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 75\textsuperscript{th} birthday
(received 23 Mar 01; accepted 31 Jan 02; published on the web 08 Feb 02)

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-\textit{a}]pyridine, imidazo[1,2-\textit{a}]pyrimidine, thiazole, imidazo[2,1-\textit{b}]thiazole, thiazolo[2,3-\textit{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\textsuperscript{1} and also as activators for phototropic compositions.\textsuperscript{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.\textsuperscript{1,3} This makes them useful as potential inhibitors for pyruvate decarboxylases, pyruvate dehydrogenases or pyruvate oxidases. Recent studies\textsuperscript{4} revealed important inhibitory properties for HIV proteases of certain \textit{\alpha}-keto-amides. Some di- or tripeptidyl \textit{\alpha}-keto esters, \textit{\alpha}-keto amides and \textit{\alpha}-keto acids show inhibitor properties of cystin proteases and may be used for the treatment of diseases which involve neurodegradation.\textsuperscript{5}
Belonging to $\alpha$-haloketons, $\alpha$-halopyruvamides and $\alpha$-halopyruvates are also valuable starting materials in organic chemistry. 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, imidazo[1,2-a]pyrimidines, thiazoles, imidazo[2,1-b]thiazoles and tiazolo-thiazoles.

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

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

**Results and Discussion**

The stable 3-halohydrines (3-halo-2-cyano-2-hydroxypropanamides and their ester analogs) are easily obtained from 2-cyano-2-oxiranes. The compounds can be easily decyanurated so that we can consider them as protected forms of compounds (3-halopyruvamides, R=CO$_2$NH$_2$ and 3-halopyruvates, R=CO$_2$Me or CO$_2$Et) (Scheme 1).

Compounds are very reactive bielectrophiles, able to react in protic and nonprotic medium with different nucleophiles. We observed that $O$-nucleophiles H$_2$O 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.

A different behaviour was observed with $N$-$N$- and $N$-$S$-binucleophiles as presented in Scheme 1. In the reaction of compound with $N$-$N$-binucleophiles like 4, 5 and 6 we obtained by the simple reflux in CH$_3$CN (or in DMF at room temperature) imidazopyridines, imidazopyrimidines and imidazothiazoles of high degree of purity with yields from 46% to 71%. $^1$H and $^{13}$C NMR spectra are compatible with the proposed structures. We performed the X-ray analysis of the compound 12a (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. Our results are also in good agreement with those found in literature. We didn't isolate the acyclic intermediate A, which according to literature can sometimes be isolated.
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$_3$CN. 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.

\[
\begin{align*}
\text{Ar} & \quad \text{CN} \\
\text{H} & \quad \text{O} \\
\text{R} & \quad \text{HX/CH}_3\text{CN} \quad \text{r.t.} \\
\text{Ar} & \quad \text{CN} \\
\text{H} & \quad \text{X} \quad \text{OH} \\
\text{R} & \quad \text{Ni(OAc)}_2/\text{CH}_3\text{CN} \quad \text{r.t.} \\
\text{Ar} & \quad \text{O} \\
\end{align*}
\]

R = CONH$_2$, CO$_2$Me, CO$_2$Et
X = Cl, Br
Ar = C$_6$H$_5$, 4-CH$_3$-C$_6$H$_4$, 4-Cl-C$_6$H$_4$, 4-NO$_2$-C$_6$H$_4$
Some reactions were performed starting from the precursor 2 (R = CONH₂, CO₂Me, CO₂Et). 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\(^1\) (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 nucleophilicity 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).](image)

**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\(_3\)CN 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$_3$C$_6$H$_4$, 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): $\nu$ 3468, 3351, 2249, 1693 cm$^{-1}$. $^1$H NMR (CDCl$_3$, CF$_3$COOH): $\delta$ 2.30 (s, 3H, CH$_3$), 5.50 (s, 1H, CHBr), 6.80 (br s, 2H, CONH$_2$), 7.25 (m, 4H, C$_6$H$_4$). $^{13}$C NMR (CDCl$_3$, CF$_3$COOH): $\delta$ 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$_6$H$_4$), 170.38 (s, CONH$_2$). HRMS: Found 254.9890. Calcd. for C$_{11}$H$_{11}$N$_2$O$_2$Br (M$^+$ - HCN) : 254.9895. Anal. Calcd. for C$_{11}$H$_{11}$N$_2$O$_2$Br: 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$_6$H$_4$, R = CO$_2$CH$_3$, X = Br) (2k). According to the general procedure methyl 2-cyano-3-(4-chlorophenyl)-2-oxiranecarboxylate (1) (2 g, 8.42 mmol) was converted to 2k in 70% yield; m.p. 135°C (MeCN). IR (Nujol): $\nu$ 3430, 2255, 1745 cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta$ 3.86 (s, 3H, OCH$_3$), 4.22 (s, 1H, OH), 5.31 (s, 1H, CHBr), 7.37 (m, 4H, C$_6$H$_4$). $^{13}$C NMR (CDCl$_3$): $\delta$ 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$_6$H$_4$), 165.58 (m, CO). Anal. Calcd. for C$_{11}$H$_{11}$N$_2$O$_2$Br: 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$_3$C$_6$H$_4$, R = CO$_2$CH$_3$, X = Br) (2l): According to the general procedure methyl 2-cyano-3-(4-methylphenyl)-2-oxiranecarboxylate (1) (2 g, 8.42 mmol) was converted to 2l in 88% yield; m.p. 130°C (MeCN). IR (Nujol): $\nu$ 3380, 2240, 1750 cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta$ 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, C₆H₄). 13C NMR (DMSO-d₆): δ 54.00 (q, 1, J = 148.80 Hz, OCH₃), 63.51 (d, 1, J = 158.81 Hz, CHBr), 76.82 (s, COH), 116.50 (s, CN), 129.72, 129.90, 131.20, 139.79 (C₆H₄), 168.30 (s, CO). Anal. Calcd. for C₁₂H₁₂N₁O₃Br₁: 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 = pNO₂C₆H₄, R = CO₂CH₂CH₃, 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-d₆): δ 1.08 (t, 3H, CH-CH= 7.1 Hz, CH₂C₃H₃), 3.40 (q, 2H, JCH-CH= 7.1 Hz, C₂H₂CH₃), 7.28 (s, 1H, CHBr), 7.79 (m, 4H, C₆H₄). 13C NMR (DMSO-d₆): δ 56.82 (q, 1, JCH= 152.30 Hz, OCH₂CH₃), 62.13 (d, 1, JCHBr= 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 procedure¹⁹. 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 (R¹= H; 1.8 g, 0.02 mol) or 6-nitro-2-pyridinamine 4b (R¹= NO₂; 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 (R¹ = H, Y = CH, Ar = pClC₆H₄) (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 (NH₂), 1660, 1648 (CO) cm⁻¹. ¹H NMR (DMSO-d₆): δ 6.98 (t, 1H, J₅,₆ = J₆,₇ = 6.8 Hz, H₆), 7.38 (s, 1H, CONH₂), 7.42 (t, 1H, J₆,₇ = J₇,₈ = 8.7 Hz, H₇), 7.57 (s, 4H, C₆H₄), 7.68 (d, 1H, J₇,₈ = 8.4 Hz, H₈), 7.74 (s, 1H, CONH₂), 8.15 (d,1H, J₅,₆ = 6.8 Hz, H₅). ¹³C NMR (DMSO-d₆): δ 114.57 (d, 1, J = 170 Hz), 118.43 (d, 1, J = 169 Hz), 125.31, 125.38, 127.47, 128.05, 129.33, 133.47, 134.27, 136.58, 143.87 (C₆H₄ and other C atoms), 165.18 (s, CONH₂). Anal. Calcd. for C₁₄H₁₀O₂N₃Cl: 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 (R¹ = NO₂, Y = CH, Ar = C₆H₅) (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 (NH₂), 1683 (CO) cm⁻¹. ¹H NMR (CDCl₃/CF₃COOH): δ 7.00 (s, 1H, CONH₂), 7.58 (s, 1H, CONH₂), 7.70 (m, CO).
5H, C₆H₅), 8.28 (d, 1H, J₇,₈ = 9.9 Hz, H₈), 8.62 (d, 1H, J₇,₈ = 11.8 Hz, H₂), 9.08 (s, 1H, H₅). ¹³C NMR (DMSO-d₆): δ 115.47, 121.49, 125.16, 128.04, 129.11, 130.54, 130.99, 133.28, 140.86, 141.15 (C₆H₅ and other C), 161.054 (s, CONH₂). Anal. Calcd. for C₁₄H₁₀O₃N₄: 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 (R¹ = H, Y = CH, Ar = pNO₂C₆H₄) (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 (NH₂), 1688 (CO) cm⁻¹. ¹H NMR (CDCl₃): δ 7.10 (t, 1H, J₅,₆ = J₆,₇ = 6.9 Hz, H₆), 7.54 (t, 1H, J₆,₇ = J₇,₈ = 8.3 Hz, H₇), 7.57 (s, 1H, CONH₂), 7.95 (s, 4H, C₆H₄), 8.32 (d, 1H, J₇,₈ = 8.3 Hz, H₈), 8.45 (d, 1H, J₅,₆ = 7.0 Hz, H₅), 8.47 (s, 1H, CONH₂). ¹³C NMR (DMSO-d₆): δ 115.42 (d, J = 170 Hz), 126.31 (d, J = 168 Hz), 123.30, 123.57, 124.59, 127.70, 132.10, 134.36, 143.51, 147.09 (pNO₂C₆H₄ and other C), 164.10 (s, CONH₂). Anal. Calcd. for C₁₄H₁₀O₃N₄: 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 (R¹ = H, Y = CH, Ar = pCH₃C₆H₄) (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 (NH₂), 1633, 1652 (CO) cm⁻¹. ¹H NMR (DMSO-d₆): δ 2.43 (s, 3H, CH₃), 7.00 (t, 1H, J₅,₆ = J₆,₇ = 6.9 Hz, H₆), 7.34 (dd, 1H, J₆,₇ = 6.9 Hz, J₇,₈ = 9.0 Hz, H₇), 7.38 (m, 4H, C₆H₄), 7.66 (s, 1H, CONH₂), 7.76 (d, 1H, J₇,₈ = 9.0 Hz, H₈), 8.10 (d, 1H, J₅,₆ = 7.0 Hz, H₅), 8.14 (s, 1H, CONH₂). ¹³C NMR (DMSO-d₆): δ 21.84 (q, J = 127 Hz, pMeC₆H₄), 53.62 (q, J = 150 Hz, OCH₃), 114.76 (q, J = 172 Hz, pMeC₆H₄), 114.76 (d, J = 169 Hz), 125.40, 125.70, 126.70, 127.96, 129.99, 131.41, 135.41, 139.24, 143.26, (pCH₃C₆H₄ and other C), 164.84 (s, CONH₂). Anal. Calcd. for C₁₅H₁₃ON₃: 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 (R¹ = 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 (R¹ = H, Y = CH, Ar = pCH₃C₆H₄, COOCH₃) (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 (NH₂), 1710 (CO) cm⁻¹. ¹H NMR (CDCl₃): δ 2.51 (s, 3H, CH₃-C₆H₄), 3.91 (s, 3H, COOCH₃), 6.95 (t, 1H, J₅,₆ = J₆,₇ = 6.9 Hz, H₆), 7.47 (dd, 1H, J₆,₇ = 6.9 Hz, J₇,₈ = 9.0 Hz, H₇), 7.52 (m, 4H, C₆H₄), 8.20 (d, 1H, J₅,₆ = 9.0 Hz, H₈), 8.20 (d, 1H, J₅,₆ = 6.9 Hz, H₅). ¹³C NMR (DMSO-d₆): δ 21.57 (q, J = 128 Hz, pMeC₆H₄), 53.62 (q, J = 150 Hz, OCH₃), 114.48 (d, J = 171 Hz), 125.45, 125.51, 126.95, 130.69, 131.00, 132.26, 135.41, 137.28, 143.76, (pCH₃C₆H₄ and other C). Anal. Calcd. for C₁₆H₁₄O₂N₂: 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\(_2\)C\(_3\)H), 4.01 (q, 2H, \(J_{CH-CH} = 7.1 \, Hz\), C\(_2\)H\(_2\)CH\(_3\)), 6.90 (t, 1H, \(J_{5,6} = 6.9Hz\), 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\(_6\)H\(_4\)), 8.05 (d, \(J_{5,6} = 7.0 \, Hz\), H\(_5\)). 13C NMR (DMSO-d\(_6\)): δ 61.2 (q, \(J = 128 \, Hz\), OCH\(_2\)C\(_3\)H), 117.6 (d, \(J = 173 \, Hz\), H\(_6\)), 121.0 (d, \(J = 169 \, Hz\)), 123.0, 123.8, 129.9, 131.2, 134.5, 134.7, 134.8, 135.8, 147.0 (pNO\(_2\)C\(_6\)H\(_4\) 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\(_6\)H\(_5\)), 7.90 (br s, 1H, CONH\(_2\)), 8.55 (m, 1H, H\(_7\)), 8.70 (m, 1H, H\(_5\)). 13C NMR (DMSO-d\(_6\)): δ 110.40 (d, \(J = 175 \, Hz\), C\(_6\)), 124.67 (m, C\(_2\)), 127.59 (s, C\(_1\)), 128.72 (d, \(J = 159.5 \, Hz\), C\(_3\), C\(_5\)), 129.20 (d, \(J = 73.55 \, Hz\), C\(_4\)), 130.97 (d, \(J = 162.9 \, Hz\), C\(_2\), C\(_6\)), 133.49 (dt, \(J = 189.25 \, Hz\), C\(_7\)), 135.95 (d, \(J = 7.12 \, Hz\), C\(_3\)), 146.23 (dd, \(J = 14.8 \, Hz\), C\(_{8a}\)), 152.82 (d, \(J = 185.5 \, Hz\), 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\(_6\)H\(_4\)), 7.90 (br s, 1H, CONH\(_2\)), 8.59 (m, 1H, H\(_7\)), 8.70 (m, 1H, H\(_5\)). 13C NMR (DMSO-d\(_6\)): δ 110.17 (d, \(J = 159.5 \, Hz\), C\(_6\)), 123.15, 126.10, 128.40 (d, \(J = 159.3 \, Hz\), C\(_2\), C\(_6\)), 132.55 (d, \(J = 165.9 \, Hz\), C\(_3\), C\(_5\)), 133.38 (d, \(J = 164.70 \, Hz\), C\(_6\)), 121.0 (d, \(J = 169 \, Hz\)), 123.0, 123.8, 129.9, 131.2, 134.5, 134.7, 134.8, 135.8, 147.0 (pClC\(_6\)H\(_4\) and other C). Anal. Calcd. for C\(_{13}\)H\(_{9}\)ON\(_4\)Cl: 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\(_6\)H\(_4\)), 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\(_5\)). 13C NMR (DMSO-d\(_6\)): δ 20.91 (q, \(J = 126.85 \, Hz\), pCH\(_3\)), 109.94 (d, \(J = 164.70 \, Hz\), C\(_6\)), 124.24 (m, C\(_2\)), 124.36 (m, C\(_1\)), 128.94 (d, \(J = 159.3 \, Hz\), C\(_3\), C\(_5\)), 130.45 (d, \(J = 164.70 \, Hz\), C\(_6\)), 124.24 (m, C\(_2\)), 124.36 (m, C\(_1\)), 128.94 (d, \(J = 159.3 \, Hz\), C\(_3\), C\(_5\)), 130.45 (d, \(J = 164.70 \, Hz\), C\(_6\)).
= 159.5 Hz, C₂, C₆), 133.13 (d, ³J = 189.08 Hz, C₇), 135.46 (d, ²J = 77.4 Hz, C₄), 138.34 (m, C₃), 145.79 (dd, ³J = 14.7 Hz, C₈a), 152.33 (d, ¹J = 188.6 Hz, C₅), 164.08 (s, CONH₂). Anal. Calcd. for C₁₄H₁₂ON₄: 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. ¹H NMR (DMSO-d₆): δ 7.29 (br s, 1H, CONH₂), 7.42 (d, ⁵J₅,₆ = 4.4 Hz, H₆), 7.80 (d, ¹J₅,₆ = 4.0 Hz, H₅), 7.65 (br s, 1H, CONH₂), 7.79 (m, 4H, C₆H₄). ¹³C NMR (DMSO-d₆): δ 116.80 (dd, ¹J = 132.58 Hz, ²J = 7.72 Hz), 119.41 (dd, ¹J = 133.28 Hz, ²J = 9.84 Hz, C₃, C₆), 127.78, 128.40, 129.03, 132.36, 133.96, 137.52, 148.52 (C₆H₄ and other three C), 164.87 (s, CONH₂). Anal. Calcd. for C₁₂H₈ON₃SCl: 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 compound 15 in 40% yield; m.p. 248 °C. ¹H NMR (CDCl₃/CF₃COOH): δ 2.44 (s, 3H, CH₃), 6.30 (s, 1H, NH), 7.60 (m, 7H, C₆H₅, CONH₂). ¹³C NMR (CDCl₃/CF₃COOH): δ 22.76 (q, ¹J = 131 Hz, CH₃), 126.50, 129.47, 129.91, 130.13, 131.70, 137.17, 159.79, 162.24, 170.86 (C₆H₅, CONH₂, CO, 3C from thiazole ring). Anal. Calcd. for C₁₂H₁₁O₂N₃S: 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 Na₂SO₄. After evaporation of dichloromethane the obtained solid product was purified by column chromatography (the reaction mixture was dissolved in CH₂Cl₂; silica; diethyl ether:petroleum ether 3:1; Rf = 0.425) to give compound 16 in 40% yield; m.p. 238°C. ¹H NMR (DMSO-d₆): δ 2.30 (s, 6H, 2 x CH₃), 5.86 (s, 1H, CONH₂), 7.40 (m, 13H, 2 x C₆H₄, C₆H₅), 9.07 (br s, 1H, CONH₂). ¹³C NMR (DMSO-d₆): δ 21.14 (q, ¹J = 125.59 Hz, CH₃), 21.49 (q, ¹J = 127.91 Hz, CH₃), 121.91, 124.61, 127.65, 128.02, 128.68, 129.19, 129.90, 130.50, 131.00, 131.38, 132.29, 135.49, 138.45, 141.65, 160.05 (C₆H₅, 2
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. 

1H NMR (CDCl3): δ 6.17 (br s, 1H, CONH2), 6.61 (s, 1H, C6H4), 6.88 (br s, 1H, CONH2), 7.32-7.40 (m, 1H, Pyrim.), 7.40 (m, 4H, C6H4), 8.50 (m, 2H, Pyrim.). 13C NMR (CDCl3): δ 50.60 (d, 1, J = 150.33 Hz, CH), 117.16 (dt, 1, J = 170.11 Hz, C4), 129.40, 129.82, 131.08, 135.04 (C6H4), 157.23 (dm, 1, J = 182.7 Hz, C3, C5), 161.64 (s, CONH2), 170.66 (m, C1), 192.08 (m, CO). Anal. Calcd. for C13H10O2N3SCl: 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 (R1 = H, Y = N, Ar = pNO2C6H4) (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 (NH2), 1650 (CO) cm⁻¹. 1H NMR (CDCl3): δ 1.70 (t, 3H, JCH-CH = 6.9 Hz, CH2C3H3), 3.83 (s, 3H, CH3), 4.40 (q, 2H, JCH-CH = 6.9 Hz, C2H2CH3), 8.05 (dd, 8H, 2 x C6H4), 9.62 (br s, 1H, CONH2), 9.64 (br s, 1H, CONH2), 9.84 (br s, 1H, CONH2), 9.95 (br s, 1H, CONH2). 13C NMR (CDCl3): δ 13.94 (q, 1, J = 128 Hz, CH2C3H3), 32.85 (q, 1, J = 141 Hz, CH3), 42.00 (t, 1, J = 141 Hz, CH2C3H3), 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 C6H4 and other 6C from thiazole ring), 163.89 (s, CONH2), 164.14 (s, CONH2). Anal. Calcd. for C23H20O6N8S2: 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 (R1 = H, Y = N, Ar = pCH3C6H4) (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 (NH2), 1670 (CO) cm⁻¹. 1H NMR (DMSO-d6): δ 3.29 (s, 3H, CH3), 3.37 (3, 3H, CH3), 7.22 (dd, 8H, 2 x C6H4), 8.05 (br s, 2H, CONH2), 8.30 (br s, 2H, CONH2). 13C
NMR (C$_5$D$_5$N-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$_6$H$_4$ and other 6C from thiazole ring), 167.89 (2s, CONH$_2$), 164.14 (s, CONH$_2$). Anal. Calcd. for C$_{24}$H$_{24}$O$_2$N$_6$S$_2$: 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) and 3 (1mmol) were dissolved in acetonitrile (50mL). The solution was heated under reflux for 24 hours. The reaction product precipitated 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$^{-1}$. $^1$H NMR (CDCl$_3$/CF$_3$COOH): δ 4.20 (s, 2H, 3-C$_2$H$_2$), 5.20 (s, 2H, 2-C$_2$H$_2$), 7.54 (m, 5H, C$_6$H$_5$), 8.50 (br s, 2H, CONH$_2$). $^{13}$C NMR (CDCl$_3$/CF$_3$COOH): 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$_6$H$_4$ and other 3 C), 157.39 (s, CONH$_2$). Anal. Calcd. for C$_{12}$H$_{11}$ON$_2$S$_2$Cl: 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$_6$H$_4$) (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$^{-1}$. $^1$H NMR (CDCl$_3$): δ 4.21 (s, 2H, 3-C$_2$H$_2$), 5.20 (s, 2H, 2-C$_2$H$_2$), 7.55 (m, 4H, C$_6$H$_4$), 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$_6$H$_4$ 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$_2$C$_6$H$_4$) (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$^{-1}$. $^1$H NMR (DMSO-d$_6$): δ 4.25 (s, 2H, 3-C$_2$H$_2$), 5.12 (s, 2H, 2-C$_2$H$_2$), 8.21 (m, 4H, C$_6$H$_4$), 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$_6$H$_4$ 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$_3$C$_6$H$_4$) (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$^{-1}$. $^1$H NMR (CDCl$_3$): δ 2.45 (s, 3H, CH$_3$), 4.19 (s, 2H, 3-C$_2$H$_2$), 5.18 (s, 2H, 2-C$_2$H$_2$), 7.42 (m, 4H, C$_6$H$_4$), 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$_6$H$_4$ and other 3 C), 169.45 (s,
CONH$_2$). Anal. Calcd. for C$_{12}$H$_{10}$O$_3$N$_3$S$_2$Cl: C, 49.91; H, 4.19; N, 8.95. Found: C, 50.01; H, 4.01; N, 8.68.

Acknowledgements

This research was supported by Ministry of Science and Technology of Slovenia. We thank prof. dr. Branko Stanovnik, Faculty of chemistry and chemical technology, Ljubljana, for elemental analysis and dr. Bogdan Kralj, Institut Jožef Stefan, Ljubljana, for mass spectrometry.

References and Notes