Nitrosation of Methyl 2-Acylamino-3-dimethylaminopropenoates. A Simple Conversion of *N*-Acylglycines into 5-Substituted 1,2,4-Oxadiazole-3-carboxylates

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A novel simple synthesis of 5-substituted-1,2,4-oxadiazole-3-carboxylates **5** from *N*-acylglycines **1**, which are transformed with DMF in the presence of phosphorus oxychloride into 2-substituted-4-dimethylaminomethyleneoxazol-5(4*H*)-ones **2**, followed by opening into 2-aroylamino-3-dimethylaminopropenoates **3**, and nitrosation to give the oximes **4** as intermediates, which cyclize spontaneously into 5-substituted-1,2,4-oxadiazole-3-carboxylates **5**. The compounds **2** can be transformed into **5** without isolation of **3** and **4**.

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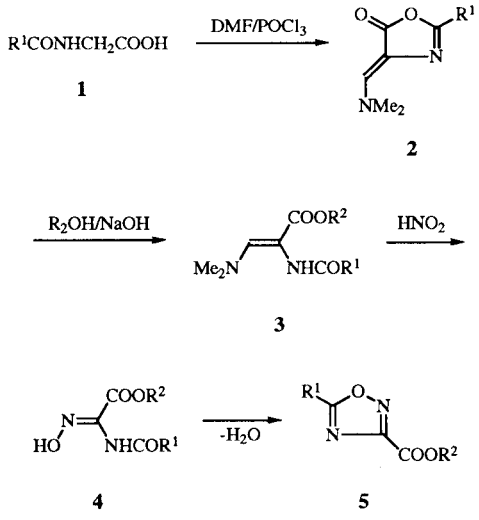
There are several methods for the preparation of 1,2,4-oxadiazole derivatives described in the literature [1]. Recently, many derivatives have been synthesized, since they play an important role as ester bio-isosteres. Among them, arecoline-derived methyloxadiazoles and quinuclidine-based ligands as agonists for cortical muscarinic cholinergic receptors in connection with Alzheimer's disease [2-4], 5-HT_3 antagonists [5] and benzodiazepine receptor partial agonists [6] have been prepared. Most of the syntheses are based on the cyclization of substituted amide oximes with carboxylic acids derivatives.

In connection with our systematic studies of methyl (*Z*)-2-benzoylamino-3-dimethylaminopropenoate and analogous compounds as versatile reagents in the synthesis of various heterocyclic systems, such as pyranones, pyridines, pyrimidines and their fused analogues [7,8], we report now a novel simple synthesis of 5-substituted-1,2,4-oxadiazole-3-carboxylates. Namely, when we treated methyl 2-benzoylamino-3-dimethylaminopropenoate (**3a**) in aqueous hydrochloric acid with sodium nitrite at 0° and if the solution was then left for one hour at room temperature, methyl 5-phenyl-1,2,4-oxadiazole-3-carboxylate (**5a**) was isolated in 78% yield. The reaction can be explained as the addition of nitrous acid to the C=C double bond, followed by elimination of *N,N*-dimethylformamide to give the oxime derivative **4a** as intermediate, which then spontaneously cyclizes into **5a**, identical with the compound prepared by an independent synthesis [9]. The formation of DMF was in fact observed when the reaction was carried out in deuterated hydrochloric acid in deuterium oxide in nmr spectrometer under the same reaction conditions. The intermediate oxime **4a**, which shows in the ir spectrum strongly hydrogen bonded hydroxy group at ν = 3150 cm^{-1} and 2400 cm^{-1}, can be isoalated only in the crude form. All attempts to purify it failed, since cyclization into **5a** is taking place by crystallization. Under essentially the same reaction conditions methyl 2-acetylamino-3-dimethylaminopropenoate (**3g**) was transformed into methyl 5-methyl-1,2,4-oxadiazole-3-carboxylate (**5g**), identical with the authentic sample [10].

It has been reported earlier, that methylene group in *N*-acylglycine derivatives is not activated for nitrosation to take place and therefore only *N*-nitroso compounds are formed [11]. Since the compounds **3a** and **3g** are prepared from hippuric acid (*N*-benzoylglycine) (**1a**) and aceturic acid (*N*-acetylglycine) (**1g**) [12,13], our observation opens a new simple synthesis of 5-substituted-1,2,4-oxadiazole-3-carboxylates from *N*-acylglycines.

In this connection a series of *N*-aroylglycines **1a,c-f**

Scheme 1



1, 3, 4, 5	2	R^1	R^2
a	**a**	Ph	Me
b	—	Ph	Et
c	**c**	2-Cl-C_6H_4	Me
d	**d**	4-Cl-C_6H_4	Me
e	**e**	4-Me-C_6H_4	Me
f	**f**	4-MeO-C_6H_4	Me
g	**g**	Me	Me

was selected and transformed with DMF in the presence of phosphorus oxychloride into 2-aryl-4-dimethylaminomethyleneoxazol-5(4*H*)-ones **2a,c-f**. These were converted with methanol or ethanol in alkaline medium into methyl or ethyl 2-aroyl-3-dimethylaminopropenoates **3a-f** followed by treatment with nitrous acid to give oxadiazoles **5a-f** in 63-78% yield. The transformation of **2** into **5**, which was carried out as a one-pot synthesis without isolation of the intermediates **3** and **4**, simplifies the procedure (Scheme 1).

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were recorded on a Varian EM 360 instrument with TMS as internal standard, ir spectra on a Perkin-Elmer 1310 infrared spectrometer and elemental analyses for C, H and N were obtained on a Perkin-Elmer CHN Analyser 2400.

The following starting compounds were prepared according to the procedures described in the literature: *N*-aroylglycines **1c-f** [14-16], methyl (*Z*)-2-benzoylamino-3-dimethylaminopropenoate (**3a**) [12,13], methyl 2-acetylamino-3-dimethylaminopropenoate (**3g**) [17] and 4-dimethylaminomethylene-2-phenyloxazol-5(4*H*)-one (**2a**) [12].

2-Aryl-4-dimethylaminomethyleneoxazol-5(4*H*)-ones **2**. General Procedure [12].

To an ice-cold solution of *N*-aroylglycine (5 mmoles) in phosphoryl chloride (1.9 g), DMF (900 mg) was added dropwise. The reaction mixture was heated for 1 hour at 50°, poured on crushed ice, the precipitate was collected by filtration and washed with water.

The following compounds were prepared in this manner:

4-Dimethylaminomethylene-2-(2-chlorophenyl)oxazol-5(4*H*)-one (**2c**).

This compound was prepared from *N*-(2-chlorobenzoyl)-glycine (**1c**, 1.07 g, 5 mmoles), phosphoryl chloride (1.9 g) and DMF (900 mg), yield 975 mg (78%), mp 180-182° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 3.25 (s, 3H, N*Me*$_2$), 3.65 (s, 3H, N*Me*$_2$), 7.25-7.6 (m, 4H, Ar (3H) and C*H*NMe$_2$), 7.85-8.1 (m, 1H, Ar).

Anal. Calcd. for $C_{12}H_{11}N_2O_2Cl$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.21; H, 4.15; N, 10.93.

4-Dimethylaminomethylene-2-(4-chlorophenyl)oxazol-5(4*H*)-one (**2d**).

This compound was prepared from *N*-(4-chlorobenzoyl)-glycine (**1d**, 1.07 g, 5 mmoles), phosphoryl chloride (1.9 g) and DMF (900 mg), yield 950 mg (76%), mp 206-207° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 3.26 (s, 3H, N*Me*$_2$), 3.62 (s, 3H, N*Me*$_2$), 7.17 (s, 1H, C*H*NMe$_2$), 7.44 (2H, Ar), 7.95 (2H, Ar).

Anal. Calcd. for $C_{12}H_{11}N_2O_2Cl$: C, 57.50; H, 4.42; N, 11.17. Found: C, 57.51; H, 4.21; N, 11.20.

4-Dimethylaminomethylene-2-(4-methylphenyl)oxazol-5(4*H*)-one (**2e**).

This compound was prepared from *N*-(4-methylbenzoyl)-glycine (**1e**, 965 mg, 5 mmoles), phosphoryl chloride (1.9 g) and DMF (900 mg), yield 730 mg (63%), mp 175-177° (from ethanol); ^{1}H nmr (DMSO-d$_6$): δ 2.40 (s, 3H, Ar-*Me*), 3.35 and 3.65 (2s, 2 x 3H, N*Me*$_2$), 7.45 (2H, Ar), 7.50 (s, 1H, NMe$_2$C*H*), 7.95 (2H, Ar).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.72; H, 6.00; N, 12.55.

4-Dimethylaminomethylene-2-(4-methoxyphenyl)oxazol-5(4*H*)-one (**2f**).

This compound was prepared from *N*-(4-methoxybenzoyl)-glycine (**1f**, 1045 mg, 5 mmoles), phosphoryl chloride (1.9 g) and DMF (900 mg), yield 870 mg (71%), mp 175.5-177.5° (from ethanol); ^{1}H nmr (DMSO-d$_6$): δ 3.25 (s, 3H, *Me*OAr), 3.55 and 3.85 (2s, 2 x 3H, N*Me*$_2$), 7.10 (2H, Ar), 7.30 (s, 1H, NMe$_2$C*H*), 7.85 (2H, Ar).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.24; H, 5.56; N, 11.17.

Methyl 5-Phenyl-1,2,4-oxadiazole-3-carboxylate (**5a**).

Methyl (*Z*)-2-benzoylamino-3-dimethylaminopropenoate (**3a**) [13] (496 mg, 2 mmoles) was suspended in water (2 ml) and aqueous hydrochloric acid (4%, 4 ml) was added. A solution of sodium nitrite (180 mg) in water (2 ml) was added dropwise to the reaction mixture at 0°. The mixture was stirred for 1 hour. The product was collected by filtration, yield 320 mg (78%), mp 112-115° (from ethanol), (lit [9] mp 116-118°; lit [10] mp 117-119°); ^{1}H nmr (deuteriochloroform): δ 4.08 (s, 3H, *Me*), 7.45-7.8 (m, 3H, *Ph*), 8.1-8.4 (m, 2H, *Ph*).

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.95; H, 3.71; N, 13.73.

Ethyl 5-phenyl-1,2,4-oxadiazole-3-carboxylate (**5b**).

4-Dimethylaminomethylene-2-phenyloxazol-5(4*H*)-one (**2a**) [12] (216 mg, 1 mmole) was suspended in ethanol (3 ml), sodium hydroxide (20 mg, 0.5 mmole) was added and the reaction mixture was refluxed for 30 minutes. Then, the solvent was evaporated *in vacuo*, water (1 ml) and hydrochloric acid (4%, 2.5 ml) were added and cooled on ice. A solution of sodium nitrite (100 mg) in water (1 ml) was added dropwise at 0° and the reaction mixture was left overnight in a stoppered vessel. The product was collected by filtration, yield 170 mg (78%), mp 47-49° (lit [9] 48-49°); ^{1}H nmr (deuteriochloroform): δ 1.47 (t, 3H, CH$_2$C*H*$_3$), 4.55 (q, 2H, C*H*$_2$CH$_3$), 7.33-7.77 (m, 3H, Ph), 7.9-8.35 (m, 2H, Ph), J_{CH_2Me} = 7.2 Hz.

Methyl 5-(2-Chlorophenyl)-1,2,4-oxadiazole-3-carboxylate (**5c**).

4-Dimethylaminomethylene-(2-chlorophenyl)oxazol-5(4*H*)-one (**2c**, 250 mg, 1 mmole) and sodium hydroxide (20 mg) was refluxed in methanol (5 ml) for 30 minutes. The solvent was evaporated *in vacuo*, the product was suspended in water (1 ml) and aqueous hydrochloric acid (4%, 2.5 ml). The reaction mixture was cooled on ice and a cold solution of sodium nitrite (100 mg in water (1 ml)) was added. After five hours of stirring in a stoppered flask, the product was collected by filtration and washed with water, yield 160 mg (67%), mp 101-103° (from ethanol) (lit [10] mp 103-104°); ^{1}H nmr (deuteriochloroform): δ 4.15 (s, 3H, *Me*), 7.37-7.83 (m, 3H, Ar), 8.1-8.38 (m, 1H, Ar).

Anal. Calcd. for $C_{10}H_7N_2O_3Cl$: C, 50.33; H, 2.96; N, 11.74. Found: C, 50.20; H, 2.64; N, 11.62.

In the same manner the following compound was prepared:

Methyl 5-(4-Chlorophenyl)-1,2,4-oxadiazole-3-carboxylate (**5d**).

This compound was prepared from 4-dimethylaminomethylene-(4-chlorophenyl)oxazol-5(4*H*)-one (**2d**), yield 170 mg (71%), mp 139-141° (from methanol); ^{1}H nmr (deuteriochloroform): δ 4.1 (s, 3H, Me), 7.55 (2H, Ar), 8.20 (2H, Ar).

Anal. Calcd. for $C_{10}H_7N_2O_3Cl$: C, 50.33; H, 2.96; N, 11.74. Found: C, 49.98; H, 2.78; N, 11.70.

Methyl 5-(4-Methylphenyl)-1,2,4-oxadiazole-3-carboxylate (**5e**).

After refluxing 4-dimethylaminomethylene-2-(4-methylphenyl)oxazol-5(4*H*)-one (**2e**, 230 mg, 1 mmole) in methanol (5 ml) containing sodium hydroxide (20 mg) for 30 minutes, the solvent was evaporated *in vacuo*, water (1 ml) and hydrochloric acid (4%, 2.5 ml) was added and the suspension was cooled on ice. Then a cold solution of sodium nitrite (100 mg in water (1 ml)) was added. After 5 hours of stirring in a stoppered flask, the product was collected by filtration, yield 150 (69%), mp 102-104° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 2.45 (s, 3H, Ar*Me*), 4.10 (s, 3H, COOMe), 7.35 (2H, Ar), 8.10 (2H, Ar).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.97; H, 4.34; N, 12.50.

In the same manner the following compound was prepared:

Methyl 5-(4-Methoxyphenyl)-1,2,4-oxadiazole-3-carboxylate (**5f**).

This compound was prepared from 4-dimethylaminomethylene-2-(4-methoxyphenyl)oxazol-5(4*H*)-one (**3f**), yield 160 mg (68%), mp 157-159° (from methanol); ^{1}H nmr (deuteriochloroform): δ 3.90 (s, 3H, *Me*OAr), 4.10 (s, 3H, COOMe), 7.05 (2H, Ar), 8.25 (2H, Ar).

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.25; H, 4.25; N, 12.05.

Methyl 5-Methyl-1,2,4-oxadiazole-3-carboxylate (**5g**).

To the cold suspension of methyl 2-acethylamino-3-dimethylaminopropenoate (**3g**, 186 mg, 1 mmole) in water (2 ml) and aqueous hydrochloric acid (4%, 2 ml), a cold solution of sodium nitrite (100 mg in water (1 ml)) was added slowly during stirring. The vessel was stoppered and left at room temperature for 5 hours, the product was collected by filtration, yield 85 mg (60%), mp 99-100° (from ethanol), lit [9] mp 100°; ^{1}H nmr (deuteriochloroform): δ 2.70 (s, 3H, *Me*), 4.05 (s, 3H, COO*Me*).

Anal. Calcd. for $C_5H_6N_2O_3$: C, 42.25; H, 4.26; N, 19.71. Found: C, 42.52; H, 4.17; N, 20.19.

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