Nitrosation of Methyl 2-Cinnamoylamino-3-dimethylamino-propenoates. Alkyl *N*-Cinnamoyloxalic Acid Hydroxyimidic Amides, Intermediates in the Synthesis of Alkyl 5-Styryl-1,2,4-oxadiazole-3-carboxylates

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Alkyl 2-(substituted cinnamoylamino)-3-dimethylaminopropenoates **5**, prepared either from glycine (**1**) and substituted cinnamoyl chlorides **2** *via* oxazol-5(4*H*)-ones **4**, or from cinnamoylglycinate with *t*-butoxy-bisdimethylaminomethane, were transformed by nitrosation into 5-substituted-1,2,4-oxadiazole-3-carboxylates **8**. The formation of alkyl *N*-cinnamoyloxalic acid hydroxyimidic amides **7**, which were isolated as intermediates, represent a novel synthesis of *N*-acyl substituted hydroxyimidic amides.

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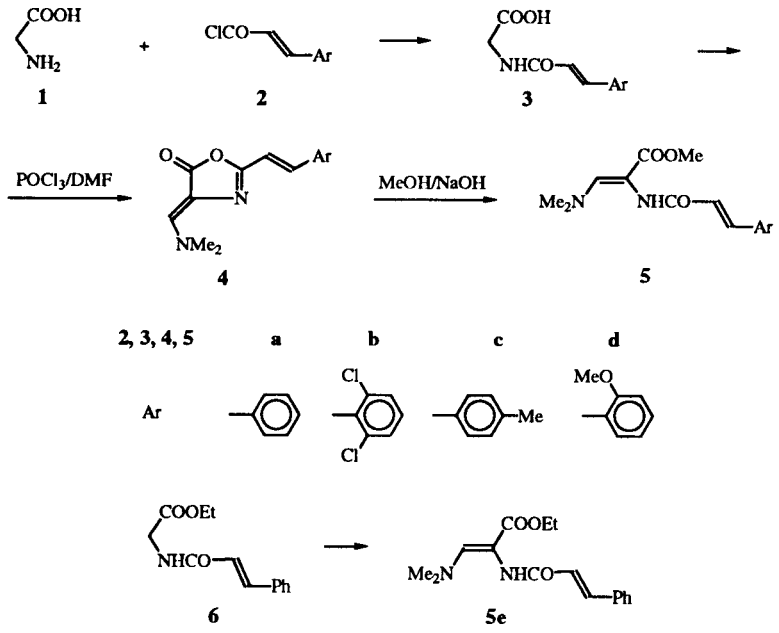
In connection with our studies on methyl (*Z*)-2-acylamino-3-dimethylaminopropenoates and analogous compounds as reagents in the synthesis of various heterocyclic systems [1,2], we have reported, recently, a novel simple synthesis of 5-substituted-1,2,4-oxadiazole-3-carboxylates by nitrosation of methyl 2-benzoylamino-3-dimethylaminopropenoates [3]. The reaction has been proposed to proceed through the corresponding *N*-cinnamoyloxalic acid hydroxyimidic amides as intermediates. However, these intermediates have not been isolated, since they cyclize under the reaction conditions into 1,2,4-oxadiazole derivatives.

In this paper we report on the preparation of substituted alkyl 5-styryl-1,2,4-oxadiazole-3-carboxylates **8**, in which intermediates, alkyl *N*-cinnamoyl substituted hydroxyimidic amides **7**, were isolated.

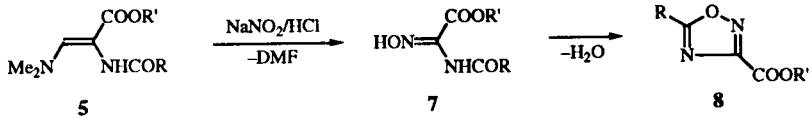
Alkyl 2-cinnamoylamino-3-dimethylaminopropenoates **5** were prepared in several steps. Cinnamoylglycines **3**, prepared from glycine **1** and cinnamoyl chlorides **2** by the procedures in the literature [4-6], were treated with phosphorous oxychloride in dimethylformamide to give derivatives of 4-dimethylaminomethylene-2-styryloxazol-5(4*H*)-one **4**, followed by methanolysis in the presence of sodium hydroxide to yield methyl 2-(substituted cinnamoylamino)-3-dimethylaminopropenoates **5**. Alternatively, ethyl 2-cinnamoylamino-3-dimethylaminopropenoate (**5e**) was prepared from ethyl *N*-cinnamoylglycinate (**6**) (Scheme 1).

Treatment of **5** with sodium nitrite in aqueous hydrochloric acid at 0° produced alkyl *N*-cinnamoyloxalic acid hydroxyimidic amides **7** in 69-84% yield, which were isolated in pure form and characterized. They can be

Scheme 1



Scheme 2



5 7 8

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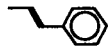
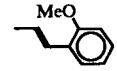
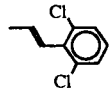
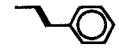
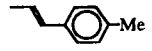
5, 7a		Me	5, 8d		Me
5, 7b		Me	5, 7, 8e		Et
5, 7c		Me			

further transformed into substituted alkyl 5-styryl-1,2,4-oxadiazole-3-carboxylates by standing in aqueous hydrochloric acid for 24 hours at room temperature (Scheme 2).

The formation of compounds **7** represent a novel method of preparation alkyl *N*-acyl substituted hydroxyimidic amides [8].

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were recorded oa a Varian EM 360 instrument with tetramethylsilane 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 compounds were prepared according to procedures described in the literature: *N*-cinnamoylglycines **3a-d** [4-6] and ethyl *N*-cinnamoylglycinate **6** [7].

2-Styryl-4-dimethylaminomethyleneoxazol-5(4*H*)-ones (**4**). General Procedure.

To an ice-cold solution of *N*-cinnamoylglycine **3** in phosphoryl chloride, dimethylformamide was added dropwise. The reaction mixture was heated at 40° for 1 hour, 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-styryloxazol-5(4*H*)-one (**4a**).

This compound was prepared from *N*-cinnamoylglycine (**3a**, 2.05 g, 10 mmoles), phosphoryl chloride (3.8 g) and dimethylformamide (1.8 g), yield 1.86 g (77%), mp 155-157° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 3.24 and 3.58 (2 s, 2 x 3H, NMe_2), 6.67 (d, 1H, C*H*=CH), 7.13 (s, 1H, C*H*NMe_2), 7.3-7.7 (m, 6H, Ph and C*H*=CH), $J_{CH=CH}$ = 17 Hz.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.12; H, 5.79; N, 11.60.

4-Dimethylaminomethylene-2-(2,6-dichlorostyryl)oxazol-5(4*H*)-one (**4b**).

This compound was prepared from *N*-(2,6-dichlorocinnamoyl)glycine (**3b**, 1.096 g, 4 mmoles), phosphoryl chloride (1.5 g) and dimethylformamide (750 mg), yield 950 mg (76%), mp 234-237° (from acetic acid); ^{1}H nmr (deuteriochloroform): δ 3.27 and 3.59 (2 s, 2 x 3H, NMe_2), 6.90 (d, 1H, C*H*=CH), 7.1-7.6 (m, 4H, 3Ar and C*H*NMe_2), 7.58 (d, 1H, C*H*=CH), $J_{CH=CH}$ = 16.9 Hz.

Anal. Calcd. for $C_{14}H_{12}N_2O_2Cl_2$: C, 54.04; H, 3.89; N, 9.00. Found: C, 53.81; H, 3.91; N, 8.93.

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

This compound was prepared from *N*-(4-methylcinnamoyl)glycine (**3c**, 1.095 g, 5 mmoles), phosphoryl chloride (1.9 g) and dimethylformamide (900 mg), yield 870 mg (68%), mp 173-175° (from water/methanol); ^{1}H nmr (deuteriochloroform): δ 2.36 (s, 3H, MeAr), 3.22 and 3.55 (2 s, 2 x 3H, NMe_2), 6.58 (d, 1H, C*H*=CH), 7.18 (2H, Ar), 7.23 (d, 1H, C*H*=CH), 7.29 (s, 1H, C*H*NMe_2), 7.45 (2H, Ar), $J_{CH=CH}$ = 16.9 Hz.

Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.29; H,6.29; N, 10.93. Found: C, 70.18; H, 6.31; N, 10.97.

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

This compound was prepared from *N*-(2-methoxycinnamoyl)-glycine (**3d**, 1.175 g, 5 mmoles), phosphoryl chloride (1.9 g) and dimethylformamide (900 mg), yield 865 mg (64%), mp 185-187° (from methanol); ^{1}H nmr (deuteriochloroform): δ 3.23 and 3.56 (2 s, 2 x 3H, NMe_2), 3.91 (s, 3H, OMe), 6.76 (d, 1H, C*H*=CH), 6.8-7.6 (m, 5H, 4Ar and C*H*NMe_2), 7.77 (d, 1H, C*H*=CH), $J_{CH=CH}$ = 16.8 Hz.

Anal. Calcd. for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N,10.29. Found: C, 65.88; H, 5.89; N, 10.16.

Methyl 2-Cinnamoylamino-3-dimethylaminopropenoate (**5a**).

4-Dimethylaminomethylene-2-styryloxazol-5(4*H*)-one (**4a**, 363 mg, 1.5 mmoles) and 30 mg of sodium hydroxide was refluxed in methanol (3 ml) for one half hour. The solvent was evaporated under reduced pressure, yield 360 mg (87%), mp 142-155° (from toluene); ^{1}H nmr (DMSO-d_6): δ 2.97 (s, 6H, NMe_2), 3.55 (s, 3H, OMe), 6.73 (d, 1H, C*H*=CH), 7.3-7.75 (m, 7H, Ph, C*H*=CH and C*H*NMe_2), 8.75 (broad s, 1H, NH), $J_{CH=CH}$ = 16 Hz.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.88; H, 6.48; N, 10.09.

Methyl 2-(2,6-Dichlorocinnamoylamino)-3-dimethylaminopropenoate (**5b**).

4-Dimethylaminomethylene-2-(2,6-dichlorostyryl)oxazol-5(4*H*)-one (**4b**, 933 mg, 3 mmoles) and 60 mg of sodium hydroxide was refluxed in methanol (6 ml) for one half hour. The solvent was evaporated under reduced pressure, yield 920 mg (89%), mp 220-221° (from methanol); ^{1}H nmr (DMSO-d_6): δ 2.98 (s, 6H, NMe_2), 3.59 (s, 3H, OMe), 6.88 (d, 1H, C*H*=CH), 7.27-7.8 (m, 5H, 3Ar and C*H*=CH and C*H*NMe_2), 9.07 (broad s, 1H, NH), $J_{CH=CH}$ = 16.8 Hz.

Anal. Calcd. for $C_{15}H_{16}N_2O_3Cl_2$: C, 52.49; H, 4.70; N, 8.16. Found: C, 52.19; H, 4.53; N, 8.01.

Methyl 2-(4-Methylcinnamoylamino)-3-dimethylaminopropenoate (**5c**).

4-Dimethylaminomethylene-2-(4-methylstyryl)oxazol-5(4*H*)-one (**4c**, 256 mg, 1 mmole) and 20 mg of sodium hydroxide was refluxed in methanol (5 ml) for one half hour. The solvent was evaporated under reduced pressure, yield 230 mg (80%), mp 224-225° (from methanol); ^{1}H nmr (DMSO-d_6): δ 2.35 (s, 3H, MeAr), 2.97 (s, 6H, NMe_2), 3.57 (s, 3H, OMe), (d, 1H, C*H*=CH), 7.31 (2H, Ar), 7.39 (s, 1H, C*H*NMe_2), 7.52 (d, 1H, C*H*=CH), 7.59 (2H, Ar), 8.76 (broad s, 1H, NH), $J_{CH=CH}$ = 16 Hz.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.63; H, 6.98; N, 9.68.

Methyl 2-(2-Methoxycinnamoylamino)-3-dimethylaminopropenoate (**5d**).

4-Dimethylaminomethylene-2-(2-methoxystyryl)oxazol-5(4*H*)-one (**4d**, 272 mg, 1 mmole) and 20 mg of sodium hydroxide was refluxed in methanol (5 ml) for one half hour. The solvent was evaporated under reduced pressure, 1 ml of methanol was added and the product was collected by filtration, yield 240 mg (79%), mp 191-193° (from methanol); ^{1}H nmr (DMSO-d_6): δ 2.97 (s, 6H, NMe_2), 3.57 (s, 3H, COOMe), 3.90 (s, 3H, *Me*OAr), (d, 1H, C*H*=CH), 6.8-7.7 (m, 5H, 4Ar and C*H*NMe_2), 7.83 (d, 1H, C*H*=CH), 8.75 (broad s, 1H, NH), $J_{CH=CH}$ = 16 Hz.

Anal. Calcd. for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.20. Found: C, 63.11; H, 6.69; N, 9.16.

Ethyl 2-Cinnamoylamino-3-dimethylaminopropenoate (**5e**).

Ethyl cinnamoylglycinate (**6**, 2.33 g, 10 mmoles) and *t*-butoxybisdimethylaminomethane (2.5 g) was heated in 5 ml of toluene at 80° for 1 hour protected from air humidity. The solvent was evaporated under reduced pressure, yield 2.5 g (87%), mp 175-189° (from toluene); ^{1}H nmr (deuteriochloroform): δ 1.25 (t, 3H, CH_2CH_3), 3.04 (s, 6H, NMe_2), 4.21 (q, 2H, CH_2CH_3), 6.63 (d, 1H, C*H*=CH), 6.95 (broad s, 1H, NH), 7.3-7.75 (m, 6H, Ph and C*H*NMe_2), 7.73 (d, 1H, C*H*=CH), J_{CH2CH3} = 7.1 Hz, $J_{CH=CH}$ = 16 Hz.

Anal. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.68; H, 7.20; N, 9.88.

Methyl *N*-Cinnamoyloxalic Acid Hydroxyimidic Amide (**7a**).

Methyl 2-cinnamoylamino-3-dimethylaminopropenoate (**5a**, 274 mg, 1 mmole) and sodium nitrite (100 mg) in 1 ml of water was cooled on ice and cooled hydrochloric acid (2 ml, 1:10) was added. The mixture, in a stoppered vessel, was stirred occasionally for 24 hours. The product was collected by filtration and washed with water, yield 195 mg (79%), mp 135-142° (precipitated with cyclohexane from ether); ^{1}H nmr (deuteriochloroform): δ 3.95 (s, 3H, OMe), 6.60 (d, 1H, C*H*=CH), 7.25-7.7 (m, 5H, Ph), 7.83 (d, 1H, C*H*=CH), 8.47 (broad s, 1H, NH), $J_{CH=CH}$ = 15.9 Hz.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.86; H, 4.87; N, 11.16.

Methyl *N*-(2,6-Dichlorocinnamoyl)oxalic Acid Hydroxyimidic Amide (**7b**).

Methyl 2-(2,6-dichlorocinnamoylamino)-3-dimethylaminopropenoate (**5b**, 343 mg, 1 mmole) and sodium nitrite (100 mg) in 1 ml of water was cooled on ice and cooled hydrochloric acid (2 ml, 1:10) was added. The mixture, in a stoppered vessel, was stirred occasionally for 24 hours. The product was collected by filtration, washed with water and dried over sodium hydroxide, yield 260 mg (82%), mp 165-168° (precipitated with petroleum ether from chloroform); ^{1}H nmr (DMSO-d_6): δ 3.81 (s, 3H, OMe), 7.18 (d, 1H, C*H*=CH), 7.4-7.8 (m, 3H, Ar), 7.75 (d, 1H, C*H*=CH), 10.9 (broad s, 1H, exchangable), 12 (s, 1H, exchangable), $J_{CH=CH}$ = 17 Hz.

Anal. Calcd. for $C_{12}H_{10}N_2O_4Cl_2$: C, 45.45; H, 3.18; N, 8.83. Found: C, 45.15; H, 3.15; N, 8.64.

Methyl *N*-(4-Methylcinnamoyl)oxalic Acid Hydroxyimidic Amide (**7c**).

Methyl 2-(4-methylcinnamoylamino)-3-dimethylaminopropenoate (**5c**, 144 mg, 0.5 mmole) and sodium nitrite (50 mg) in 0.5 ml of water was cooled on ice and cooled hydrochloric acid (1.5 ml, 1:10) was added. The mixture, in a stoppered vessel, was stirred occasionally for 24 hours. The product was collected by filtration and washed with water, yield 90 mg (69%), mp 150-153° (precipitated with petroleum ether with chloroform); ^{1}H nmr (DMSO-d_6): δ 2.34 (s, 3H, *Me*Ar), 3.73 (s, 3H, OMe), 6.97 (d, 1H, C*H*=CH), 7.26 (2H, Ar), 7.49 (2H, Ar), 7.55 (d, 1H, C*H*=CH), 10.43 (broad s, 1H, exchangable), 11.73 (s, 1H, exchangable), $J_{CH=CH}$ = 15.87 Hz.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54 ; H, 5.38; N, 10.68. Found: C, 59.71; H, 5.30; N, 10.41.

Ethyl *N*-Cinnamoyloxalic Acid Hydroxyimidic Amide (**7e**).

Ethyl 2-cinnamoylamino-3-dimethylaminopropenoate (**5e**, 288 mg, 1 mmole) and sodium nitrite (100 mg) in 1 ml of water was cooled on ice and cooled hydrochloric acid (2 ml, 1:10) was added. The mixture, in a stoppered vessel, was stirred occasionally for 24 hours. The product was collected by filtration and washed with water, yield 220 mg (84%), mp 123-128° (precipitated with cyclohexane from dichloromethane); ^{1}H nmr (deuteriochloroform): δ 1.36 (t, 3H, CH_2CH_3), 4.42 (q, 2H, CH_2CH_3), 6.64 (d, 1H, CH=CH), 7.25-7.65 (m, 5H, Ph), 7.73 (d, 1H, CH=CH), 8.57 (broad s, 1H, exchangable), 9.8 (broad s, 1H, exchangable), J_{CH2CH3} = 7.1 Hz, $J_{CH=CH}$ = 16 Hz.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.21; H, 5.07; N, 10.65.

Methyl 5-(2-Methoxystyryl)-1,2,4-oxsadiazole-3-carboxylate (**8d**).

A mixture of methyl 2-(2-methoxycinnamoylamino)-3-dimethylaminopropenoate (**5e**, 304 mg, 1 mmole), sodium nitrite (100 mg) and 1 ml of water was cooled on ice and cooled hydrochloric acid (2.5 ml, 1:10) was added. The mixture, in a stoppered vessel, was stirred occasionally for 2 days. The product was collected by filtration and washed with water, yield 100 mg (38%), mp 135-136° (from methanol); ^{1}H nmr (deuteriochloroform): δ 3.96 (s, 3H, ArOMe), 4.08 (s, 3H, COOMe), 6.8-7.7 (m, 5H, 4Ar and C*H*=CH), 8.3 (d, 1H, CH=CH), $J_{CH=CH}$ = 16.3 Hz.

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65 ; N, 10.76. Found: C, 59.94; H, 4.51; N, 10.95.

Ethyl 5-Styryl-1,2,4-oxadiazole-3-carboxylate (**8e**).

Ethyl *N*-cinnamoyloxalic acid hydroxyimidic amide (**7e**, 100 mg, 0.38 mmole) was dissolved in 1 ml of ethanol and 0.5 ml of hydrochloric acid (1:10) was added. The solution was left for one day at room temperature, 3 ml of water was added and the product collected by filtration, yield 77 mg (83%), mp 78-80° (from cyclohexane); ^{1}H nmr (deuteriochloroform): δ 1.47 (t, 3H, CH_2CH_3), 4.54 (q, 2H, CH_2CH_3), 7.05 (d, 1H, C*H*=CH), 7.42-7.47 (m, 3H, Ar), 7.58-7.62 (m, 2H, Ar), 7.98 (d, 1H, C*H*=CH), J_{CH2CH3} = 7.14 Hz, $J_{CH=CH}$ = 16.49 Hz.

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.78; H, 4.99; N, 11.59.

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