Reactions of Methyl (*E,Z*)-2-(2-Benzoyl-2-ethoxycarbonyl-1-ethenyl)-amino-3-dimethylaminopropenoate with Heteroarylhydrazines. 2-(2-Benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-heteroarylhydrazonopropanoates and 1-Heteroaryl-4-ethoxycarbonyl-3-phenylpyrazoles.

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In the reaction of methyl (*E,Z*)-2-(2-benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-dimethylaminopropenoate (**1**) with heteroarylhydrazines **2** in ethanol in the presence of catalytic amounts of hydrochloric acid two types of products were formed: methyl 2-(2-benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-heteroarylhydrazonopropanoates **4** in 73-86% yield and 1-heteroaryl-4-ethoxycarbony-3-phenylpyrazoles **5** in 5-16% yield.

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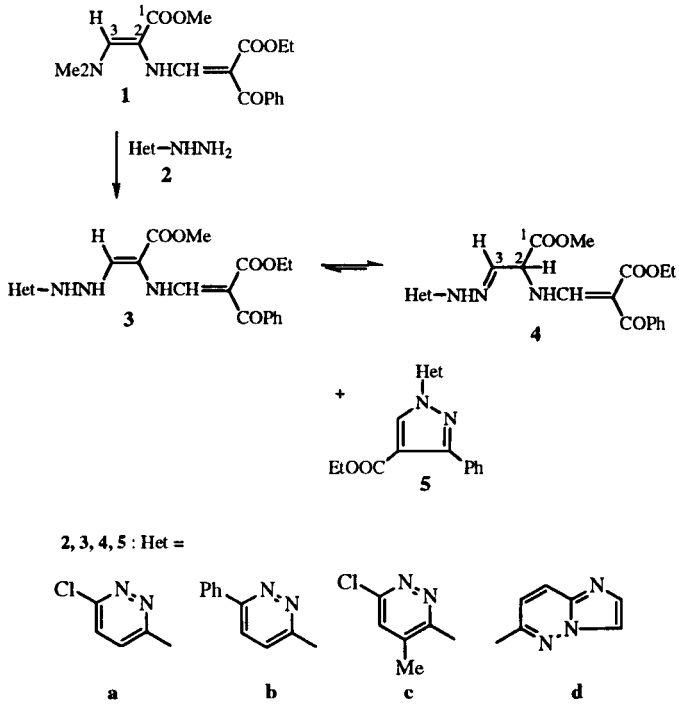
Substituted alkyl 2-acylamino-3-dimethyamino-propenoates, masked α-formyl-α-amino acids, are versatile reagents in the synthesis of β-aryl-, β-heteroaryl-, β-arylamino-, and β-heteroarylamino-α-amino acids and their α,β-dehydro analogs. These types of compounds are frequently used as intermediates in the synthesis of many heterocyclic systems, in which α-amino acid structural moiety is incorporated or partially incorporated into the heterocyclic system [1,2].

Recently, alkyl 2-(2-substituted ethenylamino)-3-dimethylaminopropenoates and related compounds have been prepared and used in the synthesis of heterocyclic systems. All these compounds react selectively with *C*- and *N*-nucleophiles, such as active methylene compounds and amines, by substitution of the dimethylamino group, to give under mild conditions intermediates, which cyclize under more vigorous conditions into various heterocyclic systems, such as pyranones, benzopyranones, pyranobenzopyranones, azolopyranones and pyranoazines, and their polycyclic analogs, especially those with a substituted amino function attached at position 3 in the newly formed pyranone, pyridinone or pyrimidinone ring [1-5]. Recently, some of these reagents have been applied as *N*-protecting groups in the synthesis of peptides [6] and heterocyclic systems with a free amino group [7], since they can be easily removed by hydrazine or hydroxylamine.

It has been reported, that dimethylaminomethyl derivatives (enaminones) react with hydrazine by substitution of the dimethylamino group to form the corresponding pyrazoles [8-10]. Recently, when reactions of ethyl (*E,Z*)-2-(2-benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-dimethylaminopropenoate with *C*-nucleophiles [11] and *N*-nucleophiles [7] have been studied, we have observed that in the reaction with hydrazine 4-ethoxycarbonyl-3-phenylpyrazole was formed among other products in low yield. This indicates that ethenylamino part of the molecule is involved in this reactions. This observation prompted us to study the reactions with monosubstituted hydrazines.

Scheme 1



In the reaction of methyl 2-(2-benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-dimethylaminopropenoate (**1**) with heteroarylhydrazines **2** two types of concurrent reactions were observed: 1) substitution of the dimethylamino group to give the corresponding 2-(2-benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-(heteroarylhydrazino)-propenoate **3** or its tautomeric form **4**, and 2) reaction involving (2-benzoyl-2-ethoxycarbonyl-1-ethenyl)amino part of the molecule, followed by elimination of the propenoate structural element, resulting in the formation of 4-ethoxycarbonyl-1-heteroaryl-3-phenylpyrazole **5**.

The following heteroarylhydrazines were selected in these studies: 6-chloro-3-hydrazinopyridazine (**2a**),

3-hydrazino-6-phenylpyridazine (**2b**), 6-chloro-4-methyl-3-hydrazinopyridazine (**2c**), and 6-hydrazinoimidazo[1,2-*b*]-pyridazine (**2d**). The reaction with **1** was carried out in ethanol in the presence of catalytic amounts of hydrochloric acid at room temperature. The tlc showed that reaction was completed in 2-7 hours giving **4** in 73-86% yield. Pyrazoles **5** were isolated from the filtrate in 5-16% yield.

The products can exist in two tautomeric forms, hydrazino form **3** or hydrazono form **4**. The ^{1}H nmr spectra show the following characteristics: a doublet of a doublet at δ = 5.0-5.5 ppm with the coupling constants J_{NHCH} = 7.8 Hz and $J_{CH\text{-}CH}$ = 4.4 Hz characteristic for the proton attached to C_2 in the structural element NH-C*H*-CH=, two doublets of doublets at δ = 9.5 ppm and δ = 10.7 ppm with the coupling constants J_{NHCH} = 13.5 Hz and J_{NHCH} = 7.8 Hz for the proton attached at nitrogen in the structural element N*H*-CH-CH=, and a singlet at δ = 11.6 ppm for the proton attached to nitrogen in the structural element Het-N*H*-N=, while the signal for the olefinic proton of N=C*H*-CH structural element is overlapped by aromatic protons at δ = 7.3-8.4 ppm. After addition of deuterium oxide to the solution in DMSO-d_6 the singlet at δ = 11.6 ppm and two doublets of doublets at δ = 9.5 ppm and δ = 10.7 ppm (for NH protons) disappeared, while the doublet of a doublet at δ = 5.5 ppm was transformed into a doublet. On the basis of this information one can conclude that the compounds exist predominantly as methyl 2-(2-benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-heteroarylhydrazonopropanoates **4**.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a Bruker Avance 300 DPX spectrometer with TMS as the internal standard, ir spectra on a Perkin-Elmer 1310 instrument, mass spectra on an Autospeck Q spectrometer and microanalyses for C, H and N on a Perkin-Elmer Analyser 2400.

Methyl (*E,Z*)-2-(2-benzoyl-2-ethoxycarbonyl-1-ethenyl)-amino-3-dimethylaminopropenoate (**1**) was prepared according to the procedure described in literature [11].

Reactions of Methyl (*E,Z*)-2-(2-Benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-dimethylaminopropenoate (**1**) with Heteroarylhydrazines **2a-d**. Synthesis of Methyl 2-(2-Benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-heteroarylhydrazonopropanoates **4** and 4-Ethoxycarbonyl-3-phenyl-1-heteroarylpyrazoles **5**.

General Procedure.

To a suspension of reagent **1** (1 mmole, 0.346 g) in ethanol (4 ml) a catalytic amount of hydrochloric acid (0.1 ml, 36%) and heteroarylhydrazine **2** (1 mmole) were added. The reaction mixture was stirred at room temperature for several hours. The reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and ether as the solvent). After the reaction was completed water (1 ml) was added. The precipitate was collected by filtration and recrystallized from an appropriate solvent to give products **4a-d**. The filtrate was evaporated *in vacuo*. To the oily residue water (2 ml) was added. The precipitate, formed after cooling, was collected by filtration and recrystallized from an appropriate solvent to give products **5a-c**.

The following compounds were prepared in this manner:

Methyl 2-(2-Benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-(6-chloropyridazinyl-3)hydrazonopropanoate (**4a**).

This compound was prepared from reagent **1** (0.346 g) and 3-hydrazino-6-chloropyridazine (**2a**, 0.144 g) by stirring at room temperature for 3 hours to give **4a** in 79% yield, mp 141-143° dec (from a mixture of ethanol and water); ms: FAB, 446 (MH$^+$); ^{1}H nmr (deuteriochloroform): δ 0.94 and 0.95 (2t, 3H, CH_2CH_3), 3.90 (s, 3H, COOMe), 3.97 and 4.04 (2q, 2H, CH_2CH_3), 4.99 (dd, 1H, *CH*COOMe), 7.36-7.49 (m, 5H, Ph(3H), C*H*=NNH, $H_{5'}$), 7.73-7.80 (m, 3H, Ph(2H), $H_{4'}$), 7.75 and 8.79 (2d, 1H, NHC*H*=), 9.77 and 10.99 (2dd, 1H, CHN*H*CH), 11.77 (br s, 1H, N*H*-Het), $J_{CH_2CH_3}$ = 7.1 Hz, $J_{NHCH=}$ = 13.5 Hz, J_{NHCH} = 7.2 Hz, $J_{CH\text{-}CH}$ = 4.0 Hz.

Anal. Calcd. for $C_{20}H_{20}N_5O_5Cl$: C, 53.88; H, 4.52; N, 15.71. Found: C, 53.53; H, 4.50; N, 16.02.

Methyl 2-(2-Benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-(6-phenylpyridazinyl-3)hydrazonopropanoate (**4b**).

This compound was prepared from reagent **1** (0.346 g) and 3-hydrazino-6-phenylpyridazine (**2b**, 0.186 g) by stirring at room temperature for 3.5 hours to give **4b** in 77% yield, mp 152-154° dec (from a mixture of ethanol and water); ms: FAB, 488 (MH$^+$); ^{1}H nmr (DMSO-d_6): δ 0.86 and 0.89 (2t, 3H, CH_2CH_3), 3.79 (s, 3H, COOMe), 3.90 and 3.98 (2q, 2H, CH_2CH_3), 5.54 (dd, 1H, *CH*COOMe), 7.36-7.52 (m, 10H, 2Ph (8H), C*H*=NNH, $H_{5'}$), 8.04-8.22 (m, 4H, Ph(2H), $H_{4'}$, NHC*H*=), 9.60 and 10.75 (2dd, 1H, CHN*H*CH), 11.67 (br s, 1H, N*H*Het), $J_{CH_2CH_3}$ = 7.1 Hz, $J_{NHCH=}$ = 13.5 Hz, J_{NHCH} = 7.8 Hz, J_{CHCH} = 4.4 Hz.

Anal. Calcd. for $C_{26}H_{25}N_5O_5$: C, 64.06; H, 5.17; N, 14.37. Found: C, 63.70; H, 4.93; N, 14.44.

Methyl 2-(2-Benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-(6-chloro-4-methylpyridazinyl-3)hydrazonopropanoate (**4c**).

This compound was prepared from the reagent **1** (0.346g) and 3-hydrazino-6-chloro-4-methylpyridazine (**2c**, 0.158 g) by stirring at room temperature for 2 hours to give **4c** in 73% yield, mp 131-132° dec (from a mixture of ethanol and water); ms: FAB, 460 (MH$^+$); ^{1}H nmr (deuteriochloroform): δ 0.94 and 0.95 (2t, 3H, CH_2CH_3), 2.08 (s, 3H, 4'-Me), 3.64 (s, 3H, COOMe), 3.97 and 4.04 (2q, 2H, CH_2CH_3), 4.99 (dd, 1H, *CH*COOMe), 7.36-7.50 (m, 5H, Ph(3H), C*H*=NNH, $H_{5'}$), 7.73-7.80 (m, 2H, Ph), 7.75 and 8.79 (2d, 1H, NHC*H*=), 9.77 and 10.99 (2dd, 1H, CHN*H*CH), 11.77 (br s, 1H, N*H*Het), $J_{CH_2CH_3}$ = 7.1 Hz, $J_{NHCH=}$ = 13.5 Hz, J_{NHCH} = 7.2 Hz, J_{CHCH} = 4.0 Hz.

Anal. Calcd. for $C_{21}H_{22}N_5O_5Cl$: C, 54.85; H, 4.82; N, 15.23. Found: C, 54.47; H, 4.98; N, 15.26.

Methyl 2-(2-Benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-(imidazo[1,2-*b*]pyridazinyl-6)hydrazonopropanoate (**4d**).

This compound was prepared from reagent **1** (0.346 g) and 6-hydrazino-imidazo[1,2-*b*]pyridazine (**2d**, 0.149 g) by stirring at room temperature for 7 hours to give **4d** in 86% yield, mp 139-141° dec (from a mixture of ethanol and water); ms: FAB, 451 (MH$^+$); ^{1}H nmr (DMSO-d_6): δ 0.85 and 0.89 (2t, 3H, CH_2CH_3), 3.78 (s, 3H, COOMe), 3.90 and 3.97 (2q, 2H, CH_2CH_3), 5.53 (dd, 1H, *CH*COOMe), 7.37-8.35 (m, 9H, Ph, C*H*=NNH, NHC*H*=, $H_{7'}$, $H_{8'}$), 8.10 (d, 1H, $H_{2'}$), 8.35 (d, 1H, $H_{3'}$), 9.52 and

10.65 (2dd, 1H, CHN*H*CH), 11.93 (br s, 1H, N*H*Het), $J_{CH_2CH_3}$ = 7.1 Hz, $J_{NHCH=}$ = 14.0 Hz, J_{NHCH} = 7.2 Hz, J_{CHCH} = 4.0 Hz, $J_{H2'H3'}$ = 1.8 Hz.

Anal. Calcd. for $C_{22}H_{22}N_6O_5$: C, 58.66; H, 4.92; N, 18.66. Found: C, 58.62; H, 5.03; N, 19.03.

4-Ethoxycarbonyl-3-phenyl-1-(6-chloropyridazinyl-3)pyrazole **5a**.

This compound was prepared from reagent **1** (0.346 g) and 3-hydrazino-6-chloropyridazine (**2a**, 0.144 g) to give **5a** in 8% yield, mp 128-129° (from a mixture of methanol and water); ms: 328 (M^+); ^{1}H nmr (deuteriochloroform): δ 1.18 (t, 3H, CH_2CH_3), 4.20 (q, 2H, CH_2CH_3), 7.33-7.41 (m, 5H, Ph), 7.57 (d, 1H, $H_{5'}$), 7.83 (d, 1H, $H_{4'}$), 8.26 (s, 1H, H_5), $J_{CH_2CH_3}$ = 7.1 Hz, $J_{H4'H5'}$ = 9.1 Hz.

Anal. Calcd. for $C_{16}H_{13}N_4O_2Cl$: C, 58.46; H, 3.99; N, 17.04. Found: C, 58.87; H, 4.05; N, 17.51.

4-Ethoxycarbonyl-3-phenyl-1-(6-phenylpyridazinyl-3)pyrazole (**5b**).

This compound was prepared from reagent **1** (0.346 g) and 3-hydrazino-6-phenylpyridazine (**2b**, 0.186 g) to give **5b** in 16% yield, mp 122-124° (from a mixture of methanol and water); ms: 370 (M^+); ^{1}H nmr (deuteriochloroform): δ 1.34 (t, 3H, CH_2CH_3), 4.32 (q, 2H, CH_2CH_3), 7.38-7.48 (m, 3H, Ph), 7.54-7.57 (m, 2H, Ph), 7.89-7.91 (m, 3H, Ph), 8.04 (d, 1H, $H_{5'}$), 8.10-8.13 (m, 2H, Ph), 8.36 (d, 1H, $H_{4'}$), 9.40 (s, 1H, H_5), $J_{CH_2CH_3}$ = 7.1 Hz, $J_{H4'H5'}$ = 9.2 Hz.

Anal. Calcd. for $C_{22}H_{18}N_4O_2$: C, 71.34; H, 4.90; N, 15.13. Found: C, 70.84; H, 4.62; N, 15.42.

4-Ethoxycarbonyl-3-phenyl-1-(6-chloro-4-methylpyridazinyl-3)pyrazole (**5c**).

This compound was prepared from reagent **1** (0.346 g) and 3-hydrazino-6-chloro-4-methylpyridazine (**2c**, 0.158 g) to give **5c** in 5% yield, mp 162-163° (from a mixture of methanol and water); ms: 342 (M^+); ^{1}H nmr (deuteriochloroform): δ 1.34 (t, 3H, CH_2CH_3), 2.76 (s, 3H, 4'-CH_3), 4.32 (q, 2H, CH_2CH_3), 7.43-7.49 (m, 3H, Ph), 7.54 (s, 1H, $H_{5'}$), 7.86-7.89 (m, 2H, Ph), 9.06 (s, 1H, H_5), $J_{CH_2CH_3}$ = 7.1 Hz.

Anal. Calcd. for $C_{17}H_{15}N_4O_2Cl$: C, 59.57; H, 4.41; N, 16.34. Found: C, 59.30; H, 4.40; N, 16.43.

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REFERENCES AND NOTES

[1] For a recent review see: B. Stanovnik, *Molecules*, **1**, 123 (1996).

[2] For a review see: B. Stanovnik, Methyl 2-Benzoylamino-3-dimethylaminopropenoate in the Synthesis of Heterocyclic Systems, Progress in Heterocyclic Chemistry, Vol. 5, H. Suschitzky and E. F. V. Scriven, eds., Pergamon Press, Oxford, 1993 pp 34-53.

[3] G. Soršak, A. Sinur, L. Golič, and B. Stanovnik, *J. Heterocyclic Chem.*, **32**, 921 (1995).

[4] R. Toplak, L. Selič, G. Soršak, and B. Stanovnik, *Heterocycles*, **45**, 555 (1997).

[5] L. Selič and B. Stanovnik, *J. Heterocyclic Chem.*, **34**, 813 (1997).

[6] J. Svete, M. Aljaž-Rožič, and B. Stanovnik, *J. Heterocyclic Chem.*, **34**, 177 (1997).

[7] S. Strah, A. Golobič, L. Golič, and B. Stanovnik, *J. Heterocyclic Chem.*, **34**, 1511 (1997).

[8] G. Menozzi, L. Mosti, and P. Schenone, *J. Heterocyclic Chem.*, **24**, 1669 (1987).

[9] J. R. Beck and M. P. Lynch, *J. Heterocyclic Chem.*, **24**, 693 (1987).

[10] P. Schenone, L. Mosti, and G. Menozzi, *J. Heterocyclic Chem.*, **19**, 1355 (1982).

[11] S. Strah, S. Golič Grdadolnik, and B. Stanovnik, *J. Heterocyclic Chem.*, **34**, 263 (1997).