Methyl 2-[Bis(acetyl)ethenyl]aminopropenoate in the Synthesis of Heterocyclic Systems

Lovro Selič and Branko Stanovnik*

Faculty of Chemistry and Chemical Technology, University of Ljubljana, Ljubljana, Slovenia

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Methyl 2-[bis(acetyl)ethenyl]aminopropenoate (**4**) was prepared in 3 steps from acetylacetone (**1**) via 4-(*N,N*-dimethylamino)-3-acetylbut-3-en-2-one (**2**) and methyl *N*-[2,2-bis(acetyl)ethenyl]glycinate (**3**). Compound **4** reacts with *N*- and *C*-nucleophiles to give fused heterocyclic systems. Derivatives of pyrido[1,2-*a*]pyrimidones **14-16** and thiazolo[3,2-*a*]pyrimidones **17** and **18** were prepared from 2-aminopyridines and 2-aminothiazoles, respectively. With *C*-nucleophiles derivatives of pyrido[1,2-*a*]-pyridinone **19** and 2*H*-1-benzopyran-2-one **20-22** were prepared.

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Recently, the synthesis of various derivatives of 2*H*-pyran-2-one and fused pyran-2-one has arisen a great interest, since many of them have been found as nonpeptide HIV proteaze inhibitors [1,2].

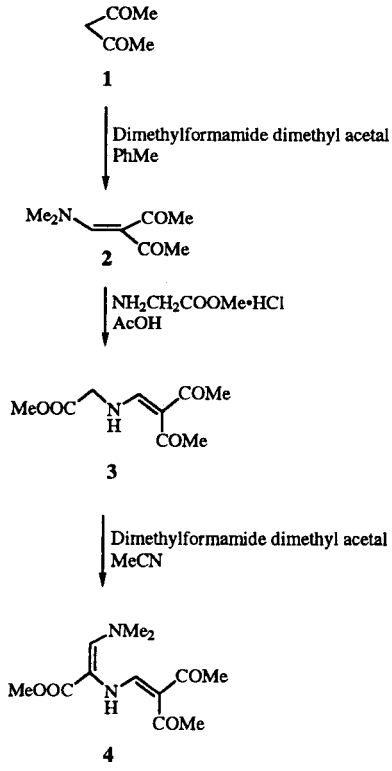
2-Amino substituted 2-dimethylaminopropenoates are versatile synthons for preparation of 2*H*-pyran-2-ones and other heterocyclic systems with an amino acid structural element incorporated or partially incorporated into the cyclic systems [3,4].

In this connection the following compounds have been prepared recently: methyl (*Z*)-2-benzoylamino-3-dimethylaminopropoenoate [6], methyl (*Z*)-2-acetylamino-3-dimethylaminopropenoate [7] and methyl (*Z*)-2-acetylamino-3(2-methyl-3-nitrophenyl)aminopropenoate [7], and 2-substituted propenoates, such as ethyl (*Z*)-2-[2,2-bis(ethoxycarbonyl)vinyl]aminopropenoate [8] and ethyl 2-[2-benzoyl-2-ethoxycarbonyl-1-ethenyl]amino-3-dimethylaminopropenoate [9].

In this paper we describe the preparation of methyl 2-[2,2-bis(acetyl)ethenyl]amino-3-dimethylaminopropenoate (**4**) and its application in the synthesis of heterocyclic systems.

4-(*N,N*-Dimethylamino)-3-acetylbut-3-en-2-one (**2**) was prepared from acetylacetone (**1**) with *N,N*-dimethylformamide dimethyl acetal by heating in toluene according to the procedure described in the literature [10]. This was, without purification, transformed with methyl glycinate hydrochloride by heating in acetic acid for 1 hour into methyl *N*-[2,2-bis(acetyl)ethenyl]glycinate (**3**) in 60% yield [11] (Scheme 1).

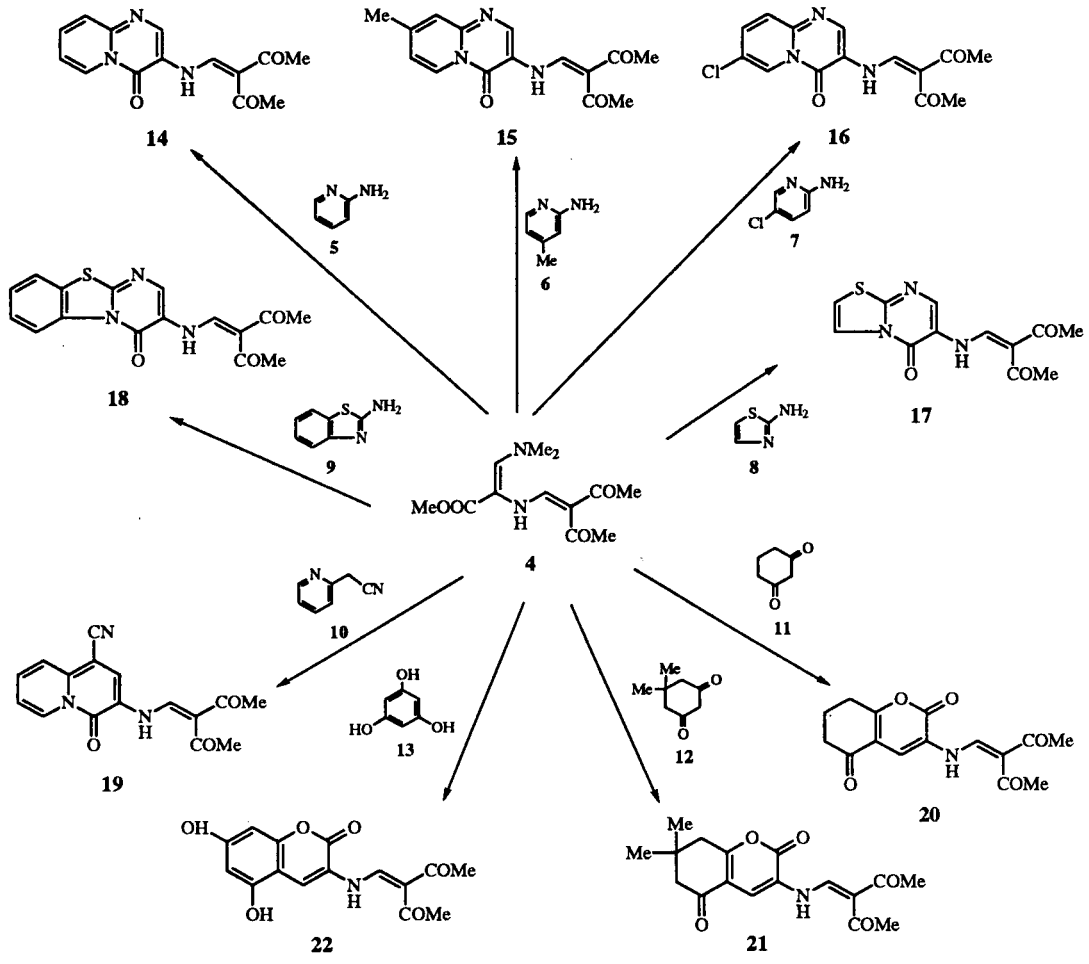
Scheme 1



The structure of compound **3** was determined by ^{1}H nmr spectrum in deuteriochloroform. It shows two singlet at δ = 2.25 and 2.47 ppm, each integrating for three protons, for methyl protons of acetyl groups, a singlet at δ = 3.77 ppm, integrating for three protons, for ester methyl group, a doublet at δ = 4.10 ppm, integrating for two protons, with a coupling constant J_{CH_2NH} = 6.2 Hz, for methylene group, a doublet at δ = 7.67 ppm, for one proton attached to the olefinic double bond, with the coupling constant J_{CHNH} = 12.9 Hz, and a degenerated triplet of a doublet at δ = 11.07 ppm, for the proton attached to nitrogen.

Compound **3** was further treated with *N,N*-dimethylamino dimethyl acetal by heating in acetonitrile for 4 hours to form methyl 2-[2,2-bis(acetyl)ethenyl]amino-3-dimethylaminopropenoate (**4**) in 98% yield (Scheme 1). The structure of the compound was comfirmed by ^{1}H nmr spectrum in deuterated dimethyl sulfoxide, which shows two singlets at δ = 2.18 and 2.34 ppm, each integrating for three protons, for two acetyl methyl groups, a singlet at δ = 2.99 ppm integrating for six protons, for dimethylamino group, a singlet at δ = 3.60 ppm, integrating for three protons, for the ester methyl group, a singlet at δ =

Scheme 2

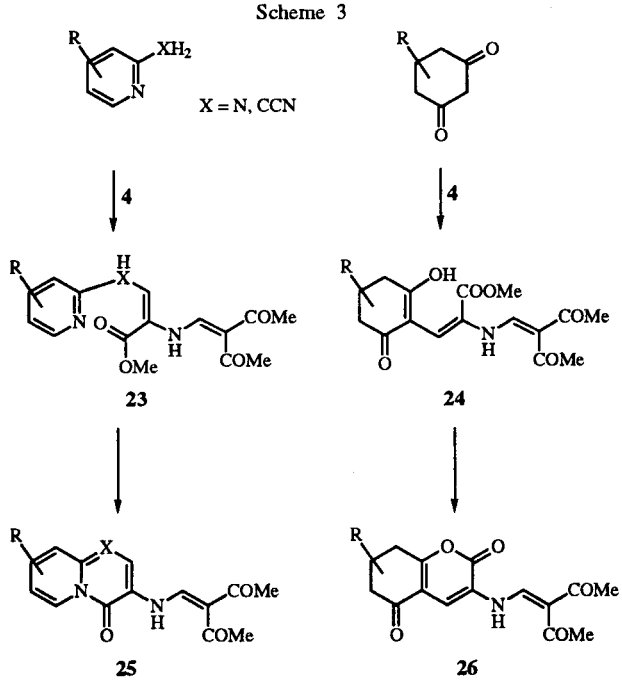


7.86 ppm, for olefinic proton next to dimethylamino group, a doublet at $\delta = 7.86$ ppm, with a coupling constant $J_{CHNH} = 13.0$ Hz, for the proton next to NH group, which shows doublet at $\delta = 11.41$ ppm.

The most reactive group in compound **4** is the enamine group. Formally, the dimethylamino group can be substituted with *N*- and *C*-nucleophiles. The following α-amino heterocycles were selected as *N*-nucleophiles: 2-aminopyridine (**5**), 2-amino-4-methylpyridine (**6**), 2-amino-5-chloropyridine (**7**), 2-aminothiazole (**8**) and 2-aminobenzothiazole (**9**). They were treated with an equimolar amount of **4** in acetic acid under reflux for 1.5 to 2.5 hours. Derivatives of pyrido[1,2-*a*]pyrimidine **14-16**, thiazolo[3,2-*a*]pyrimidine **17**, benzothiazolo[3,2-*a*]pyrimidine **18** were formed (Scheme 2).

C-Nucleophiles react similarly to give either fused pyridinones or pyranones. Two types of *C*-nucleophiles were selected. 2-Pyridilacetonitrile (**10**), having an active methylene group at α-position in respect to the ring nitrogen atom, reacted with **4** to give pyrido[1,2-*a*]pyridine derivative **19**, while cyclic 1,3-diketones, such as cyclo-

Scheme 3



hexane-1,3-diones **11** and **12**, and 1,3,5-trihydroxybenzene as a potential cyclic 1,3,5-triketone, gave after further cyclization with a hydroxy group at α-position the corresponding benzopyran-2-one derivatives **20-22** (Scheme 2).

The intermediates **23** and **24** were not isolated, since they cyclize under the reaction conditions into fused systems **25** and **26**, respectively (Scheme 3).

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a Varian EM 360 L and Bruker Avance DPX 300 spectrometers with TMS as the internal standard, ir spectra on a Perkin-Elmer 1310 or 727 B spectrometer and elemental analyses for C, H and N on a Perkin-Elmer CHN Analyser 2400.

Methyl *N*-[2,2-Bis(acetyl)ethenyl]glycinate (**3**).

To a solution of of acetylacetone (1; 10.3 g, 0.1 mole) in toluene (20 ml), *N,N*-dimethylformamide dimethyl acetal (19.5 ml, 0.13 mole) was added and the mixture was heated for 2 hours under reflux. After that, the volatile components were evaporated *in vacuo*. Methyl glycinate hydrochloride (12.56 g, 0.1 mole) and acetic acid (20 ml) as a solvent were added. The mixture was heated for 1 hour under reflux. The volatile components were evaporated *in vacuo*. The oily residue was crystallized from ethanol to give **3**, yield 11.95 g (60%), mp 110°; ^{1}H nmr (deuteriochloroform): δ 2.25 and 2.47 (s, COMe), 3.77 (s, COOMe), 4.10 (d, CH_2NH), 7.67 (d, C*H*NH), 11.07 (m, NH), J_{CHNH} = 12.9 Hz, J_{CH_2NH} = 6.2 Hz.

Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 53.99; H, 6.68; N, 7.05.

Methyl 2-[2,2-Bis(acetyl)ethenyl]amino-3-dimethylaminopropenoate (**4**).

To a solution of of **3** (19.92 g, 0.1 mole) in acetonitrile (40 ml), *N,N*-dimethylformamide dimethyl acetal (22.5 ml, 0.15 mole) was added and the mixture was heated for 4 hours under reflux. After that, the volatite components were evaporated and solid residue was crystallized from ethyl acetate to give **4** in 98% yield, mp 130-131°; ^{1}H nmr (DMSO-d_6): δ 2.18 and 2.34 (s, COMe), 2.99 (s, NMe_2), 3.60 (s, COOMe), 7.30 (s, H_3), 7.86 (d, C*H*NH), 11.41 (d, NH); J_{CHNH} = 13.0 Hz.

Anal. Calcd. for $C_{12}H_{18}N_2O_4$: C, 56.68; H, 7.13; N, 11.02. Found: C, 56.88; H, 7.06; N, 11.16.

Reactions Between Heteroaryl Amines and *C*-Nucleophiles.

General Procedure.

To a solution of heteroaryl amine (1 mmole) or *C*-nucleophile (1 mmole) in acetic acid (4 ml), equimolar amount of compound **4** (348 mg, 1 mmole) was added, and the mixture was heated under reflux for several hours. Reaction was followed by tlc (DC-Alufolien Kieselgel 60 F 254, 0.2 mm, E. Merck, and chloroform/methanol 10:1 as solvent). After the reaction was completed, acetic acid was evaporated and the solid residue recrystallized from an appropriate solvent.

The following compounds were prepared in this manner:

3-[2,2-Bis(acetyl)ethenyl]amino-*4H*-pyrido[1,2-*a*]pyrimidin-4-one (**14**).

This compound was prepared from 2-aminopyridine (**5**), 2.5 hours of reflux, in 26% yield, mp 254-255° (from toluene); ^{1}H nmr (DMSO-d_6): δ 2.39 and 2.41 (s, COMe), 7.41 (dd, H_7), 7.77 (dd, H_9), 7.90 (dd, H_8), 8.66 (d, C*H*NH), 8.94 (s, H_2), 8.98 (dd, H_6), 12.61 (d, NH), $J_{H_6H_8}$ = 1.5 Hz, $J_{H_8H_9}$ = 8.8 Hz, $J_{H_7H_9}$ = 1.3 Hz, J_{CHNH} = 12.4 Hz.

Anal. Calcd. for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.55; H, 4.80; N, 15.15.

8-Methyl-3-[2,2-bis(acetyl)ethenyl]amino-*4H*-pyrido-[1,2-*a*]pyrimidin-4-one (**15**).

This compound was prepared from 2-amino-4-methylpyridine (**6**), 2.5 hours of reflux, in 17% yield, mp 250° (from toluene); ^{1}H nmr (DMSO-d_6): δ 2.39 (s, 2 x COMe), 2.47 (s, 8-Me), 7.28 (dd, H_7), 7.59 (d, H_9), 8.64 (d, C*H*NH), 8.87 (s, H_2), 8.88 (d, H_6), 12.58 (d, NH), $J_{H_6H_7}$ = 7.3 Hz, $J_{H_7H_9}$ = 1.7 Hz, J_{CHNH} = 12.4 Hz.

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.48; H, 5.29; N, 14.65.

7-Chloro-3-[2,2-bis(acetyl)ethenyl]amino-*4H*-pyrido-[1,2-*a*]pyrimidin-4-one (**16**).

This compound was prepared from 2-amino-5-chloropyridine (**7**), 2 hours of reflux, in 24% yield, mp 228-230° (from toluene); ^{1}H nmr (DMSO-d_6): δ 2.40 (s, 2 x COMe), 7.79 (d, H_9), 7.92 (dd, H_8), 8.65 (d, C*H*NH), 8.94 (s, H_2), 8.95 (d, H_6), 12.58 (d, NH), $J_{H_6H_8}$ = 2.2 Hz, $J_{H_8H_9}$ = 9.5 Hz, J_{CHNH} = 12.4 Hz.

Anal. Calcd. for $C_{14}H_{12}ClN_3O_3$: C, 55.00; H, 3.96; N, 13.74. Found: C, 54.61; H, 3.85; N, 13.65.

6-[2,2-Bis(acetyl)ethenyl]amino-*5H*-thiazolo[3,2-*a*]pyrimidin-5-one (**17**).

This compound was prepared from 2-aminothiazole (**8**), 2 hours of reflux in 41% yield, mp 255-256° (from toluene); ^{1}H nmr (DMSO-d_6): δ 2.36 and 2.40 (s, COMe), 7.64 (d, H_2), 8.13 (d, H_3), 8.55 (d, C*H*NH), 8.63 (s, H_7), 12.42 (d, NH), $J_{H_2H_3}$ = 4.8 Hz, J_{CHNH} = 13.0 Hz.

Anal. Calcd. for $C_{12}H_{11}N_3O_3S$: C, 51.98; H, 4.00; N, 15.15. Found: C, 52.11; H, 3.85; N, 14.88.

3-[2,2-Bis(acetyl)ethenyl]amino-*4H*-benzothiazolo[3,2-*a*]pyrimidin-4-one (**18**).

This compound was prepared from 2-aminobenzothiazole (**9**), 2.5 hours of reflux, in 11% yield, mp 250-255° (from toluene); ^{1}H nmr (DMSO-d_6): δ 2.41 and 2.49 (s, COMe), 7.59-7.65 (m, H_8, H_7), 8.07-8.10 (m, H_9), 8.53 (d, C*H*NH), 8.62 (s, H_2), 8.94-8.97 (m, H_6), 12.51 (d, NH), J_{CHNH} = 13.0 Hz.

Anal. Calcd. for $C_{16}H_{13}N_3O_3S$: C, 58.71; H, 4.00; N, 12.84. Found: C, 58.56; H, 3.92; N, 12.59.

1-Cyano-3-[2,2-bis(acetyl)ethenyl]amino-*4H*-pyrido-[1,2-*a*]pyridin-4-one (**19**).

This compound was prepared from 2-pyridylacetonitrile (**10**), 1.5 hours of reflux, in 37% yield, mp >270° dec (from a mixture of DMF and ethanol); ^{1}H nmr (DMSO-d_6): δ 2.41 and 2.42 (s, COMe), 7.48 (dd, H_7), 7.87 (dd, H_8), 7.97 (d, H_9), 8.58 (d, C*H*NH), 8.77 (s, H_2), 9.12 (d, H_6), 12.77 (d, NH), $J_{H_6H_7}$ = 7.2 Hz, $J_{H_8H_9}$ = 8.8 Hz, J_{CHNH} = 13.0 Hz.

Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found: C, 64.96; H, 4.22; N, 14.12.

5-Oxo-3-[2,2-bis(acetyl)ethenyl]amino-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (**20**).

This compound was prepared from 1,3-cyclohexanedione (**11**), 2.5 hours of reflux, in 21% yield, mp 167-169° (from toluene); ^{1}H nmr (DMSO-d_6): δ 2.08 (t, CH_2), 2.38 and 2.41 (s, COMe), 2.50-2.56 (m, CH_2), 2.84 (t, CH_2), 8.06 (s, H_4), 8.48 (d, C*H*NH), 12.37 (d, NH), $J1_{CH_2CH_2}$ = 6.2 Hz, $J2_{CH_2CH_2}$ = 6.3 Hz, J_{CHNH} = 12.5 Hz.

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 61.98; H, 5.12; N, 4.73.

7,7-Dimethyl-5-oxo-3-[2,2-bis(acetyl)ethenyl]amino-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (**21**).

This compound was prepared from 5,5-dimethyl-1,3-cyclohexanedione (**12**), 2 hours of reflux in 28% yield, mp 196-197° (from toluene); ^{1}H nmr (DMSO-d_6): δ 1.08 (s, 2 x 7-Me), 2.38 and 2.41 (s, COMe), 2.45 (s, 2H, CH_2), 2.82 (s, CH_2), 8.05 (s, H_4), 8.48 (d, C*H*NH), 12.37 (d, NH), J_{CHNH} = 12.6 Hz.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 63.98; H, 6.20; N, 4.43.

5,7-Dihydroxy-3-[2,2-bis(acetyl)ethenyl]amino-2*H*-1-benzopyran-2-one (**22**).

This compound was prepared from 1,3,5-trihydroxybenzene (**13**), 1.5 hours of reflux, in 61% yield, mp >270° (from a mixture of DMF and toluene); ^{1}H nmr (DMSO-d_6): δ 2.39 and 2.40 (s, COMe), 6.26 and 6.34 (d, H_6, H_8), 8.19 (s, H_4), 8.46 (d, C*H*NH), 10.32 and 10.73 (bs, 5-OH, 7-OH), 12.49 (d, NH), J_{H6H8} = 2.0 Hz, J_{CHNH} = 12.9 Hz.

Anal. Calcd. for $C_{15}H_{13}NO_6 \cdot {}^1/_2H_20$: C, 57.69; H, 4.52; N, 4.49. Found: C, 57.35; H, 4.22; N, 4.35.

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