl-1,2,4-oxadiazolyl-3-carboxamide (5d)** was synthesized from amidoxime **1e** and CCl_3COCl by refluxing for 90 min in 68% yield (0.24 g), m.p. 144—146 °C (from toluene). Found (%): C, 34.17; H, 1.36; Cl, 30.61; N, 16.18. $C_{10}H_5Cl_3N_4O_4$. Calculated (%): C, 34.14; H, 1.42; Cl, 30.30; N, 15.93. ^{1}H NMR, δ: 7.85 (d, 2 H, H_{arom}, J = 9.0 Hz); 8.25 (d, 2 H, H_{arom}, J = 9.0 Hz); 11.25 (s, 1 H, NH). MS, m/z (for ^{35}Cl): 350 $[M]^+$.

***N*-(2,3-Dimethylphenyl)-5-trichloromethyl-1,2,4-oxadiazolyl-3-carboxamide (5e)** was synthesized from amidoxime **1h** and CCl_3COCl by refluxing for 90 min in 58% yield (0.19 g), m.p. 184—186 °C (from toluene). Found (%): C, 43.15; H, 3.10;

Cl, 31.83; N, 12.50. $C_{12}H_{10}Cl_3N_3O_2$. Calculated (%): C, 43.08; H, 3.01; Cl, 31.79; N, 12.56. ^{1}H NMR, δ: 2.05 (s, 3 H, Me); 2.50 (s, 3 H, Me); 7.00 (m, 2 H, H_{arom}); 7.35 (d, 1 H, H_{arom}); 10.25 (s, 1 H, NH). MS, *m/z* (for ^{35}Cl): 333 $[M]^+$.

***N*-(Thiazol-2-yl)-5-trichloromethyl-1,2,4-oxadiazolyl-3-carboxamide (5f)** was synthesized from amidoxime **1i** and CCl_3COCl by refluxing for 2 h in 40% yield (0.13 g), m.p. 148—150 °C (from chloroform). Found (%): C, 26.76; H, 1.15; Cl, 34.15; N, 17.95. $C_7H_3Cl_3N_4O_2S$. Calculated (%): C, 26.88; H, 0.96; Cl, 34.08; N, 17.92. ^{1}H NMR, δ: 3.40 (s, 1 H, NH); 7.30 (m, 1 H, $H_{thiazole}$); 7.60 (m, 1 H, $H_{thiazole}$). MS, *m/z* (for ^{35}Cl): 312 $[M]^+$.

***N*-(4-Aminosulfonylphenyl)-5-trichloromethyl-1,2,4-oxadiazolyl-3-carboxamide (5g)** was synthesized from amidoxime **1f** and $ClCH_2COCl$ by refluxing for 2.5 h in 60% yield (0.27 g), m.p. 205—207 °C (from toluene). Found (%): C, 31.32; H, 1.95; Cl, 27.50; N, 14.39. $C_{10}H_7Cl_3N_4O_4S$. Calculated (%): C, 31.21; H, 1.82; Cl, 27.69; N, 14.56. ^{1}H NMR, δ: 7.30 (s, 2 H, NH_2); 7.85 (m, 2 H, H_{arom}); 7.95 (m, 2 H, H_{arom}); 11.35 (s, 1 H, NH). MS, *m/z* (for ^{35}Cl): 384 $[M]^+$.

Reactions of 3-carbamoyl-5-trichloromethyl-1,2,4-oxadiazoles with *N*-nucleophiles (general procedure). Freshly distilled amine (10 mmol) was added to a solution of 3-carbamoyl-5-trichloromethyl-1,2,4-oxadiazole **5** (3 mmol) in MeOH (10 mL). Then (TLC monitoring) the solvent was distilled off on a rotary evaporator. Water (30 mL) was poured on the oily residue obtained after evaporation, and the mixture was left over 1 h. The solid precipitate was filtered off, dried, and recrystallized from ethanol. This procedure was used to produce compounds **6a—g** and **7a—f**.

***N*-Phenyl-5-morpholino-1,2,4-oxadiazolyl-3-carboxamide (6a)** was synthesized from oxadiazole **5a** and morpholine, the duration of the reaction was 3 h, and the yield was 0.4 g (34%), m.p. 155—157 °C. Found (%): C, 57.10; H, 5.15; N, 20.29. $C_{13}H_{14}N_4O_3$. Calculated (%): C, 56.93; H, 5.11; N, 20.44. ^{1}H NMR, δ: 3.65 (s, 4 H, CH_2); 3.75 (s, 4 H, CH_2); 7.15 (m, 1 H, H_{arom}); 7.35 (m, 2 H, H_{arom}); 7.65 (m, 2 H, H_{arom}); 10.45 (s, 1 H, NH). MS, *m/z*: 274 $[M]^+$.

***N*-(4-Nitrophenyl)-5-morpholino-1,2,4-oxadiazolyl-3-carboxamide (6b)** was synthesized from oxadiazole **5d** and morpholine, the reaction duration was 3 h, and the yield was 0.20 g (68%), m.p. 235—237 °C. Found (%): C, 48.87; H, 4.15; N, 21.79. $C_{13}H_{13}N_5O_5$. Calculated (%): C, 48.91; H, 4.10; N, 21.94. ^{1}H NMR, δ: 3.65 (m, 4 H, CH_2); 3.75 (m, 4 H, CH_2); 8.00 (d, 2 H, H_{arom}, J = 8.9 Hz); 8.30 (d, 2 H, H_{arom}, J = 8.9 Hz); 11.00 (s, 1 H, NH). MS, *m/z*: 319 $[M]^+$.

***N*-(4-Nitrophenyl)-5-piperidino-1,2,4-oxadiazolyl-3-carboxamide (6c)** was synthesized from oxadiazole **5d** and piperidine, the reaction duration was 3 h, and the yield was 0.18 g (65%), m.p. 233—235 °C. Found (%): C, 52.95; H, 4.70; N, 22.19. $C_{14}H_{15}N_5O_4$. Calculated (%): C, 52.99; H, 4.76; N, 22.07. ^{1}H NMR, δ: 1.65 (m, 6 H, CH_2); 3.65 (m, 4 H, CH_2); 8.00 (d, 2 H, H_{arom}, J = 8.9 Hz); 8.25 (d, 2 H, H_{arom}, J = 8.9 Hz); 11.00 (s, 1 H, NH). MS, *m/z*: 317 $[M]^+$.

***N*-(2,3-Dimethylphenyl)-5-piperidino-1,2,4-oxadiazolyl-3-carboxamide (6d)** was synthesized from oxadiazole **5e** and piperidine, the reaction duration was 3 h, and the yield was 0.12 g (58%), m.p. 171—173 °C. Found (%): C, 63.94; H, 6.53; N, 18.49. $C_{16}H_{20}N_4O_2$. Calculated (%): C, 63.98; H, 6.71; N, 18.65. ^{1}H NMR, δ: 1.65 (m, 6 H, CH_2); 2.10 (s, 3 H, Me); 2.30 (s, 3 H, Me); 3.60 (m, 4 H, CH_2); 7.10 (m, 3 H, H_{arom}); 10.00 (s, 1 H, NH). MS, *m/z*: 300 $[M]^+$.

***N*-(2,3-Dimethylphenyl)-5-morpholino-1,2,4-oxadiazolyl-3-carboxamide (6e)** was synthesized from oxadiazole **5e** and morpholine, the reaction duration was 3 h, and the yield was 0.11 g (56%), m.p. 200—202 °C. Found (%): C, 57.10; H, 5.15; N, 20.29. $C_{15}H_{18}N_4O_3$. Calculated (%): C, 59.59; H, 6.00; N, 18.53. ^{1}H NMR, δ: 2.10 (s, 3 H, Me); 2.30 (s, 3 H, Me); 3.60 (m, 4 H, CH_2); 3.75 (m, 4 H, CH_2); 7.10 (m, 3 H, H_{arom}); 10.05 (s, 1 H, NH). MS, *m/z*: 302 $[M]^+$.

***N*-Phenyl-5-guanidino-1,2,4-oxadiazolyl-3-carboxamide (6f)** was synthesized from oxadiazole **5a** and guanidine, isolated from guanidine nitrate (0.5 g, 5 mmol) in MeOH (5 mL) by the treatment with KOH (0.3 g, 5 mmol) in MeOH (5 mL), and filtered off from KNO_3. The duration of the reaction was 24 h, and the yield was 0.8 g (90%), m.p. 218—222 °C. Found (%): C, 48.69; H, 4.10; N, 34.20. $C_{10}H_{10}N_6O_2$. Calculated (%): C, 48.78; H, 4.07; N, 34.13. MS, *m/z*: 246 $[M]^+$.

***N*-(4-Aminosulfonylphenyl)-5-morpholino-1,2,4-oxadiazolyl-3-carboxamide (6g)** was synthesized from oxadiazole **5g** and morpholine during 24 h in 50% yield (0.5 g), m.p. 204—206 °C (from EtOH). Found (%): C, 44.23; H, 4.35; N, 19.73. $C_{13}H_{15}N_5O_5S$. Calculated (%): C, 44.19; H, 4.25; N, 19.83. ^{1}H NMR, δ: 3.60 (m, 4 H, CH_2); 3.75 (m, 4 H, CH_2); 7.30 (s, 2 H, NH_2); 7.80 (m, 2 H, H_{arom}); 7.95 (m, 2 H, H_{arom}); 10.85 (s, 1 H, NH). MS, *m/z*: 353 $[M]^+$.

N*-Phenyl-5-(2,2-dimethylhydrazonomethyl)-1,2,4-oxadiazolyl-3-carboxamide (7a).** ***A. Synthesis from oxadiazole **5a**. Product **7a** was synthesized from oxadiazole **5a** and 1,1-dimethylhydrazine (0.1 g, 1.6 mmol) during 12 h. The yield was 0.06 g (75%), m.p. 239—240 °C with decomposition (from EtOH). Found (%): C, 55.38; H, 4.93; N, 27.15. $C_{12}H_{13}N_5O_2$. Calculated (%): C, 55.59; H, 5.02; N, 27.03. ^{1}H NMR, δ: 3.65 (s, 6 H, Me); 7.25 (t, 1 H, H_{arom}, J = 7.3 Hz); 7.35 (m, 2 H, H_{arom}); 7.75 (d, 2 H, H_{arom}, J = 8.0 Hz); 10.10 (s, 1 H, NH); 11.75 (s, 1 H, CH=). MS, *m/z*: 259 $[M]^+$.

B. Synthesis from oxadiazole **4a**. Hydrazone **7a** was synthesized from oxadiazole **4a** (50 mg, 0.2 mmol) and 1,1-dimethylhydrazine (0.2 g, 3 mmol) during 12 h in 50% yield (20 mg). MS, *m/z*: 259 $[M]^+$.

***N*-(3,4-Dichlorophenyl)-5-(2,2-dimethylhydrazinomethyl)-1,2,4-oxadiazolyl-3-carboxamide (7b)** was synthesized from oxadiazole **5b** (0.5 mmol) and 1,1-dimethylhydrazine (0.15 g, 2.5 mmol). The reaction duration was 24 h, and the yield was 0.12 g (66%), m.p. 246—248 °C. Found (%): C, 43.67; H, 3.20; Cl, 21.55; N, 21.70. $C_{12}H_{11}Cl_2N_5O_2$. Calculated (%): C, 43.92; H, 3.38; Cl, 21.61; N, 21.34. ^{1}H NMR, δ: 3.65 (s, 6 H, Me); 7.65 (m, 1 H, H_{arom}); 7.75 (m, 1 H, H_{arom}); 8.10 (s, 1 H, H_{arom}); 10.25 (s, 1 H, NH); 11.70 (s, 1 H, CH=). MS, *m/z*: 327, 329, 331 $[M]^+$.

***N*-(4-Chlorophenyl)-5-(2,2-dimethylhydrazinomethyl)-1,2,4-oxadiazolyl-3-carboxamide (7c)** was synthesized from oxadiazole **5c** (0.3 g, 0.9 mmol) and 1,1-dimethylhydrazine (0.30 g, 5 mmol). The duration of the reaction was 24 h, and the yield was 0.11 mg (44%), m.p. 243—245 °C. Found (%): C, 49.14; H, 4.20; Cl, 12.19; N, 23.70. $C_{12}H_{12}ClN_5O_2$. Calculated (%): C, 49.07; H, 4.12; Cl, 12.07; N, 23.84. ^{1}H NMR, δ: 3.65 (s, 6 H, Me); 7.35 (d, 2 H, H_{arom}, J = 8.7 Hz); 7.75 (d, 2 H, H_{arom}, J = 8.7 Hz); 10.25 (s, 1 H, NH); 11.70 (s, 1 H, CH=). MS, *m/z*: 293, 295 $[M]^+$.

***N*-(4-Nitrophenyl)-5-(2,2-dimethylhydrazinomethyl)-1,2,4-oxadiazolyl-3-carboxamide (7d)** was synthesized from oxadiazole **5d** (0.14 g, 0.5 mmol) and 1,1-dimethylhydrazine (0.15 g, 2.5 mmol) during 24 h in 67% yield (0.08 g), m.p. 216—218 °C. Found (%): C, 47.67; H, 4.14; N, 27.70. $C_{12}H_{12}N_6O_4$. Calculated (%): C, 47.37; H, 3.98; N, 27.62. ^{1}H NMR, δ: 3.65 (s, 6 H, Me); 7.75 (d, 2 H, H_{arom}, J = 9.0 Hz); 7.95 (d, 2 H, H_{arom}, J = 9.0 Hz); 10.25 (s, 1 H, NH); 11.70 (s, 1 H, CH=). MS, m/z: 304 $[M]^+$.

***N*-(2,3-Dimethylphenyl)-5-(2,2-dimethylhydrazinomethyl)-1,2,4-oxadiazolyl-3-carboxamide (7e)** was synthesized from oxadiazole **5e** (0.3 g, 1 mmol) and 1,1-dimethylhydrazine (0.30 g, 5 mmol) during 24 h in 42% yield (0.11 g), m.p. 252—254 °C. Found (%): C, 58.67; H, 5.72; N, 24.70. $C_{14}H_{17}N_5O_2$. Calculated (%): C, 58.53; H, 5.96; N, 24.38. ^{1}H NMR, δ: 2.10 (s, 3 H, Me); 2.70 (s, 3 H, Me); 3.60 (s, 6 H, Me); 7.10 (m, 3 H, H_{arom}); 9.80 (s, 1 H, NH); 11.70 (s, 1 H, CH=). MS, m/z: 287 $[M]^+$.

***N*-(4-Aminosulfonylphenyl)-5-(2,2-dimethylhydrazinomethyl)-1,2,4-oxadiazolyl-3-carboxamide (7f)** was synthesized from oxadiazole **5g** (0.2 g, 5 mmol) and 1,1-dimethylhydrazine (1.5 g, 25 mmol) during 24 h in 59% yield (0.10 g), m.p. 216—218 °C. Found (%): C, 42.67; H, 4.23; N, 24.70. $C_{12}H_{14}N_6O_4S$. Calculated (%): C, 42.60; H, 4.17; N, 24.84. ^{1}H NMR, δ: 3.65 (s, 6 H, Me); 7.20 (s, 2 H, NH_2); 7.75 (m, 2 H, H_{arom}); 7.95 (m, 2 H, H_{arom}); 10.25 (s, 1 H, NH); 11.70 (s, 1 H, CH=). MS, m/z: 338 $[M]^+$.

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