Reactivity of 3-halo-2-oxopropanamides and 3-halo-2-cyano-2-hydroxypropanoates: synthesis of S and N containing heterocycles

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Dedicated to Professor Miha Tišler, University of Ljubljana, on occasion of his 75th birthday

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Abstract

The reaction and the proposed mechanism of 3-halopyruvamides 3 and their ester analogs with *S* and *N* binucleophiles is described. Compounds from imidazo[1,2-*a*]pyridine, imidazo[1,2-*a*]pyrimidine, thiazole, imidazo[2,1-*b*]thiazole, thiazolo[2,3-*b*]thiazole and dithiadiazafulvalene series, substituted by an amide or ester group, are presented.

Keywords: Oxirane, halohydrine, halopyruvamide, imidazopyridine, imidazopyrimidine, imidazothiazole, thiazolothiazole, DTDAF

Introduction

3-Halopyruvamides and their ester analogs are interesting in enzymology[1] and also as activators for phototropic compositions.[2] One of the greatest advantages of 3-halopyruvamides compared to 3-halopyruvates is that pyruvate dependent enzymes bind them like pyruvates, but are not able to accept them as substrat during the catalytic process.[1,3] This makes them useful as potential inhibitors for pyruvate decarboxylases, pyruvate dehydrogenases or pyruvate oxidases. Recent studies[4] revealed important inhibitory properties for HIV proteases of certain α-keto-amides. Some di- or tripeptidyl α-keto esters, α-keto amides and α-keto acids show inhibitor properties of cystin proteases and may be used for the treatment of diseases which involve neurodegradation.[5]

Belonging to α-haloketons, α-halopyruvamides and α-halopyruvates are also valuable starting materials in organic chemistry.[6] As bielectrophiles they are expected to react with different nucleophiles in protic or nonprotic medium and so they can be useful starting materials to reach heterocyclic compounds of pharmaceutical interest: imidazo[1,2-*a*]pyridines,[7,8] imidazo[1,2-*a*]pyrimidines,[8] thiazoles,[9-12] imidazo[2,1-*b*]thiazoles[13-15] and tiazolo-thiazoles.[16-18]

We already described a regioselective ring opening of the readily accessible 2-cyano-2-oxiranecarboxamides **1** leading to stable 3-halohydrines **2** which by decyanuration give the corresponding 3-haloketones **3** (Scheme 1). The reactivity of the latter compounds **3** towards *O*-nucleophiles and the synthesis of the first stable α-diols and hemiketals from these series, until then detected only by spectroscopic means, was discussed too.[19,20]

In this publication we describe the reactivity of the compounds **3** towards *N*- and *S*-nucleophiles and the synthesis of various heterocyles, especially the imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines, thiazoles, imidazo[2,1-*b*]thiazoles, tiazolo[2,3-*b*]thiazoles and dithiadiaza-fulvalenes.

Results and Discussion

The stable 3-halohydrines **2** (3-halo-2-cyano-2-hydroxypropanamides and their ester analogs) are easily obtained from 2-cyano-2-oxiranes **1**.[19,20] The compounds **2** can be easily decyanurated so that we can consider them as protected forms of compounds **3** (3-halopyruvamides, R=CO_2NH_2 and 3-halopyruvates, R=CO_2Me or CO_2Et) (Scheme 1).

Compounds **3** are very reactive bielectrophiles, able to react in protic and nonprotic medium with different nucleophiles. We observed that *O*-nucleophiles H_2O and ROH react in an equilibrium reaction exclusively with the electrophilic center of the carbonyl groups. Stable diols and hemiketals were isolated for the first time in that series of compounds.[18]

A different behaviour was observed with *N*,*N*- and *N*,*S*-binucleophiles as presented in Scheme 1. In the reaction of compound **3** with *N*,*N*-binucleophiles like **4**, **5** and **6** we obtained by the simple reflux in CH_3CN (or in DMF at room temperature) imidazopyridines **12**, imidazopyrimidines **13** and imidazothiazoles **14** of high degree of purity with yields from 46% to 71%. ^1H and ^{13}C NMR spectra are compatible with the proposed structures. We performed the X-ray analysis of the compound **12a**[21] (Figure 1) which confirms that obtained compounds are the result of the reaction of the most nucleophilic nitrogen with the carbon bearing halogen of the compound **3**. Our results are also in good agreement with those found in literature.[22,23] We didn't isolate the acyclic intermediate **A**, which according to literature can sometimes be isolated.[23]

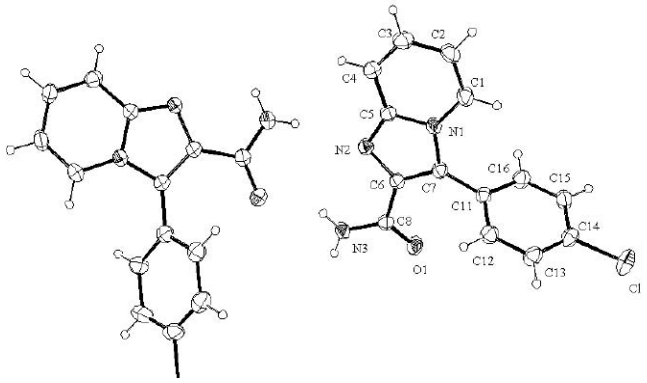
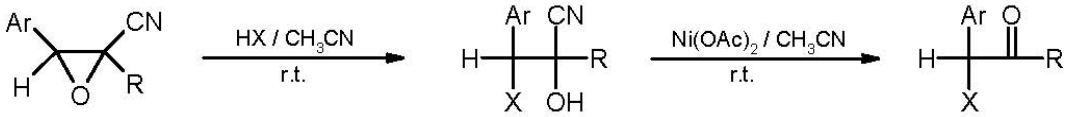


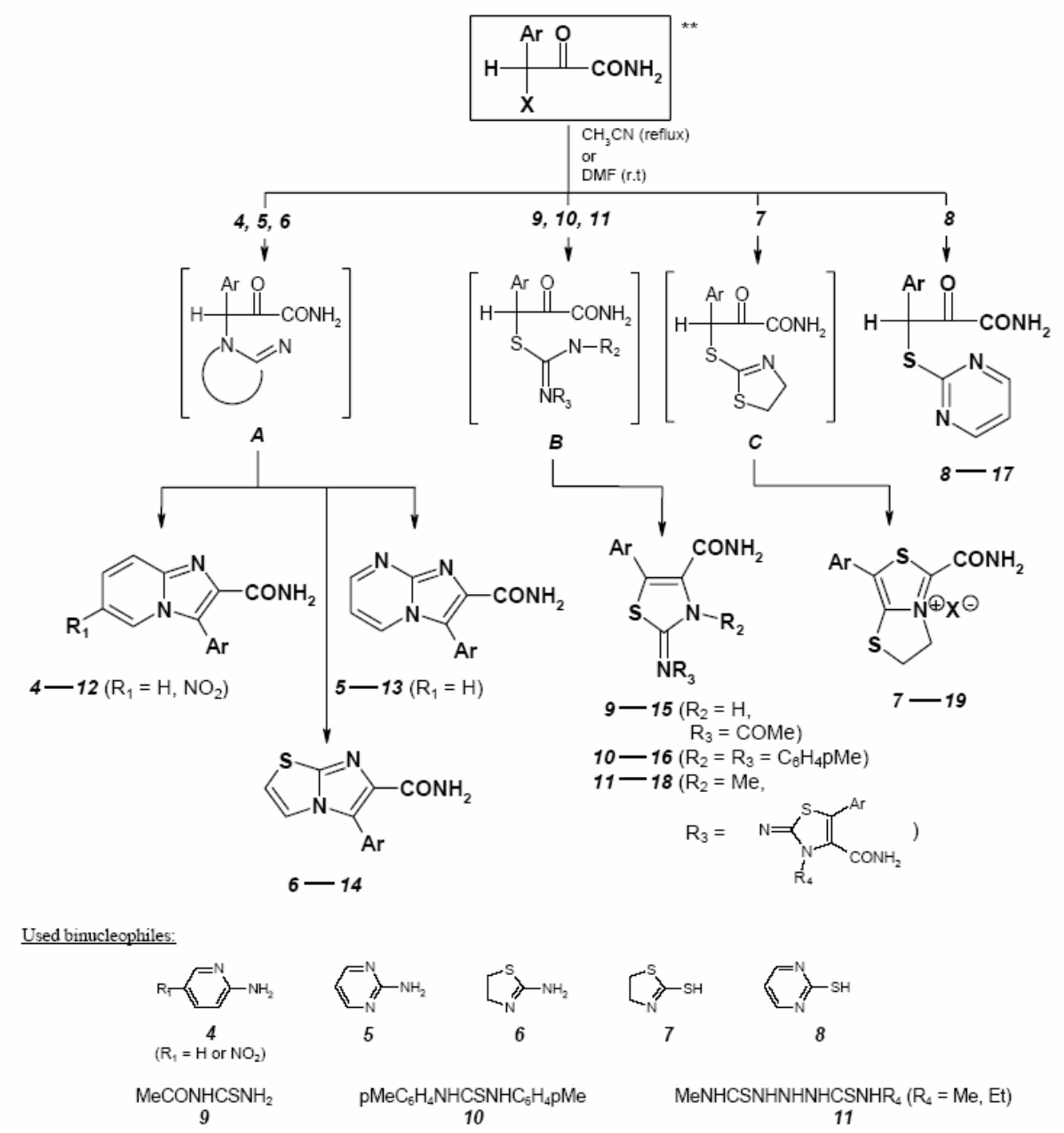
Figure 1. Compound 12a (R_1 = H, Y = CH, Ar = pClC_6H_4.

When mixed *N,S*-binucleophiles **9**, **10** and **11** were used in the reaction with haloketons **3,** thiazoles **15** and 2-imino-thiazolidines **16** and **18** were easily formed at reflux in CH_3CN. Yields of pure crude compounds varied from 50% to 83%. Synthesized compounds seem to be the result of the reaction of the exocyclic sulphur with the carbon bearing halogen of the compound **3**. Postulated intermediate **B** leads after heterocyclisation to **15**, **16** and **18** which were in good agreement with spectroscopic data. Intermediate like B was already proposed with similar compounds.[24,25] Halopyruvamides **3**, halopyruvates **3** and their protected form **2** proved to be useful intermediates in the synthesis of heterocyclic compounds of interest in the field of organic materials.[26,27] With hydrazinedicarbothioamides **11** extended dithiadiazafulvalenes (DTDAF) **18** were formed.



1 **2** **3**

R = $CONH_2$, CO_2Me, CO_2Et
X = Cl, Br
Ar = C_6H_5, 4-CH_3-C_6H_4, 4-Cl-C_6H_4, 4-NO_2-C_6H_4



** Some reactions were performed starting from the precursor 2 (R = $CONH_2$, CO_2Me, CO_2Et). See experimental part.

Scheme 1

The same orientation was observed with 2-pyrimidinethiol **8** and 4,5-dihydro-1,3-thiazole-2-thiol **7**. In the case of the reaction of **3** with **8**, cyclisation didn't occur and the only isolated product was **17** (70% yields). It is interesting to note that the formation of **17** is the result of the reaction of *S*-nucleophile with carbon bearing halogen rather than with carbon bearing a carbonyl group unlike *O*-nucleophiles. With 4,5-dihydro-1,3-thiazole-2-thiol **7** we observed the formation

of products **19** (the synthesis is possible also starting from 3-halohydrines **2** which transformed *in situ* in 3-haloketons **3** able to react with the nucleophile). X-ray diffraction showed that the real structure was thiazolo-thiazolium halide **19**[21] (Figure 2), which obviously resulted from a sulfur transposition. In the case of intermediate **C** (Scheme 1) heterocyclisation is a priori difficult because of lower nucleophilisity of the nitrogen atom in the 4,5-dihydro-1,3-thiazole ring. We suppose that transposition of the sulfur atom occurs through thiirane intermediate[28] resulting in the formation of the product **19**. This is not surprising because we already observed[29] similar transpositions and in some cases sulphur was eliminated.[28,30]

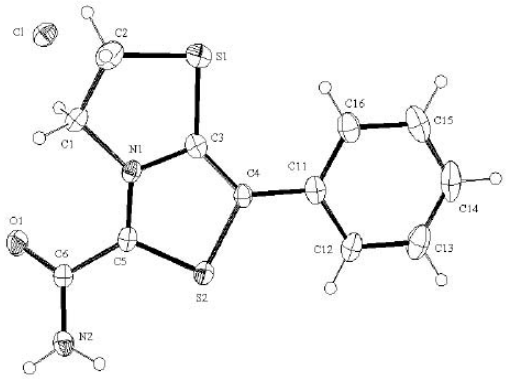


Figure 2. Compound **19a** (Ar = Ph).

Conclusions

3-Halopyruvamides **3** and their ester analogs as well as their protected 3-halohydrine form **2** are very reactive bielectrophiles which can react with different *O*-, *S*- and *N*-nucleophiles. Unlike *O*-nucleophiles which give stable diols and hemiketals as the result of the reaction with the carbonyl group of title compounds, reaction products with *S*- and *N*-nucleophiles are rather the result of the reaction with the carbon bearing halogen. The reaction passes probably through an acyclic intermediate which was isolated in one case as 3-aryl-2-oxo-3-(2-pyrimidinylsulfanyl)propan amide **17**. With 4,5-dihydro-1,3-thiazole-2-thiol **7** we obtained the thiazolo-thiazolium salt **19**, resulting from the transposition of sulphur. The proposed synthetic route is a convenient method for the preparation of different imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines, thiazoles, imidazo[2,1-*b*]thiazoles, thiazolo[2,3-*b*]thiazoles and dithiadiazafuevalenes having amide or ester functional groups. Products were obtained in a pure form with reasonable yields by the simple reflux in CH_3CN or sometimes at room temperature in DMF.

Experimental Section

General Procedures. ^{1}H NMR spectra were recorded at 80 MHz on a Bruker WP 80 spectrometer or at 300 MHz on a Bruker AM 300 spectrometer, ^{13}C NMR broadband decoupled spectra and ^{13}C NMR coupled spectra at 75 MHz on a Bruker AM 300 spectrometer using tetramethylsilane as internal reference. High resolution mass spectra were obtained with a Varian Mat 311 mass spectrometer. IR spectra were determined with a Perkin-Elmer 225 or 1420 spectrometer. Melting points were taken with a Kofler hot stage apparatus.

General procedure for the preparation of oxiranes 1

The starting oxiranes **1** (R= $CONH_2$) were easily prepared by treating the corresponding cyano ester oxiranes with ammonia according to a described procedure.[20]

General procedure for the preparation of 3-halohydrines 2

Hydrobromic acid (18 mol/L or 47 %; 38 mL) was added to the solution of the oxirane **1** (9.2 mmol) dissolved in MeCN (30 mL) and left 3h at room temperature under stirring and then without stirring for 12h. Formed crystals were washed with water (to pH = 7), dried *in vacuo* (50°C, 100mbar, 24h) and recrystallised from MeCN. The crude product was pure enough for the preparation of pyruvamides **3** and heterocycles forming reactions.

3-Bromo-2-cyano-2-hydroxy-3-(4-methylphenyl)propanamide (Ar = $pCH_3C_6H_4$, R = $CONH_2$, X = Br) (**2j**). According to the general procedure 3-(4-methylphenyl)-2,2-oxirandicarbonitrile (**1**) (2 g, 10,9 mmol) was converted to **2j** in 93% yield; m.p. 210°C (MeCN). IR (Nujol): ν 3468, 3351, 2249, 1693 cm^{-1}. ^{1}H NMR ($CDCl_3$, CF_3COOH): δ 2.30 (s, 3H, CH_3), 5.50 (s, 1H, CHBr), 6.80 (br s, 2H, $CONH_2$), 7.25 (m, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$, CF_3COOH): δ 20.88 (q, 1*J* = 127 Hz, CH_3), 44.71 (d, 1*J* = 157 Hz, CHBr), 76.68 (d, 2*J* = 5.78 Hz, COH), 113.16 (m, CN) 129.68, 129.02, 125.88, 142.95 (C_6H_4), 170.38 (s, $CONH_2$). HRMS: Found 254.9890. Calcd. for $C_{11}H_{11}N_2O_2Br$ (M^+;. - HCN) : 254.9895. Anal. Calcd. for $C_{11}H_{11}N_2O_2Br$: C, 46.67; H, 3.92; N, 9.89. Found: C, 46.46; H, 3.87; N, 9.80.

Methyl 3-bromo-2-cyano-2-hydroxy-3-(4-chlorophenyl)propanoate (Ar = $pClC_6H_4$, R = CO_2CH_3, X = Br) (**2k**). According to the general procedure methyl 2-cyano-3-(4-chlorophenyl)-2-oxirancarboxylate (**1**) (2 g, 8.42 mmol) was converted to **2k** in 70% yield; m.p. 135°C (MeCN). IR (Nujol): ν 3430, 2255, 1745 cm $^{-1}$. ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 3H, OCH_3), 4.22 (s, 1H, OH), 5.31 (s, 1H, CHBr), 7.37 (m, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$): δ 52.41 (d, 1*J* = 155.81 Hz, CHBr), 55.26 (q, 1*J* = 150.18 Hz, OCH_3), 75.04 (s, COH), 115.77 (t, CN) 128.79, 130.60, 132.37, 136.16 (C_6H_4), 165.58 (m, CO). Anal. Calcd. for $C_{11}H_9N_1O_3Br_1C_{l1}$: C, 41.48; H, 2.85; N, 4.40. Found: C, 41.13, H, 2.83; N, 4.30.

Methyl 3-bromo-2-cyano-2-hydroxy-3-(4-methylphenyl)propanoate (Ar = $pCH_3C_6H_4$, R = CO_2CH_3, X = Br) (**2l**): According to the general procedure methyl 2-cyano-3-(4-methylphenyl)-2-oxirancarboxylate (**1**) (2 g, 8.42 mmol) was converted to **2l** in 88% yield; m.p. 130°C (MeCN). IR (Nujol): ν 3380, 2240, 1750 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3),

4.25 (s, 1H, OH), 5.32 (s, 1H, CHBr), 7.22 (m, 4H, C_6H_4). 13C NMR (DMSO-d_6): δ 54.00 (q, 1J = 148.80 Hz, OCH_3), 63.51 (d, 1J = 158.81 Hz, CHBr), 76.82 (s, COH), 116.50 (s, CN), 129.72, 129.90, 131.20, 139.79 (C_6H_4), 168.30 (s, CO). Anal. Calcd. for $C_{12}H_{12}N_1O_3Br_1$: C, 48.34; H, 4.06; N, 4.70. Found: C, 47.82; H, 3.98; N, 4.58.

Ethyl 3-bromo-2-cyano-2-hydroxy-3-(4-nitrophenyl)propanoate (Ar = $pNO_2C_6H_4$, R = $CO_2CH_2CH_3$, X = Br) (**2m**). According to the general procedure ethyl 2-cyano-3-(4-nitrophenyl)-2-oxirancarboxylate (**1**) (2 g, 7.63 mmol) was converted to **2m** in 71% yield; m.p. 155°C (MeCN). IR (Nujol): ν 3385, 2209, 1700 cm^{-1}. 1H NMR (DMSO-d_6): δ 1.08 (t, 3H, J_{CH-CH}= 7.1 Hz, CH_2CH_3), 3.40 (q, 2H, J_{CH-CH}= 7.1 Hz, CH_2CH_3), 7.28 (s, 1H, CHBr), 7.79 (m, 4H, C_6H_4). ^{13}C NMR (DMSO-d_6): δ 56.82 (q, 1J = 152.30 Hz, OCH_2CH_3), 62.13 (d, 1J = 162.3 Hz, CHBr), 73.70 (s, COH), 111.74 (m, CN), 124.05, 129.84, 138.50, 149.40 (C6H4), 168.32 (s, CO).

General procedure for the preparation of 3-halo-2-oxopropanamides (3)

3-Halo-2-oxopropanamides **3** were easily prepared starting from the corresponding cyano oxiranes **1** according to the described procedure[19]. As compounds **3** react rapidly when heating with water present in the medium to form diols, it is important to use dry solvent for the reaction as for the recrystallisation.

General procedure for the preparation of imidazo[1,2-*a*]pyridine-2-carboxamides 12a - 12d

2-Pyridinamine **4a** (R^1= H; 1.8 g, 0.02 mol) or 6-nitro-2-pyridinamine **4b** (R^1= NO_2; 1.39g, 0.02 mol) was added to the stirred solution of halopyruvamide **3** (X = Cl, in the case **12a** X = Br; 0.01mol) in acetonitrile (30mL). The reaction mixture was heated under reflux for 12h. After cooling the solvent was partialy removed and the solid product was filtered off, washed with acetonitrile, dried and recrystallised from MeCN. The same yields were obtained in DMF as solvent (10h, room temperature). At the end of the reaction the solvent was evaporated and EtOH added to the solid. The crude product which precipitated was recrystallised from MeCN.

3-(4-Chlorophenyl)imidazo[1,2-*a*]pyridine-2-carboxamide (R^1 = H, Y = CH, Ar = $pClC_6H_4$) (**12a**). According to the general procedure 3-bromo-2-oxo-3-(4-chlorophenyl)propanamide **3** (2,76 g, 10 mmol) was converted to **12a** in 51% yield; m.p. 254 °C. IR: ν 3483, 3318, 3166 (NH_2), 1660, 1648 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 6.98 (t, 1H, $J_{5,6}$ = $J_{6,7}$ = 6.8 Hz, H_6), 7.38 (s, 1H, $CONH_2$), 7.42 (t, 1H, $J_{6,7}$ = $J_{7,8}$ = 8.7 Hz, H_7), 7.57 (s, 4H, C_6H_4), 7.68 (d, 1H, $J_{7,8}$ = 8.4 Hz, H_8), 7.74 (s, 1H, $CONH_2$), 8.15 (d,1H, $J_{5,6}$ = 6.8 Hz, H_5). ^{13}C NMR (DMSO-d_6): δ 114.57 (d, ^1J = 170 Hz), 118.43 (d, ^1J = 169 Hz), 125.31, 125.38, 127.47, 128.05, 129.33, 133.47, 134.27, 136.58, 143.87 (C_6H_4 and other C atoms), 165.18 (s, $CONH_2$). Anal. Calcd. for $C_{14}H_{10}ON_3Cl$: C, 61.89; H, 3.71; N, 15.47; Cl, 13.05. Found: C, 61.87; H, 3.68; N, 15.47; Cl, 13.07.

6-Nitro-3-phenylimidazo[1,2-*a*]pyridine-2-carboxamide (R^1 =NO_2, Y = CH, Ar = C_6H_5) (**12b**). According to the general procedure 3-chloro-2-oxo-3-phenylpropanamide **3** (1.97 g, 10 mmol) was converted to **12b** in 46% yield; m.p. 260 °C. IR: ν 3452, 3272, 3132 (NH_2), 1683 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$/CF_3COOH): δ 7.00 (s, 1H, $CONH_2$), 7.58 (s, 1H, $CONH_2$), 7.70 (m,

5H, C_6H_5), 8.28 (d, 1H, $J_{7,8}$ = 9.9 Hz, H_8), 8.62 (d, 1H, $J_{7,8}$ =11.8 Hz, H_7), 9.08 (s, 1H, H_5). ^{13}C NMR (DMSO-d_6): δ 115.47, 121.49, 125.16, 128.04, 129.11, 130.54, 130.99, 133.28, 140.86, 141.15 (C_6H_5 and other C), 161.054 (s, $CONH_2$). Anal. Calcd. for $C_{14}H_{10}O_3N_4$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.10; H, 3.47; N, 19.85.

3-(4-Nitrophenyl)imidazo[1,2-*a*]pyridine-2-carboxamide (R^1 = H, Y = CH, Ar = p$NO_2C_6H_4$) (**12c**). According to the general procedure 3-chloro-3-(4-nitrophenyl)-2-oxopropanamide **3** (2.44 g, 10 mmol) was converted to **12c** in 40% yield; m.p. 260 °C. IR: ν 3440, 3240, 3115 (NH_2), 1688 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.10 (t, 1H, $J_{5,6}$ = $J_{6,7}$ = 6.9 Hz, H_6), 7.54 (t, 1H, $J_{6,7}$ = $J_{7,8}$ = 8.3 Hz, H_7), 7.57 (s, 1H, $CONH_2$), 7.95 (s, 4H, C_6H_4), 8.32 (d, 1H, $J_{7,8}$ = 8.3 Hz, H_8), 8.45 (d, 1H, $J_{5,6}$ = 7.0 Hz, H_5), 8.47 (s, 1H, $CONH_2$). ^{13}C NMR (DMSO-d_6): δ 115.42 (d, ^1J = 170 Hz), 126.31 (d, ^1J = 168 Hz), 123.30, 123.57, 124.59, 127.10, 132.10, 135.21, 136.50, 143.51, 147.09 (p$NO_2C_6H_4$ and other C), 164.10 (s, $CONH_2$). Anal. Calcd. for $C_{14}H_{10}O_3N_4$: C, 59.57; H, 3.57; N, 19.85. Found: C, 59.00; H, 3.58; N, 19.56.

3-(4-Methylphenyl)imidazo[1,2-*a*]pyridine-2-carboxamide (R^1 = H, Y = CH, Ar = p$CH_3C_6H_4$) (**12d**). According to the general procedure 3-chloro-3-(4-methylphenyl)-2-oxopropanamide **3** (2.12 g, 10 mmol) was converted to **12d** in 28% yield; m.p. 225 °C. IR: ν 3471, 3342, 3163 (NH_2), 1633, 1652 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.43 (s, 3H, CH_3), 7.00 (t, 1H, $J_{5,6}$ = $J_{6,7}$ = 6.9 Hz, H_6), 7.34 (dd, 1H, $J_{6,7}$ = 6.9 Hz, $J_{7,8}$ =9.0 Hz, H_7), 7.38 (m, 4H, C_6H_4), 7.66 (s, 1H, $CONH_2$), 7.76 (d, 1H, $J_{7,8}$ = 9.0 Hz, H_8), 8.10 (d, 1H, $J_{5,6}$ = 7.0 Hz, H_5), 8.14 (s, 1H, $CONH_2$). ^{13}C NMR (DMSO-d_6): δ 21.84 (q, ^1J = 127 Hz, pMeC_6H_4), 114.76 (d, ^1J = 169 Hz), 125.40, 125.70, 126.70, 127.96, 129.99, 131.41, 135.41, 139.24, 143.26, (p$CH_3C_6H_4$ and other C), 164.84 (s, $CONH_2$). Anal. Calcd. for $C_{15}H_{13}ON_3$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.17; H, 5.33; N, 16.68.

General procedure for the preparation of imidazo[1,2-*a*]pyridine-2-carboxylates (12e) and (12f)

2-Pyridinamine **4** (R^1= H; 0.49g; 1.93 mmol) dissolved in MeCN (5mL) was added to the stirred solution of halopyruvates **3** (X= Cl or Br; 3.86 mmol) in MeCN (5mL). The reaction mixture was heated under reflux for 10h. MeCN was partially evaporated and left cooling. Formed crystals were filtered off and recrystallised from MeCN.

Methyl 3-(4-methylphenyl)imidazo[1,2-*a*]pyridine-2-carboxylate (R^1 = H, Y = CH, Ar = p$CH_3C_6H_4$, $COOCH_3$) (**12e**). According to the general procedure methyl 3-chloro-3-(4-methylphenyl)-2-oxopropanoate **3** (2.66 g, 10 mmol) was converted to **12e** in 61% yield; m.p. 122 °C. IR: ν 3452, 3410, 3100 (NH_2), 1710 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.51 (s, 3H, CH_3-C_6H_4), 3.91 (s, 3H, $COOCH_3$), 6.95 (t, 1H, $J_{5,6}$ = $J_{6,7}$ = 6.9 Hz, H_6), 7.47 (dd, 1H, $J_{6,7}$ = 6.9 Hz, $J_{7,8}$ = 9.0 Hz, H_7), 7.52 (m, 4H, C_6H_4), 8.20 (d, 1H, $J_{7,8}$ = 9.0 Hz, H_8), 8.20 (d, 1H, $J_{5,6}$ = 6.9 Hz, H_5). ^{13}C NMR (DMSO-d_6): δ 21.57 (q, ^1J = 128 Hz, p$CH_3C_6H_4$), 53,62 (q, ^1J = 150 Hz, OCH_3), 114.48 (d, ^1J = 171 Hz), 125.45, 125.51, 126.95, 130.69, 131.00, 132.26, 135.41, 137.28, 143.76, (p$CH_3C_6H_4$ and other C). Anal. Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.10; H, 5.27; N, 10.52.

Ethyl 3-(4-nitrophenyl)imidazo[1,2-*a*]pyridine-2-carboxylate (R^1 = H, Y = CH, Ar = $pNO_2C_6H_4$, $COOCH_2CH_3$) (**12f**). According to the general procedure ethyl 3-chloro-3-(4-nitrophenyl)-2-oxopropanoate **3** (2.47 g, 10 mmol) was converted to **12f** in 32% yield; m.p. 258 °C. IR: ν 3421, 3338, 3145 (NH_2), 1700, 1682 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.00 (t, 3H, J_{CH-CH} = 7.1 Hz, CH_2CH_3), 4.01 (q, 2H, J_{CH-CH} = 7.1 Hz, CH_2CH_3), 6.90 (t, 1H, $J_{5,6}$ = 6.9Hz, $J_{6,7}$ = 6.9 Hz, H_6), 7.47 (t, 1H, $J_{6,7}$ = 6.9 Hz, $J_{7,8}$ = 8.3 Hz, H_7), 8.20 (d, 1H, $J_{7,8}$ = 8.3 Hz, H_8), 7.52 (m, 4H, C_6H_4), 8.05 (d, 1H, $J_{5,6}$ = 7.0 Hz, H_5). ^{13}C NMR (DMSO-d_6): δ 61.2 (q, ^1J = 128 Hz, OCH_2CH_3), 117.6 (d, ^1J = 173 Hz), 121.0 (d, ^1J = 169 Hz), 123.0, 123.8, 129.9, 131.2, 134.5, 134.7, 134.8, 135.8, 147.0 ($pNO_2C_6H_4$ and other C).

General procedure for the preparation of imidazo[1,2-*a*]pyrimidine-2-carboxamides (13)
2-Pyrimidinamine **5** (0.19g, 2 mmol) was added to the stirred solution of halopyruvamides **3** (1mmol) in acetonitrile (30mL) and heated under reflux for 24 hours. After cooling the solvent was partially removed *in vacuo* to give the crude solid product which was filtered off, washed with acetonitrile and dried. Product was recrystallised from MeCN.

3-Phenylimidazo[1,2-*a*]pyrimidine-2-carboxamide (R^1 = H, Y = N, Ar = Ph) (**13a**). According to the general procedure 3-chloro-2-oxo-3-phenylpropanamide **3** (0.197 g, 1 mmol) was converted to **13a** in 61% yield; m.p. 260 °C. IR: ν 3448, 3300 (NH_2), 1668, 2627 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.10 (m, 1H, H_6), 7.42 (br s, 1H, $CONH_2$), 7.55 (m, 5H, C_6H_5), 7.90 (br s, 1H, $CONH_2$), 8.55 (m, 1H, H_7), 8.70 (m, 1H, H_5). ^{13}C NMR (DMSO-d_6): δ 110.40 (d, ^1J = 175 Hz, C_6), 124.67 (m, C_2), 127.59 (s, $C_{1'}$), 128.72 (d, ^1J = 159.5 Hz, $C_{3'}$, $C_{5'}$), 129.20 (d, ^2J = 73.55 Hz, $C_{4'}$), 130.97 (d, ^1J = 162.9 Hz, $C_{2'}$, $C_{6'}$), 133.49 (dt, ^1J = 189.25 Hz, C_7), 135.95 (d, ^3J = 7.12 Hz, C_3), 146.23 (dd, ^3J = 14.8 Hz, C_{8a}), 152.82 (d, ^1J = 185.5 Hz, C_5), 164.41 (s, $CONH_2$). Anal. Calcd. for $C_{13}H_{10}ON_4$: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.64; H, 4.37; N, 23.62.

3-(4-Chlorophenyl)imidazo[1,2-*a*]pyrimidine-2-carboxamide (R^1 = H, Y = N, Ar = $pClC_6H_4$) (**13b**). According to the general procedure 3-bromo-3-(4-chlorophenyl)-2-oxo-propanamide **3** (0.267 g, 1 mmol) was converted to **13b** in 71% yield; m.p. 274 °C. IR: ν 3390, 3272 (NH_2), 2660, 1671 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 7.11 (m, 1H, H_6), 7.47 (br s, 1H, $CONH_2$), 7.57 (m, 4H, C_6H_4), 7.90 (br s, 1H, $CONH_2$), 8.59 (m, 1H, H_7), 8.70 (m, 1H, H_5). ^{13}C NMR (DMSO-d_6): δ 110.17 (d, ^1J = 178 Hz, C_6), 123.15, 126.10, 128.40 (d, ^1J = 168.0 Hz, $C_{2'}$, $C_{6'}$), 132.55 (d, ^1J = 165.9 Hz, $C_{3'}$, $C_{5'}$), 133.38 (d, $C_{7'}$), 133.62 ($C_{4'}$), 135.58, 145.92, 152.74 (d, ^1J = 185 Hz, C_5), 163.85 (s, $CONH_2$). Anal. Calcd. for $C_{13}H_9ON_4Cl$: C, 57.26; H, 3.33; N, 20.55; Cl, 13.00. Found: C, 56.60; H, 3.13; N, 20.15; Cl, 13.06.

3-(4-Methylphenyl)imidazo[1,2-*a*]pyrimidine-2-carboxamide (R^1 = H, Y = N, Ar = $pCH_3C_6H_4$) (**13c**): According to the general procedure 3-chloro-3-(4-methylphenyl)-2-oxopropanamide **3** (0.242 g, 1 mmol) was converted to **13c** in 56% yield; m.p. 266 °C. IR: ν 3403, 3271 (NH_2), 2652, 1668, (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 7.12 (m, 1H, H_6), 7.40 (m, 4H, C_6H_4), 7.43 (br s, 1H, $CONH_2$), 7.88 (br s, 1H, $CONH_2$), 8.55 (m, 1H, H_7), 8.68 (m, 1H, H_5). ^{13}C NMR (DMSO-d_6): δ 20.91 (q, ^1J = 126.85 Hz, pCH_3), 109,94 (d, ^1J = 164.70 Hz, C_6), 124.24 (m, C_2), 124.36 (m, $C_{1'}$), 128.94 (d, ^1J = 159.3 Hz, $C_{3'}$, $C_{5'}$), 130.45 (d, ^1J

= 159.5 Hz, $C_{2'}$, $C_{6'}$), 133.13 (d, ^1J = 189.08 Hz, C_7), 135.46 (d, ^2J = 77.4 Hz, $C_{4'}$), 138.34 (m, C_3), 145.79 (dd, ^3J = 14.7 Hz, C_{8a}), 152.33 (d, ^1J = 188.6 Hz, C_5), 164.08 (s, $CONH_2$). Anal. Calcd. for $C_{14}H_{12}ON_4$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.57; H, 4.88; N, 22.27.

General procedure for the preparation of 5-(4-chlorophenyl)imidazo[2,1-b][1,3]thiazole-6-carboxamide (14)

1,3-Thiazol-2-amine **6** (0.2g, 2mmol) was added to the stirred solution of 3-chloro-3-(4-chlorophenyl)-2-oxopropanamide **3** (0.232g, 1mmol) in acetonitrile (20mL). The solution was heated under reflux for 6 hours. After cooling the precipitate was filtered off and washed with acetonitrile. The crude product was recrystallised from MeCN to give compound **14** in 50% yield, m.p. 240 °C. ^{1}H NMR (DMSO-d_6): δ 7.29 (br s, 1H, $CONH_2$), 7.42 (d, $J_{5,6}$ = 4.4 Hz, H_6), 7.80 (d, 1H, $J_{5,6}$ = 4.0 Hz, H_5), 7.65 (br s, 1H, $CONH_2$), 7.79 (m, 4H, C_6H_4). ^{13}C NMR (DMSO-d_6): δ 116.80 (dd, ^1J = 132.58 Hz, ^2J = 7.72 Hz), 119.41 (dd, ^1J = 133.28 Hz, ^2J = 9.84 Hz, C_5, C_6), 127.78, 128.40, 129.03, 132.36, 133.96, 137.52, 148.52 (C_6H_4 and other three C), 164.87 (s, $CONH_2$). Anal. Calcd. for $C_{12}H_8ON_3SCl$: C, 51.90; H, 2.90; N, 15.13. Found: C, 52.07; H, 2.87; N, 15.03.

General procedure for the preparation of 2-(acetylamino)-5-phenyl-1,3-thiazole-4-carboxamide (15)

N-Acetylthiourea **9** (0.118mg, 1mmol) was added to the solution of 3-chloro-2-oxo-3-phenylpropanamide **3** (0.197g, 1mmol) in dioxane (2mL). The solution was heated under reflux for 10 minutes. The reaction mixture was put into a refrigerator for 1 hour (4°C). The precipitate was filtered off and recrystallised from dioxane to give compund **15** in 40% yield; m.p. 248 °C. ^{1}H NMR ($CDCl_3$/CF_3COOH): δ 2.44 (s, 3H, CH_3), 6.30 (s, 1H, NH), 7.60 (m, 7H, C_6H_5, $CONH_2$). ^{13}C NMR ($CDCl_3$/CF_3COOH): δ 22.76 (q, ^1J = 131 Hz, CH_3), 126.50, 129.47, 129.91, 130.13, 131.70, 137.17, 159.79, 162.24, 170.86 (C_6H_5, $CONH_2$, CO, 3C from thiazole ring). Anal. Calcd. for $C_{12}H_{11}O_2N_3S$: C, 55.16; H, 4.24; N, 16.08. Found; C, 54.98; H, 3.85; N,16.53.

General procedure for the preparation of 3-(4-methylphenyl)-2-[(4-methylphenyl)imino]-5-phenyl-2,3-dihydro-1,3-thiazole-4-carboxamide (16)

N,N'-Di-(4-methylphenyl)thiourea **10** (0.256g, 1mmol) was added to the stirred solution of 3-chloro-2-oxo-3-phenylpropanamide **3** (0.197g, 1mmol) in dioxane (2mL). The solution was heated under reflux for 5 minutes. The dark reaction mixture was extracted with dichloromethane, the extract washed with water and dried over Na_2SO_4. After evaporation of dichloromethane the obtained solid product was purified by column chromatography (the reaction mixture was dissolved in CH_2Cl_2; silica; diethylether:petrolether 3:1; R_f = 0.425) to give compound **16** in 40% yield; m.p. 238°C. ^{1}H NMR (DMSO-d_6): δ 2.30 (s, 6H, 2 x CH_3), 5.86 (s, 1H, $CONH_2$), 7.40 (m, 13H, 2 x C_6H_4, C_6H_5), 9.07 (br s, 1H, $CONH_2$). ^{13}C NMR (DMSO-d_6): δ 21.14 (q, ^1J = 125.59 Hz, CH_3), 21.49 (q, ^1J = 127.91 Hz, CH_3), 121.91, 124.61, 127.65, 128.02, 128.68, 129.19, 129.90, 130.50, 130.71, 131.00, 133.29, 135.49, 138.45, 141.65, 160.05 (C_6H_5, 2

x C_6H_4, 3C from thiazole ring), 167.40 (s, $CONH_2$)**.** Anal. Calcd. for $C_{24}H_{21}ON_3S$: C, 72.15; H, 5.30; N, 10.52. Found; C, 71.70; H, 5.53; N, 10.12.

General procedure for the preparation of 3-(4-chlorophenyl)-2-oxo-3-(2-pyrimidinyl-sulfanyl)propanamide (17)

2-Pyrimidinthiol **8** (0.224, 2mmol) was added to the stirred solution of 3-bromo-3-(4-chlorophenyl)-2-oxopropanamide **3** (0.276g, 1mmol) in acetonitrile (30mL). The solution was heated under reflux for 3 hours. The solvent was removed *in vacuo* to give the crude solid product, which was washed with water and recrystallised from toluene to give compound **17** in 60% yield; m.p. 156°C. ^{1}H NMR ($CDCl_3$): δ 6.17 (br s, 1H, $CONH_2$), 6.61 (s, 1H, C*H*), 6.88 (br s, 1H, $CONH_2$), 7.32-7.40 (m, 1H, Pyrim.), 7.40 (m, 4H, C_6H_4), 8.50 (m, 2H, Pyrim.). ^{13}C NMR ($CDCl_3$): δ 50.60 (d, ^1J = 150.33 Hz, CH), 117.16 (dt, ^1J = 170.11 Hz, C_4), 129.40, 129.82, 131.08, 135.04 (C_6H_4), 157.23 (dm, ^1J = 182.7 Hz, C_3, C_5), 161.64 (s, $CONH_2$), 170.66 (m, C_1), 192.08 (m, CO). Anal. Calcd. for $C_{13}H_{10}O_2N_3SCl$: C, 50.74; H, 3.28; N, 13.65. Found: C, 50.37; H, 3.30; N, 13.45.

General procedure for the preparation of 2-{2-[4-(aminocarbonyl)-3-alkyl-5-(4-aryl)-2,3-dihidro-1,3-thiazol-2-yliden]hydrazono}-3-methyl-5-(4-aryl)-2,3-dihydro-1,3-thiazoles (18)

Hydrazinedicarbothioamide **11** (1mmol) was added to the stirred solution of halopyruvamide **3** (2mmol) in acetonitrile (60mL). The solution was heated under reflux for 10 hours. The product precipitated during the reaction time. The product was filtered off, washed with acetonitrile and recrystallised from dimethylformamide.

2-{2-[4-(Aminocarbonyl)-3-ethyl-5-(4-nitrophenyl)-2,3-dihidro-1,3-thiazol-2-yliden] hydrazono}-3-methyl-5-(4-nitrophenyl)-2,3-dihydro-1,3-thiazoles-4-carboxamide (R^1 = H, Y = N, Ar = p$NO_2C_6H_4$) (**18a**). According to the general procedure 3-chloro-2-oxo-3-(4-nitrophenyl)propanamide **3** (0.197 g, 1 mmol) was converted to **18a** in 40% yield; m.p. 315 °C. IR: ν 3430, 3300 (NH_2), 1650 (CO) cm^{-1}. ^{1}H NMR (C_5D_5N-d_5): δ 1.70 (t, 3H, $J_{CH\text{-}CH}$ = 6.9 Hz, CH_2CH_3), 3.83 (s, 3H, CH_3), 4.40 (q, 2H, $J_{CH\text{-}CH}$ = 6.9 Hz, CH_2CH_3), 8.05 (dd, 8H, 2 x C_6H_4), 9.62 (br s, 1H, $CONH_2$), 9.64 (br s, 1H, $CONH_2$), 9.84 (br s, 1H, $CONH_2$), 9.95 (br s, 1H, $CONH_2$).^{13}C NMR (C_5D_5N-d_5): δ 13.94 (q, ^1J = 128 Hz, CH_2CH_3), 32.85 (q, ^1J = 141 Hz, CH_3), 42.00 (t, ^1J = 141 Hz, CH_2CH_3), 111.47, 111.62, 124.56, 124.92, 127.34, 127.39, 136.22, 139.18, 139.23, 146.31, 146.34, 150.72, 157.72, 158.66 (2 x C_6H_4 and other 6C from thiazole ring), 163.89 (s, $CONH_2$), 164.14 (s, $CONH_2$). Anal. Calcd. for $C_{23}H_{20}O_6N_8S_2$: C, 48.59; H, 3.55; N, 19.71; S, 11.28. Found: C, 48.89; H, 3.44; N, 18.97; S, 10.72.

2-{2-[4-(Aminocarbonyl)-3-ethyl-5-(4-methylphenyl)-2,3-dihidro-1,3-thiazol-2-yliden] hydrazono}-3-methyl-5-(4-methylphenyl)-2,3-dihydro-1,3-thiazoles-4-carboxamide (R^1 = H, Y = N, Ar = Ar = p$CH_3C_6H_4$) (**18b**). According to the general procedure 3-chloro-2-oxo-3-(4-methylphenyl)propanamide **3** (0.178 g, 1 mmol) was converted to **18b** in 80% yield; m.p. 302 °C. IR: ν 3390, 3136 (NH_2), 1670 (CO) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.29 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 7.22 (dd, 8H, 2 x C_6H_4), 8.05 (br s, 2H, $CONH_2$), 8.30 (br s, 2H, $CONH_2$). ^{13}C

NMR (C_5D_5N-d_5): δ 20.63 (q, ^1J = 140 Hz, 2 x pCH_3), 30.86 (q, ^1J = 141 Hz, 2 x CH_3), 111.61, 126.25, 128.52, 129.29, 131.49, 136.67, 161.03 (2 x C_6H_4 and other 6C from thiazole ring), 167.89 (2s, $CONH_2$), 164.14 (s, $CONH_2$). Anal. Calcd. for $C_{24}H_{24}O_2N_6S_2$: C, 58.76; H, 4.52; N, 17.13; S, 13.02. Found: C, 58.12; H, 4.69; N, 16.76; S, 12.48.

General procedure for the preparation of 7-carbamoyl-5-aryl-2,3-dihydro[1,3]thiazolo[4,3-b][1,3]thiazol-4-ium chloride (19)

4,5-Dihydro-1,3-thiazole-2-thiol (0.238 g, 2mmol) **7** and **3** (1mmol) were dissolved in acetonitrile (50mL). The solution was heated under reflux for 24 hours. The reaction product percipitated after cooling. It was filtered off and washed with acetonitrile. The crude solid product was recrystallised from MeCN.

7-Carbamoyl-5-phenyl-2,3-dihydro[1,3]thiazolo[4,3-*b*][1,3]thiazol-4-ium chloride (Ar = Ph) (**19a**). According to the general procedure 3-chloro-2-oxo-3-phenylpropanamide **3** (0.197 g, 1 mmol) was converted to **19a** in 40% yield; m.p. 229 °C. IR: ν 3140 (NH_2), 1680 (CO) cm^{-1}. ^1H NMR ($CDCl_3/CF_3COOH$): δ 4.20 (s, 2H, 3-CH_2), 5.20 (s, 2H, 2-CH_2), 7.54 (m, 5H, C_6H_5), 8.50 (br s, 2H, $CONH_2$). ^{13}C NMR ($CDCl_3/CF_3COOH$): δ 36.85 (t, ^1J = 150 Hz, CH_2), 55.86 (t, ^1J = 154 Hz, CH_2), 126.12, 127.32, 130.52, 131.95, 132.33, 148.03, 152.80, 157.39 (C_6H_5 and other 3 C), 157.39 (s, $CONH_2$). Anal. Calcd. for $C_{12}H_{11}ON_2S_2Cl$: C, 48.24 H, 3.71; N, 9.38. Found: C, 47.77; H, 3.67; N, 9.30.

7-Carbamoyl-5-(4-chlorophenyl)-2,3-dihydro[1,3]thiazolo[4,3-*b*][1,3]thiazol-4-ium chloride (Ar = $pClC_6H_4$) (**19b**). According to the general procedure 3-chloro-3-(4-chlorophenyl)-2-oxopropanamide **3** (0.232 g, 1 mmol) was converted to **19b** in 30% yield; m.p. 248 °C. IR: ν 3120 (NH_2), 1685 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.21 (s, 2H, 3-CH_2), 5.20 (s 2H, 2-CH_2), 7.55 (m, 4H, C_6H_4), 8.69 (br s, 2H, $CONH_2$). ^{13}C NMR ($CDCl_3$): δ 36.85 (t, ^1J = 150 Hz, CH_2), 55.60 (t, ^1J = 154 Hz, CH_2), 112.47, 116.24, 120.02, 124.26, 128.33, 130.60, 138.62, 147.57 (C_6H_4 and other 3 C), 156.90 (s, $CONH_2$).

7-Carbamoyl-5-(4-nitrophenyl)-2,3-dihydro[1,3]thiazolo[4,3-*b*][1,3]thiazol-4-ium chloride (Ar = $pNO_2C_6H_4$) (**19c**). According to the general procedure 3-chloro-3-(4-nitrophenyl)-2-oxopropanamide **3** (0.242 g, 1 mmol) was converted to **19c** in 26% yield; m.p. 153 °C. IR: ν 3100 (NH_2), 1692 (CO) cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.25 (s, 2H, 3-CH_2), 5.12 (s, 2H, 2-CH_2), 8.21 (m, 4H, C_6H_4), 8.92 (br s, 1H, $CONH_2$), 9.53 (br s, 1H, $CONH_2$). ^{13}C NMR (DMSO-d_6): δ 40.34 (t, ^1J = 150 Hz, CH_2), 56.00 (t, ^1J = 154 Hz, CH_2), 125.33, 125.90, 128.89, 131.00, 134.20, 148.48, 149.65, 155.58 (C_6H_4 and other 3 C), 157.50 (s, $CONH_2$).

7-Carbamoyl-5-(4-methylphenyl)-2,3-dihydro[1,3]thiazolo[4,3-*b*][1,3]thiazol-4-ium chloride (Ar = $pCH_3C_6H_4$) (**19d**). According to the general procedure 3-chloro-3-(4-methylphenyl)-2-oxopropanamide **3** (0.211 g, 1 mmol) was converted to **19d** in 41% yield; m.p. 200 °C. IR: ν 3160 (NH_2), 1680 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 4.19 (s, 2H, 3-CH_2), 5.18 (s, 2H, 2-CH_2), 7.42 (m, 4H, C_6H_4), 8.62 (br s, 1H, $CONH_2$), 9.53 (br s, 1H, $CONH_2$). ^{13}C NMR ($CDCl_3$): δ 19.82 (q, ^1J = 127 Hz, CH_3), 38.75 (t, ^1J = 150 Hz, CH_2), 58.87 (t, ^1J = 154 Hz, CH_2), 76.80, 77.30, 113.20, 127.57, 128.88, 155.33, 155.42, 155.50 (C_6H_4 and other 3 C), 169.45 (s,

$CONH_2$). Anal. Calcd. for $C_{12}H_{10}O_3N_3S_2Cl$: C, 49.91, H, 4.19; N, 8.95. Found: C, 50.01; H, 4.01; N, 8.68.

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