Rearrangement with Oxide Ion Transfer in Reactions of 4-Chloro-2-oxo-2,3-dihydrothiazole-5-carbaldehyde with Ureas. cis-(Z)–trans-(E) Isomerism of N-(2,4-Dioxothiazolidin-5-ylidenemethyl)ureas

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Abstract—4-Chloro-2-oxo-2,3-dihydrothiazole-5-carbaldehyde reacted with monosubstituted ureas to give cis-(Z)- and trans-(E)-N-(2,4-dioxothiazolidin-5-ylidenemethyl)ureas via rearrangement involving oxide ion transfer. cis (Z) Isomers were formed in methanol or dimethylformamide, while both individual cis (Z) and trans (E) isomers and their mixtures were isolated in the reaction performed in acetic acid.

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Reactions of β-halovinyl aldehydes with formamide [1] and guanidine or urea derivatives [2] lead to the corresponding pyrimidine derivatives; however, publications on the reactions with ureas are few in number. We examined reactions of 4-chloro-2-oxo-2,3-dihydrothiazole-5-carbaldehyde (I) with monosubstituted ureas IIa–IIj. The reactions were carried out in methanol, DMF, and acetic acid. As a result, we isolated 40–70% of isomeric cis-(Z)- and trans-(E)-N-(2,4-dioxothiazolidin-5-ylidenemethyl)ureas IIIa, IIIb, IIIe, IIIIh, IVc, IVe, and IVf which were formed via rearrangement involving oxide ion transfer according to Scheme 1. Alternative structures of hydrated thiazolopyrimidinones like V and VI were ruled out on the basis of the 1H NMR data.

Aldehyde I reacted with N-p-tolylurea to give compounds having the same composition and similar melting points but different 1H NMR spectra. From ureas IIg, IIi, and IIj in acetic acid we obtained mixtures of products. Comparison of the 1H NMR

Scheme 1.

![Scheme 1](image-url)

R = CH₂CH₂ (a), PhCH₂ (b), Ph (c), o-MeC₆H₄ (d), m-MeC₆H₄ (e), p-MeC₆H₄ (f), o-MeOC₆H₄ (g), p-MeOC₆H₄ (h), p-BrC₆H₄ (i), p-ClC₆H₄ (j).
spectra (DMSO-d$_6$) of compounds IIIf [δ, ppm: 11.83 s (1H, NH, ring), 9.65 d (1H, N$^1$H, urea, J = 12 Hz), 9.15 s (1H, N$^2$H, urea), 8.02 d (1H, =CHNN, J = 12 Hz), 7.35 d (2H, H$_{arom}$, J = 8 Hz), 7.07 d (2H, H$_{arom}$, J = 8 Hz), 2.28 s (3H, CH$_3$)] and IVf [δ, ppm: 11.93 s (1H, NH, ring), 10.26 d (1H, N$^1$H, urea, J = 12 Hz), 9.90 s (1H, N$^2$H, urea), 7.62 d (1H, =CHNN, J = 12 Hz), 7.33 d (2H, H$_{arom}$, J = 8 Hz), 7.03 d (2H, H$_{arom}$, J = 8 Hz), 2.29 s (3H, CH$_3$)] revealed an appreciable downfield shift of the N$^1$H and N$^2$H signals of compound IVf relative to the corresponding signals of urea IIIf. The observed shift is typical of structures with an intramolecular hydrogen bond [3]. In our case, it may result from participation of the N$^1$H and N$^2$H protons in dynamic equilibrium between quasispiroindolizine structures [4] with six- and eight-membered H-bonded rings (structures IVA and IVB, respectively; Scheme 2). Thus the presence or absence of intramolecular hydrogen bond is indicative of trans (E) or cis (Z) structure of the isolated products.

Scheme 2.

In view of the above stated, compound IVf is trans (E) isomer, while IIIf is cis (Z) isomer. Likewise, the trans-(E)-isomer structure was assigned to compounds IVC and IVE which were isolated in the reactions of chloroaldehyde I with ureas IIc and IIE in acetic acid, while the reactions of I with ureas IIa and IIB in methanol were assumed to give cis (Z) isomers. In addition, we were able to identify particular isomers in the isomer mixtures obtained by the reactions of compound I with ureas IIId, IIg, IIi, and IIj in acetic acid.

The proposed reaction mechanism (Scheme 1) follows from the fact that in all cases the reaction gives only the corresponding ureas, regardless of the solvent; therefore, the process cannot be regarded as substitution with subsequent cleavage involving acetate ion.

EXPERIMENTAL

The $^1$H NMR spectra were recorded on a Varian Gemini 200 spectrometer from solutions in DMSO-d$_6$. Initial 4-chloro-2-oxo-2,3-dihydrothiazole-5-carboxaldehyde was synthesized by the procedure developed previously [5]. Substituted ureas were synthesized by the cyanate method [6].

N-[(Z)-2,4-Dioxothiazolidin-5-ylidenemethyl]-ureas IIIa and IIIb (general procedure). A mixture of 1.64 g (10 mmol) of 4-chloro-2-oxo-2,3-dihydrothiazole-5-carboxaldehyde (I), 0.82 g (10 mmol) of sodium acetate, and 10 mmol of N-allyl- or N-benzylurea in 8 ml of methanol was heated for 4 h under reflux. The mixture was then kept for 1 h at room temperature, and the precipitate was filtered off and washed with cold water and 5 ml of methanol.

N-Allyl-N'-[(Z)-2,4-dioxothiazolidin-5-ylidenemethyl]urea (IIIa). Yield 1.25 g (45%), fine colorless crystals, mp 208–210°C. $^1$H NMR spectrum, δ, ppm: 12.03 s (1H, NH, ring), 9.55 d (1H, N$^1$H, urea, J = 12 Hz), 7.91 d (1H, =CHNN, J = 12 Hz), 6.73 t (1H, N$^3$H, urea), 5.84 m (1H, =CH, allyl), 5.11 t (2H, =CH$_2$, allyl), 3.76 t (2H, CH$_2$, allyl). Found, %: C 42.35; H 4.02; N 18.53; S 14.00. C$_{12}$H$_7$N$_2$O$_3$S. Calculated, %: C 42.38; H 3.99; N 18.49; S 14.11.

N-Benzyl-N'-[(Z)-2,4-dioxothiazolidin-5-ylidenemethyl]urea (IIIb). Yield 1.11 g (40%), yellowish crystals, mp 237–239°C. $^1$H NMR spectrum, δ, ppm: 12.04 s (1H, NH, ring), 9.60 d (1H, N$^1$H, urea, J = 12 Hz), 7.95 d (1H, =CHNN, J = 12 Hz), 7.27 m (5H, H$_{arom}$, J = 8 Hz), 7.04 t (1H, N$^3$H, urea), 4.33 t (2H, PhCH$_2$). Found, %: C 52.02; H 4.03; N 15.18; S 11.51. C$_{12}$H$_7$N$_2$O$_3$S. Calculated, %: C 51.98; H 4.00; N 15.15; S 11.56.

N-[(Z)-2,4-Dioxothiazolidin-5-ylidenemethyl]-N'- (4-tolyl)urea (IIIh). A mixture of 1.63 g (10 mmol) of compound I, 1.50 g (10 mmol) of N-p-tolylurea, and 8 ml of DMF was heated for 3 h at 70°C. After 24 h, the precipitate was filtered off and washed with 1 ml of DMF and 5 ml of ice water. Yield 1.75 g (63%), colorless crystals, mp 246–248°C. $^1$H NMR spectrum, δ, ppm: 11.83 s (1H, NH, ring), 9.65 d (1H, N$^1$H, urea, J = 12 Hz), 9.15 s (1H, N$^2$H, urea), 8.02 d (1H, =CHNN, J = 12 Hz), 7.35 d (2H, H$_{arom}$, J = 8 Hz), 7.08 d (2H, H$_{arom}$, J = 8 Hz). Found, %: C 52.10; H 4.05; N 15.23; S 11.67. C$_{12}$H$_7$N$_2$O$_3$S. Calculated, %: C 51.98; H 4.00; N 15.15; S 11.56.

N-[(Z)-2,4-Dioxothiazolidin-5-ylidenemethyl]-N'- (4-methoxyphenyl)urea (IIIh). A mixture of 1.63 g