THE SYNTHESIS AND TRANSFORMATIONS OF METHYL 2-[2,2-BIS(ETHOXYCARBONYL)ETHENYL]AMINO-3-DIMETHYL-AMINOBUT-2-ENOATE. THE SYNTHESIS OF 3-AMINO-2-METHYL-4*H*-PYRIDO[1,2-*a*]PYRIMIDIN-4-ONES

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Abstract - Methyl 2-[2,2-bis(ethoxycarbonyl)ethenyl]amino-3-dimethylaminobut-2-enoate (**3**) was prepared from methyl *N*-2,2-bis(ethoxycarbonyl)vinylglycinate (**2**) and DMADMA, and used as a reagent for the preparation of substituted 3-amino-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines (**13-17**), 4*H*-benzothiazolo[3,2-*a*]pyrimidin-4-one (**18**), 5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**19**), and 4-methyl-tetrahydro-2*H*-1-benzopyran-2-ones (**20**) and (**21**).

Amino- and *N*-substituted aminomethylenemalonates and related compounds are of an importance in the synthesis and have been used extensively in the preparation of variety of heterocyclic systems.[1] A wide variety of bicyclic systems with a bridgehead nitrogen atom, especially fused pyrimidinones, has been prepared.[1]

On the other hand, for preparation of substituted 3-aminoazolo- and azinopyrimidin-4-ones, either 4-ethoxyalkylidene-2-phenyl-5(4*H*)oxazolones[2] or alkyl 2-acylamino-3-dimethylaminopropenoates[3,4] have been used.

3-Benzoylamino-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones and 6-benzoylamino-7-methyl-5*H*-thiazolo-[3,2-*a*]pyrimidin-5-ones have been prepared from 2-aminopyridine and 2-aminothiazole by treatment with 4-ethoxyethilidene-2-phenyl-5(4*H*)oxazolone.[2]

Recently, a group of substituted alkyl (2-substituted ethenyl)amino-3-dimethylaminopropenoates, such as ethyl (*Z*)-2-[2,2-bis(ethoxycarbonyl)vinyl]amino-3-dimethylaminopropenoate,[5,6] alkyl 2-[2-benzoyl-2-ethoxycarbonylethenyl]amino-3-dimethylaminopropenoate,[7] and methyl 2-[2,2-bis(acetyl)ethenyl]amino-3-

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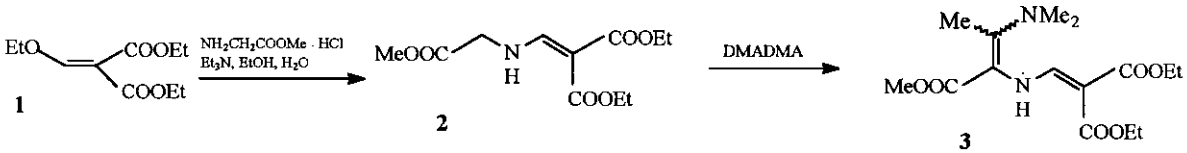
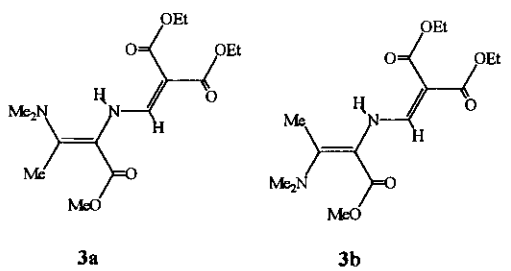
dimethylaminopropenoate,[8] has been prepared and employed as reagents for the synthesis of various heterocyclic systems[3,4] with a protected amino group at position 3 of the newly formed pyrimidinone ring. Since the *N*-protecting group can be easilly removed, fused 3-aminopyrimidinones can be easilly prepared.[9] In this paper we present, as an extension of our research in this area, the synthesis of methyl 2-[2,2-bis(ethoxycarbonyl)ethenyl]amino-3-dimethylaminobut-2-enoate (**3**) and its application for the synthesis of fused 3-amino-2-methyl substituted pyrimidinones and fused 3-amino-4-methyl-2*H*-1-pyran-2-ones. Compound (**3**) was prepared from methyl *N*-2,2-bis(ethoxycarbonyl)vinylglycinate (**2**), obtained from methyl glycinate and diethyl ethoxymethylenemalonate (**1**),[10] by treatment with with *N,N*-dimethylacetamide dimethyl acetal (DMADMA) without solvent (Scheme 1).

Scheme 1

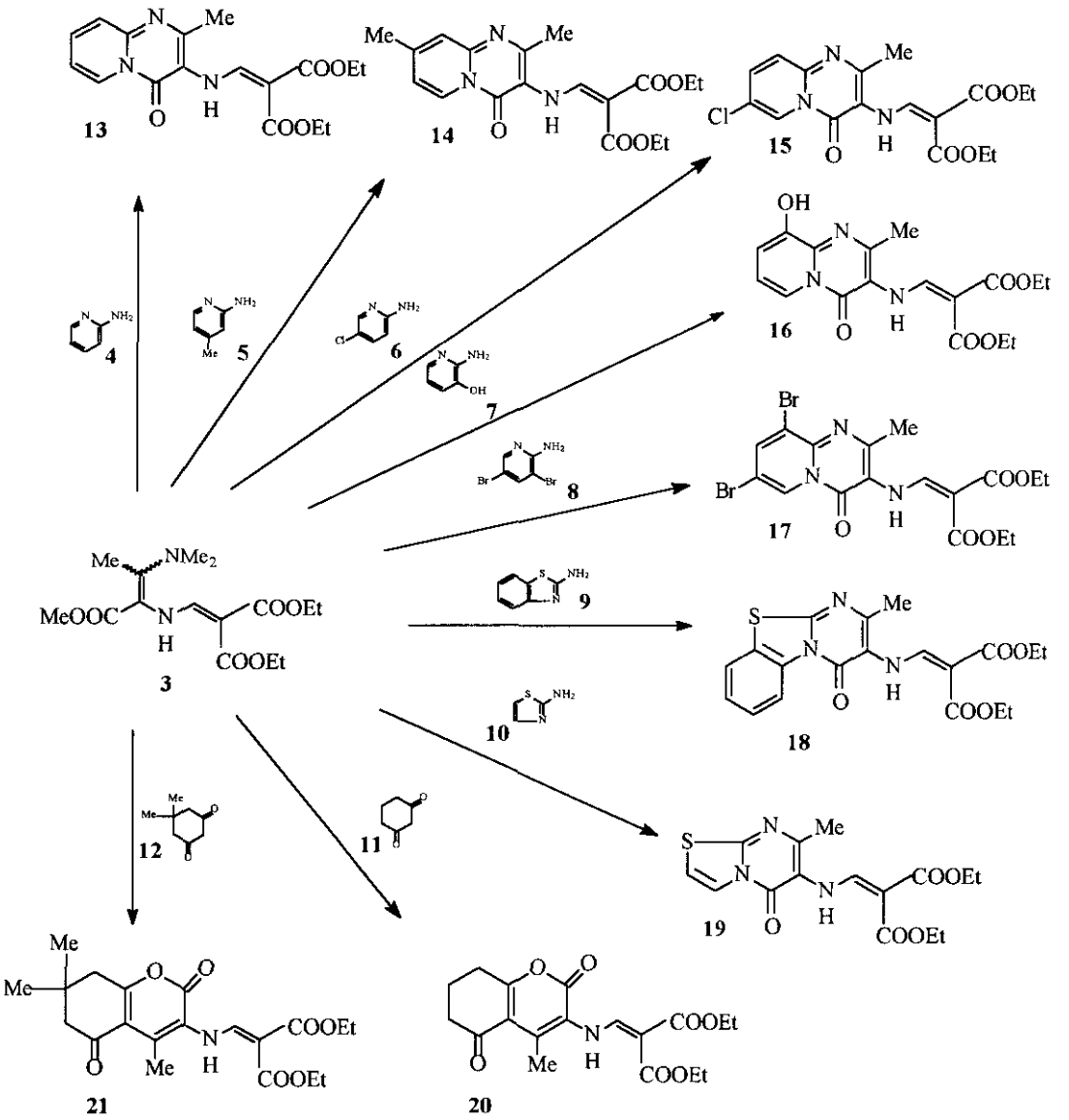


The structure of compound (**3**) was established by ^{1}H NMR spectra. Namely, the compound dissolved in DMSO-d_6 showed in ^{1}H NMR spectrum two sets of signals in a ratio of 2:1, which indicates an equilibrium between two isomers. The most characteristic is the chemical shift difference for the methyl group attached to the double bond, δ=2.37 ppm and δ= 2.00 ppm, which indicates the existence of two isomers (*Z*)- and (*E*)- in the solution. The magnitude of the coupling constants J_{CHNH}= 13.9 - 14.3 Hz, strongly suggests the trans (antiperiplanar) orientation of both hydrogens in respect to each other. The final proof for both structures was obtained by NOESY experiment. In (*Z*)-isomer (**3a**), NH signal shows a crosspeak with a dimethylamino group, while in (*E*)-isomer (**3b**), NH signal shows a crosspeak with a methyl group (Scheme 2).

Scheme 2



Scheme 3



Compound (**3**) reacts with *N*- and *C*- nucleophiles in which *N,N*-dimethylamino group is substituted. The following *N*-nucleophiles were selected: 2-aminopyridine (**4**), 2-amino-4-methylpyridine (**5**), 2-amino-5-chloropyridine (**6**), 2-amino-3-hydroxypyridine (**7**), 2-amino-3,5-dibromopyridine (**8**), 2-aminobenzothiazole (**9**) and 2-aminothiazole (**10**). They were transformed directly into the corresponding derivatives of 3-[2,2-bis(ethoxycarbonyl)ethenyl]amino-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidine-4-ones (**13-17**), and thiazolo[3,2-*a*]pyrimidines (**18**) and (**19**), respectively (Scheme 3).

In the reaction of compound (**3**) with 1,3-cyclohexanedione (**11**) and dimedone (**12**) 3-[2,2-bis(ethoxycarbonyl)ethenyl]amino-4-methyl-5-oxo-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one derivatives (**20**) and (**21**) were formed (Scheme 3).

2,2-Bis(ethoxycarbonyl)ethenyl- group as *N*-protecting group can be easily removed. For example, when compound (**13**) and (**19**) were treated with solution of hydrazine hydrate in ethanol at reflux, the corresponding free 3-amino- and 6-amino- derivatives (**22**) and (**23**) were formed, respectively (Scheme 4).

Scheme 4

The method represents an alternative in comparison with previously described synthesis,[12-14] resulting in better yields of 3-amino-4*H*-pyrido[1,2-*a*]pyrimidine-4-ones.

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 spectrophotometer, MS spectra on AutoSpecQ spectrometer and elemental analyses for C, H and N on a Perkin-Elmer CHN Analyser 2400.

Methyl *N*-[2,2-Bis(ethoxycarbonyl)ethenyl]glycinate (2). To a suspension of methyl glycinate hydrochloride (50.22 g, 400 mmol) in 200 mL of ethanol, triethylamine (55.6 mL, 400 mmol) and diethyl ethoxymethylenemalonate (**1**, 80 mL, 400 mmol) were added. After that, the mixture was stirred and left overnight. Volatile compounds were evaporated *in vacuo*, and to solid residue water (100-200 mL) was

added and the mixture was heated until everything dissolved. After cooling, white precipitate was collected by filtration and recrystallized from ethanol to give **2** in 98% yield (101.61 g), mp 66-71°; ^{1}H NMR (DMSO-d_6): δ 1.19 and 1.22 (t, COOEt), 3.68 (s, COOMe), 4.05 and 4.12 (q, COOEt), 4.27 (d, NHCH_2), 7.98 (d, NHC*H*), 9.12 (m, NH); J_{CH2CH3}= 7.2 Hz, J_{CHNH}= 14.7 Hz, J_{CH2NH}= 6.0 Hz. *Anal.* Calcd for $C_{11}H_{17}NO_6$: C, 50.94; H, 6.61; N, 5.40. Found: C, 51.18; H, 6.66; N, 5.35.

Methyl 2-[2,2-Bis(ethoxycarbonyl)ethenyl]amino-3-dimethylaminobut-2-enoate (3). To 10 mmol (2.59 g) of methyl *N*-[2,2-bis(ethoxycarbonyl)ethenyl]glycinate **(2)**, we added 30 mmol (4.8 mL) of dimethylacetamide dimethyl acetal. Suspension was heated under reflux for 7 h. Volatile components were evaporated *in vacuo*, to give **3** in ~75% yield (2.46 g), (65% (*Z*)-configuration). Compound (**3**) was used in reactions without further purification. MS, M^+ = 328; ^{1}H NMR (DMSO-d_6): δ 1.18 and 1.23 (t, COOEt), 2.00 (s, *E*-Me), 2.37 (s, *Z*-Me), 2.88 (s, *Z*-Me_2N), 2.97 (s, *E*-NMe_2), 3.57 (s, COOMe), 4.04 and 4.13 (q, COOEt), 7.57 (d , *E*-C*H*NH), 7.61 (d, *Z*-C*H*NH), 9.59 (d, *Z*-CHN*H*), 9.78 (d, *E*-CHN*H*); J_{CH2CH3}=7.2 Hz, $J_{CHNH(Z)}$=14.32 Hz, $J_{CHNH(E)}$= 13.94 Hz. NOESY (DMSO-d_6): minor NH signal (35%, *E*) shows a crosspeak with Me group, while major NH signal (65%, *Z*) shows a crosspeak with NMe_2 group.

General Procedure for Reactions of 3 with Heteroaryl Amines and *C*-Nucleophiles. To a solution of heteroaryl amine (1 mmol) or *C*-nucleophile (1 mmol) in acetic acid (4 mL), equimolar amount of compound (**3**) (328 mg; 1 mmol) 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:

2-Methyl-3-[2,2-bis(ethoxycarbonyl)ethenyl]amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (13). This compound was prepared from 2-aminopyridine (**4**), 3 h of reflux, in 28% yield, mp 187-188° (from mixture of toluene/2-propanol 1:1); ^{1}H NMR (CF_3COOD): δ 0.98 and 1.05 (t, COOEt), 2.39 (s, 2-Me), 4.06 and 4.11 (q, COOEt), 7.30-8.25 (m, H_7, H_8, H_9), 8.40 (s, C*H*NH), 9.04 (dd, H_6); J_{H6H8}= 2 Hz, J_{H6H7}= 10 Hz, J_{CH2CH3}=7 Hz. *Anal.* Calcd for $C_{17}H_{19}N_3O_5$: C, 59.09; H, 5.34; N, 12.34. Found: C, 59.12; H, 5.55; N, 12.17.

2,8-Dimethyl-3-[2,2-bis(ethoxycarbonyl)ethenyl]amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (14). This compound was prepared from 2-amino-4-methylpyridine (**5**), 3 h of reflux, in 30% yield, mp 187-188°

(from ethanol); ^{1}H NMR (CF_3COOD): δ 0.94 and 1.04 (t, COOEt), 2.40 (s, 2-Me), 2.42 (s, 8-Me), 4.05 and 4.06 (q, COOEt), 7.32 (dd, H_7), 7.49 (dd, H_9), 8.38 (s, C*H*NH), 8.85 (dd, H_6); J_{H6H7}= 8 Hz, J_{H6H9}= 1 Hz, J_{H7H9}= 2 Hz, J_{CH2CH3}= 7 Hz. *Anal.* Calcd for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 59.98; H, 5.88; N, 11.65.

7-Chloro-2-methyl-3-[2,2-bis(ethoxycarbonyl)ethenyl]amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (15). This compound was prepared from 2-amino-5-chloropyridine (**6**), 3 h of reflux, in 40% yield, mp 190-191° (from 2-propanol); ^{1}H NMR (CF_3COOD): δ 1.00 (t, 2xCOOEt), 2.35 (s, 2-Me), 4.08 (q, 2xCOOEt), 7.75 (d, H_9), 8.12 (dd, H_8), 8.45 (s, C*H*NH), 9.04 (d, H_6); J_{H6H8}= 2 Hz, J_{H8H9}= 10 Hz, J_{CH2CH3}= 7 Hz. *Anal.* Calcd for $C_{17}H_{18}N_3O_5Cl$: C, 53.76; H, 4.78; N, 11.06. Found: C, 53.56; H, 4.49; N, 11.10.

9-Hydroxy-2-methyl-3-[2,2-bis(ethoxycarbonyl)ethenyl]amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (16). This compound was prepared from 2-amino-3-hydroxypyridine (**7**), 3 h of reflux, in 15% yield, mp 165-166° (from 2-propanol); ^{1}H NMR (CF_3COOD): δ 0.95 and 1.04 (t, COOEt), 2.42 (s, 2-Me), 4.05 and 4.12 (q, COOEt), 7.12-7.76 (m, H_7, H_8), 8.38 (s, C*H*NH), 8.55 (dd, H_6); J_{H6H8}= 2 Hz, J_{H6H7}= 10 Hz, J_{CH2CH3}= 7 Hz. *Anal.* Calcd for $C_{17}H_{19}N_3O_6$: C, 56.51; H, 5.30; N, 11.63. Found: C, 56.09; H, 5.17; N, 11.66.

7,9-Dibromo-2-methyl-3-[2,2-bis(ethoxycarbonyl)ethenyl]amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (17). This compound was prepared from 2-amino-3,5-dibromopyridine (**8**), 3 h of reflux, in 60% yield, mp 178-180° (from mixture of toluene/2-propanol 1:1); ^{1}H NMR (CF_3COOD): δ 0.95 and 1.00 (t, COOEt), 2.42 (s, 2-Me), 4.05 and 4.08 (q, COOEt), 8.40 (s, C*H*NH), 8.42 (d, H_8), 9.07 (d, H_6); J_{H6H8}= 2 Hz, J_{CH2CH3}= 7 Hz. *Anal.* Calcd for $C_{17}H_{17}N_3O_5Br_2$: C, 40.58; H, 3.41; N, 8.35. Found: C, 40.39; H, 3.27; N, 8.43.

2-Methyl-3-[2,2-bis(ethoxycarbonyl)ethenyl]amino-4*H*-benzothiazolo[3,2-*a*]pyrimidin-4-one (18). This compound was prepared from 2-aminobenzothiazole (**9**), 3 h of reflux, in 10% yield, mp 165-170° (from mixture of toluene/ethanol 1:1); ^{1}H NMR (CF_3COOD): δ 0.94 and 1.02 (t, COOEt), 2.30 (s, 2-Me), 4.00 and 4.12 (q, COOEt), 7.32-7.68 (m, H_7, H_8, H_9), 8.45 (s, C*H*NH), 8.57-8.92 (m, H_6); J_{CH2CH3}= 7 Hz. *Anal.* Calcd for $C_{19}H_{19}N_3O_5S$: C, 56.85; H, 4.77; N, 10.47. Found: C, 56.67; H, 4.59; N, 10.25.

7-Methyl-6-[2,2-bis(ethoxycarbonyl)ethenyl]amino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (19). This compound was prepared from 2-aminothiazole (**10**), 3 h of reflux, in 20% yield, mp 188-189° (from 2-

propanol); ^{1}H NMR (DMSO-d_6): δ 1.20 and 1.28 (t, COOEt), 2.35 (s, 7-Me), 4.05 and 4.18 (q, COOEt), 7.58 (d, H_2), 8.08 (d, H_3), 8.72 (d, C*H*NH), 10.45 (d, 1H, NH); J_{H2H3}= 5 Hz, J_{CHNH}=15 Hz, J_{CH2CH3}= 7 Hz. *Anal.* Calcd for $C_{15}H_{17}N_3O_5S$: C, 51.27; H, 4.88; N, 11.96. Found: C, 51.02; H, 4.77; N, 12.07.

4-Methyl-5-oxo-3-[2,2-bis(ethoxycarbonyl)ethenyl]amino-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (20). This compound was prepared from 1,3-cyclohexandione (**11**), 3 h of reflux, in 24% yield, mp 153-154° (from 2-propanol); ^{1}H NMR (DMSO-d_6): δ 1.15 and 1.22 (t, COOEt); 2.00 (t, CH_2), 2.25-2.65 (m, CH_2), 2.40 (s, 4-Me), 2.88 (t, CH_2), 4.08 and 4.20 (q, COOEt), 8.38 (d, C*H*NH), 10.30 (d, NH); J_{CH2CH2}= 6 Hz, J_{CHNH}= 15 Hz, J_{CH2CH3}= 7 Hz. *Anal.* Calcd for $C_{18}H_{21}NO_7$: C, 59.50; H, 5.83; N, 3.85. Found: C, 59.30; H, 5.72; N, 3.93.

7,7,4-Trimethyl-5-oxo-3-[2,2-bis(ethoxycarbonyl)ethenyl]amino-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one (21). This compound was prepared from 5,5-dimethyl-1,3-cyclohexandione (**12**), 3.5 h of reflux, in 40% yield, mp 134-136° (from 2-propanol); MS, M^+= 391; ^{1}H NMR (DMSO-d_6): δ 1.05 (s, 2x7-Me), 1.24 (t, 2xCOOEt), 2.44 (s, CH_2), 2.46 (s, 4-Me), 2.84 (s, CH_2), 4.15 (q, 2xCOOEt), 8.42 (d, C*H*NH), 9.33 (d, NH); J_{CHNH}= 15 Hz, J_{CH2CH3}= 7 Hz. *Anal.* Calcd for $C_{20}H_{25}NO_7 \cdot H_2O$: C, 58.67; H, 6.65; N, 3.42. Found: C, 58.58; H, 6.40; N, 3.56.

General Procedure for Removal of the 2,2-Bis(ethoxy)ethenyl Group. To a starting compound (1 mmol), 0.5M solution of hydrazine hydrate in ethanol (4 mL), was added. The mixture was heated under reflux for 0.5 h. After that, mixture was cooled until precipitate was formed, which was further collected by filtration and recrystallized from an appropriate solvent.

3-Amino-7-chloro-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (22). This compound was prepared from 7-chloro-2-methyl-3-[2,2-bis(ethoxycarbonyl)ethenyl]amino-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**13**), in 71% yield, mp 262-263° (from ethanol); MS, M^+ = 209; ^{1}H NMR (CF_3COOD): δ 2.42 (s, 2-Me), 7.72 (d, H_9), 8.12 (dd, H_8), 8.90 (d, H_6); J_{H8H9}= 10 Hz, J_{H6H8}= 3 Hz. *Anal.* Calcd for $C_9H_8N_3OCl$: C, 51.57; H, 3.85; N, 20.04. Found: C, 51.31; H, 3.73; N, 20.16.

6-Amino-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (23). This compound was prepared from 7-methyl-6-[2,2-bis(ethoxycarbonyl)ethenyl]amino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**19**), in 47% yield, mp 142-145° (from ethanol); ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 7-Me), 4.55 (s, NH_2), 7.39 (d, H_2), 7.87 (d,

H_3); J_{H2H3}= 4.9 Hz. *Anal.* Calcd for $C_7H_7N_3OS$: C, 46.40; H, 3.89; N, 23.19. Found: C, 46.36; H, 3.93; N, 23.99.

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REFERENCES AND NOTES

1. For a review see: J. Hermecz, G. Kereszturi, and L. Vasvari-Debreczy, *Aminomethylenemalonates and Their Use in the Heterocyclic System, Advances in Heterocyclic Chemistry,* **1992**, *54*, pp. 1-452.
2. O. Tsuge and M. Noguchi, *Heterocycles*, **1981**, *16*, 1981.
3. B. Stanovnik, *Methyl 2-Benzoylamino-3-dimethylaminopropenoate in the Synthesis of Heterocyclic Systems,* in *Progress of Heterocyclic Chemistry;* ed. by H. Sushitzky and E. F. V. Scriven, Pergamon Press, Oxford, **1993**, Vol. 5, pp. 34-53.
4. B. Stanovnik, *Molecules*, **1996**, *1*, 123.
5. G. Soršak, A. Sinur, L. Golič, and B. Stanovnik, *J. Heterocycl. Chem.*, **1995**, *32*, 921.
6. R. Toplak, L. Selič, G. Soršak, and B. Stanovnik, *Heterocycles*, **1997**, *45*, 555.
7. S. Strah, S. Golič Grdadolnik, and B. Stanovnik, *J. Heterocycl. Chem.*, **1997**, *33*, 263.
8. L. Selič and B. Stanovnik, *J. Heterocycl. Chem.*, **1997**, *34*, 813.
9. L. Selič, S. Strah, R. Toplak, and B. Stanovnik, *Heterocycles,* **1998**, *47*, No.2, in print.
10. Prepared in a similar way as described in the lit.[11]
11. T. Momose, T. Tanaka, T. Yokota, N. Nagamoto, and K. Yamada, *Chem. Pharm. Bull.*, **1978**, *26*, 2224.
12. G. Horváth, I. Hermecz, A. Horváth, M. Pongor-Csákvári, L. Pusztay, A. I. Kiss, L. Czakó, and O. H. Abdirizak, *J. Heterocycl. Chem.*, **1985**, *22*, 481.
13. J. Smodiš, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.*, **1994**, *31*, 125.
14. J. Parrick and H. K. Rami, *J. Chem. Res. (M)*, **1990**, 2411.

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