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RESEARCH ARTICLE

2-(1′-Alkoxyvinyl) thiazolidines: synthesis and study of ring-chain tautomerism

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2-Alkoxypropenals react with 2-aminoethanethiol to yield mixtures of tautomeric 2-(1-alkoxyvinyl)thiazolidines and imino thiols. The ring-chain tautomeric equilibria, studied by ^{1}H NMR spectroscopy, were strongly dependent on the solvent polarity, ratio of reagents, and pH of the medium.

Keywords: Thiazolidine; Tautomerism; Condensation; Enal; Iminothiol; Cysteamine

1. Introduction

Interest in 1,3-thiazolidine chemistry has grown because this heterocycle is part of the structure of many natural compounds [1–6]. Moreover, some 2-alkylsubstituted thiazolidines possess radioprotective, antimutation [7], antihypertensive [8], and hepatoprotective activities [9]. 2-Alkylthiazolidines were designed to release the free thiolamine *in vivo* by non-enzymatic ring opening followed by hydrolysis [7, 9–11].

Most 2-substituted thiazolidines reported during the past two decades were synthesized by condensation of 2-aminoethanethiols with aromatic aldehydes or aldoses (mannose, arabinose, rhamnose, glucose, galactose) [7, 12–15], usually resulting in stable crystalline substances. Their tautomeric equilibria in solution are completely [13, 16, 17] or predominantly [12] shifted towards the ring-closed forms. Conversely, thiazolidines derived from formaldehyde and its homologues have not yet been investigated properly [10, 11, 18, 19], as only indirect proof has sometimes been documented for the existence of their open-chain forms [20]. In general, as with many saturated 1,3-heterocycles, an important characteristic is the ring-chain tautomerism [17].

The present study aimed to synthesize previously unknown 2-alkylthiazolidines by the reaction of 2-aminoethanethiol (cycteamine [7]) with 2-alkoxypropenals, and to investigate the ring-chain tautomerism of the compounds in solvents of different polarity. *A priori* success

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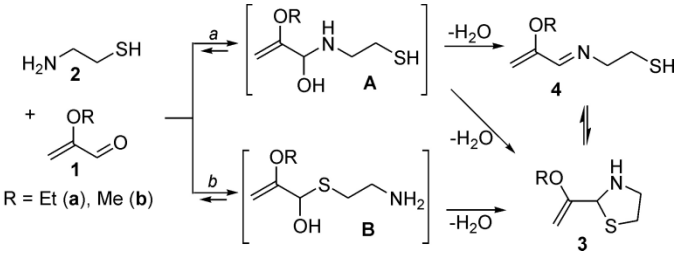
in terms of the chemo- and regioselectivity of this reaction was not obvious because the functionalized alkanethiols–2-mercaptoethanol [21] and 1,2- and 1,3-dithiols [22] – were earlier shown to add to 2-alkoxypropenals in neutral and acid media, following the Markovnikov pattern, to yield the methylglyoxal *O*, *S*-ketals. However, in the presence of bases (K_2CO_3, Et_3N) the addition of thiols to 2-alkoxypropenals occurs at the 1,4-position, leading to 3-alkylthio-2-alkoxypropenals in 75–100% yields [23]. Primary amines react with 2-ethoxypropenal to afford the Schiff bases [24], though there is a mention that in the acrolein reaction with nucleosides the primary amino groups of cytosine and thymine can add at the 1,4-position [25]. As the above examples show, the direction of an attack on the C=C bond or the CHO group of 2-alkoxypropenals depends on the nucleophile nature, catalyst, and reaction medium.

In the reaction of 2-alkoxypropenals with 2-aminoethanethiol the 1,2-addition of amino group could be expected. The resulting intermediate (**A**) could eliminate water in two ways to form vinylthiazolidine **3** or iminethiol **4**. Attack of the sulfhydryl group on the carbonyl carbon to form monothiosemiacetals is sometimes considered as the alternative initial stage (direction *b*) [18]. A similar reaction sequence has been observed in the interaction of α,β-unsaturated ketones with β-aminothiols [26].



SCHEME 1

2. Results and discussion

As we have proved, the reaction of 2-alkoxypropenals **1** with an equimolar amount of 2-aminoethanethiol without a basic catalyst, such as with 2-aminoethanol [27], occurs only at the carbonyl group to form tautomers **3** and **4**. The interaction was monitored by ^{1}H NMR; in $CDCl_3$ the content of iminothiol **4** was monitored by the singlet near δ 7.59 ppm (CH=N) and two doublets at δ 4.57 and 4.65 ppm (CH_2=). The thiazolidine cycle of **3** was easily determined by the singlet of proton in position 2 at δ 4.99 and doublets at δ 4.02 and 4.26 ppm (CH_2=).

To exclude the influence of the evolved water the reaction was studied in the presence of the 4Å molecular sieves. This exothermal reaction took 10 h CH_2Cl_2, and over 24 h in benzene, to achieve complete conversion of initial reagents (table 1, runs 2,3). The resulting tautomers **3a** and **4a** were formed in ratios of 2:1 (CH_2Cl_2) and 1.3:1 (C_6H_6). In $CHCl_3$ in the presence of 4Å molecular sieves, the reaction rate equals that in C_6H_6. Notably, in all three solvents only the ring tautomer **3** was isolated by vacuum distillation. Distilled **3a** is stable at 20 °C, and 16 days after distillation its ^{1}H NMR spectrum in $CDCl_3$ is unchanged, *i.e.* the open-chain tautomer does not form. The high stability of the ring forms of **3a** and **3b** was proved by ^{1}H NMR monitoring in DMSO-d_6 for 17–20 days.

The tautomeric equilibrium of thiazolidine–aminothiol depends on solvent polarity [12]. To reveal the influence of solvent polarity on (1) the reaction rate, (2) the time to achieve tautomeric equilibrium, and (3) the equilibrium ratio of the resulting tautomers, we studied the process dynamics in benzene, $CDCl_3$ and DMSO-d_6 by ^{1}H NMR (table 1). The change in reagent conversion and tautomer ratio was monitored immediately in an NMR ampoule with no binding of liberated water. The role of water as a solvent in nucleophilic addition reactions to the carbonyl group was revisited in the late 1990s [28, 29]. In the investigated

Table 1. Dependence of conversion of initial reagents **1** and **2** and the change in tautomers ratio **3**:**4** on reaction time, solvent nature and initial ratio of reagents at 20 °C.

	C_6H_6 (ε 2.28)			$CDCl_3$(ε 4.81)						DMSO-d_6(ε 46.45)					
Time	(No.)	Ratio **3a**:**4a**	Conversion of **1a** (%)	(No.)	Ratio **3a**:**4a**	Conversion of **1a** (%)	(No.)	Ratio **3b**:**4b**	Conversion of **1a** (%)	(No.)	Ratio **3a**:**4a**	Conversion of **1a** (%)	(No.)	Ratio **3b**:**4b**	Conversion of **1a** (%)
10 min							(8-1)	0.13:1	45[a]	(9-1)	1:1.3	60			
15 min										(9-2)	1:1.2	60			
20 min							(8-2)	0.16:1	45				(12-1)	0.7:1	82
30 min	(1-1)	1.2:1	98				(8-3)	0.15:1	45	(9-3)	1:1.1	60	(12-2)	0.8:1	82
1 h	(1-2)	1.1:1	98	(4)	0:100	44[a]	(8-4)	0.18:1	45	(10)	0.100	40[a]	(12-3)[b]	1.1:1	86
1 h				(5)	0.1:1	90[c]									
1 h				(6)	85–100:0	100[d]									
1 h				(7-1)	8:1	79				(11-1)	1.7:1	99	(12-4)	1.4:1	86
2 h				(7-2)	3:1	87	(8-5)	0.16:1	45	(11-2)	1.4:1	99	(12-5)	1.7:1	93
3 h				(7-3)	2.5:1	97	(8-6)	0.17:1	45	(11-3)	1.3:1	100	(12-6)	1.8:1	100
4 h				(7-4)	2.5:1	97				(11-4)	1.2:1	100	(12-7)	1.7:1	100
7.5 h				(7-5)	1.7:1	98				(11-5)	1.18:1	100	(12-8)[e]	1.4:1	100
16 h	(2)	1:1	75[f]												
24 h	(3)	1.3:1	86[f]												

[a]More than 2.5-fold excess of **1**. [b]After 40 min. [c]In a slight excess of **1**. [d]Two-fold excess of **2**. [e]After 5 days. [f]With molecular sieves 4 Å.

reaction, the water educed seems to increase considerably the reaction medium polarity that leads to a rise in reaction rate. Thus, for the experiment in C_6H_6 without molecular sieves the conversion of 2-ethoxypropenal reaches 98% in 30 min (**3a**:**4a** of 1.2:1) (run no. 1-1). Extending the experiment duration to 1 h does not change the conversion and affects only slightly the tautomeric ratio (runs 1 and 2). Compared to the above experiment (runs 2 and 3), the reaction accelerates in the presence of water by a factor of 50 (water content is about 3.5%). With increasing solvent polarity in the series C_6H_6, $CDCl_3$, DMSO-d_6, the tautomeric equilibrium **3a**:**4a** is somewhat shifted to the open-chain form. Thus, in $CDCl_3$ the tautomeric ratio **3a**:**4a** changes from 8:1 (after 1 h) to 1.7:1 (after 7.5 h) (runs 7-1–7-5). In DMSO-d_6 the conversion of the initial **1a** is 99% after 1 h (run 11-1). The tautomeric ratio **3a**:**4a** is 1.7:1 after 1 h and becomes constant at 1.18:1 after 7.5 h (run 11-1–5). The high stability of open-chain forms of **4** as compared with the unstable chain tautomers of thiazolidines described in the literature may be attributed to the increased benefits of π,π-conjugation.

Previous studies on the mechanism of thiazolidine formation for the 2-unsubstituted analogue were established using kinetic measurements [20]. Schiff bases were shown to be the intermediates of this reaction. Nevertheless, it has been suggested that, under thermodynamically favorable conditions, the hemithioacetal (here **B**) is produced before the α-hydroxyalkylamine (here **A**).

When discussing the mechanism of tautomerization **3**–**4** one should take into account that it proceeds in three stages: detachment of the proton from the HS-group, formation of the S–C bond and proton addition to the nitrogen atom. The sequence of this stage is determined by the acidity of the HS and NH groups, as well as by protic properties of the medium [30]. Reproducibility of the results on the tautomerization of **3a** and **4a** in $CDCl_3$ and DMSO-d_6 allows the inference to be made that the preference between routes *a* or *b* in the absence of a catalyst depends dramatically on the pH of the medium. Thus, it may depend strongly on the concentration of free group SH of initial amino thiol **2** or intermediate **A**, as well as on the basicity of thiazolidine **3** and intermediate amines **A** and **B**. These factors lead, apparently, in our case to the fact that the open-chain **4a** or **4b** predominates in the mixture during the first 10–30 min of reaction, when the conversion is 40–80% complete (runs 8-1, 9-1–3, 12-1, 12-2). Over the next 30 min, the ring form content builds up (runs 7-1, 11-1, 12-4) reaching a point 3–5 times higher in less polar $CDCl_3$ than in DMSO. Perhaps at this stage the reaction assumes its greater pace in an alternative mode of cycle formation (direction *b*). In 1 h, after achieving high conversion degrees (80–100%), the process reaches equilibrium (runs 7-1–5, 11-1–5, and 12-6–8). Even in less polar $CDCl_3$ the open-chain form may dominate if the reaction takes place in a twofold or larger excess of aldehyde **1**. Thus, after complete conversion of **2** (as the limiting reagent), the amount of linear form appears to approach 90–100% (runs 4, 5, 10, 8-1). In the latter run (reaction with **1b**) the ratio **3b**:**4b** no longer changes.

Conversely, more than 2.5-fold excess of aminothiol fosters formation of the ring form (runs 6). The ring form may be stabilized in excess aminothiol by formation of intermolecular ammonium associates. This is in agreement with the observation that the tautomeric ratio of **3b**:**4b** = 0.5:1 shifts abruptly to the ring form after the addition of a catalytic amount of CF_3SO_3H. Thus the pH of the medium is as important a parameter of the reaction in question as the polarity of the medium.

3. Experimental

3.1 *General*

^{1}H NMR spectra were recorded on a Bruker DPX 400 spectrometer at 400 MHz; $CDCl_3$ and DMSO-d_6 were used as solvent, and HMDS as internal reference. IR spectra were measured on a Specord 75IR spectrometer. GC-MS analysis was performed using an HP 5971 A mass-selective detector (electron impact, 70 eV) coupled with an HP 5890 gas chromatograph

(Ultra-2 column, 5% phenylmethylsilicone; injector temperature 250 °C; oven temperature 70 to 280 °C at 20 °C min^{-1}).

2-Alkoxypropenals were obtained by the Mannich reaction [31]. 2-Ethoxypropenal (**1a**): ^{1}H NMR ($CDCl_3$), δ(ppm): 9.26 (s, 1H), 5.2 (d, $J = 2.8$ Hz, 1H), 5.08 (d, $J = 2.7$ Hz, 1H), 3.88 (q, $J = 7.0$ Hz, 2H), 1.38 (t, $J = 7.0$ Hz, 3H). 2-Methoxypropenal (**1b**): ^{1}H NMR ($CDCl_3$), δ (ppm): 9.29 (s, 1H), 5.22 (d, $J = 2.94$ Hz, 1H), 5.07 (d, $J = 3.18$ Hz), 3.69 (s, 3H).

3.2 *Condensation of 2-alkoxypropenal 1a and 1b with 2-aminothiol 2 (general procedure)*

To a round-bottom flask containing chloroform (5 ml) was added aminoethanthiol (9.74 mmol) and 2-alkoxypropenal (9.74 mmol). The reaction mixture was then stirred and left to stand for 1 h at 22 °C, dried over $MgSO_4$, filtered from the drying agent, and evaporated under reduced pressure. Products were isolated by vacuum distillation. Yields were determined by ^{1}H NMR spectroscopy before distillation.

In runs 2 and 3 the above interaction was carried out in the presence of molecular sieves 4Å (1.5 g).

3.3 *Reaction of 2-ethoxypropenal (1a) with 2-aminoethanethiol*

(a) In benzene. Overall yield 98%. Ratio **3a**:**4a**, 1.2:1 in 30 min and 1.1:1 in 1 h. 2-(1-Ethoxyvinyl)thiazolidine (**3a**): yield 32% (after distillation); bp 87 °C (2 mmHg); ^{1}H NMR ($CDCl_3$), δ (ppm): 4.99 (s, 1H), 4.26 (d, $^2J = 2.4$ Hz, 1H), 4.02 (d, $^2J = 2.4$ Hz, 1H), 3.82 (q, $J = 7.0$ Hz, 2H), 3.56 (m, 2H), 3.10 (m, 1H), 2.99 (m, 1H), 1.31 (t, $J = 7.0$ Hz, 3H). m/z 159 (66) $[M]^+$, 130 (42) $[M - Et]^+$, 114 (3) $[M - OEt]^+$, 102 (23), 98 (7), 88 (100) $[NHCH_2CH_2SCH]^+$, 84 (39) $[CH_2{=}C(OEt)CH]^+$, 74 (8) $[NCH_2CH_2S]^+$, 68 (8), 61 (12) $[CH_2CH_2SH]^+$, 59 (12), 45 (17) $[OEt]^+$. Elemental analysis (%) for **3a** $C_7H_{13}NOS$, calcd.: C 52.79, H 8.23, N 8.80, S 20.14; found: C 52.77, H 7.98, N 8.48, S 20.01.

2-Ethoxy-3-(2-mercaptoethylimino)propene (**4a**). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.59 (t, $^4J = 1.1$ Hz, 1H), 4.65 (d, $^2J = 2.3$ Hz, 1H), 4.57 (d, $^2J = 2.3$ Hz, 1H), 3.90 (q, $^3J = 7.0$ Hz, 2H), 3.79 (ddd, $^3J = 7.0$ Hz, $^4J = 1.1$ Hz, 1H), 2.98 (t, $J = 7.0$ Hz, 1H), 1.38 (t, $^3J = 7.0$ Hz, 3H). m/z 159 (1) $[M]^+$, 130 (55) $[M{-}Et]^+$, 114 (3) $[M{-}OEt]^+$, 104 (8), 88 (40) $[CH{=}NCH_2CH_2SH]^+$, 84 (14) $[CH_2{=}C(OEt)CH]^+$, 76 (11), 71 (7) $[CH_2{=}C\text{-}EtO]^+$, 59 (40), 47 (41) $[CH_2SH]^+$.

(b) *In DMSO-d_6*. Total yield of **3a** and **4a** 99%; ratio **3a**:**4a** = 1.7 : 1. 2-(1-Ethoxyvinyl) thiazolidine (**3a**) ^{1}H NMR (DMSO-d_6), δ (ppm): 4.90 (s, 1H), 4.22 (d, $^2J = 1.8$ Hz, 1H), 3.94 (d, $^2J = 1.8$ Hz, 1H), 3.73 (q, $^3J = 7.0$ Hz, 2H), 3.21 (m, 1H), 2.98 (m, 1H), 2.88 (m, 1H), 2.76 (m, 2H), 1.22 (t, $J = 7.0$ Hz, 3H).

2-Ethoxy-3-(2-mercaptoethylimino)propene (**4a**) ^{1}H NMR (DMSO-d_6), δ (ppm): 7.72 (t, $^4J = 1.1$ Hz, 1H), 4.65 (d, $^2J = 1.8$ Hz, 1H), 4.68 (d, $^2J = 1.8$ Hz, 1H), 3.78 (q, $^3J = 7.2$ Hz, 2H), 3.69 (t, $^3J = 6.6$ Hz, 2H), 2.98 (t, $^3J = 6.6$ Hz, 2H), 1.26 (t, $^3J = 7.2$ Hz, 3H).

3.4 *Reaction of 2-methoxypropenal (1b) with 2-amino thiol (2)*

This was performed following the above general procedure. The total yield of **3b** and **4b** was 100% (before distillation). The product was a mixture of tautomers **3b** and **4b** (0.26:1).

2-(1-Methoxyvinyl)thiazolidine (**3b**): after distillation the yield of **3b** was 34%; bp 94 °C (4 mmHg); mp 50 °C; ^{1}H NMR ($CDCl_3$), δ (ppm): 4.99 (s, 1H), 4.28 (d, $^2J = 2.5$ Hz, 1H), 4.06 (d, $^2J = 2.5$ Hz, 1H), 3.61 (s, 3H), 3.80 (t, $J = 7.0$ Hz, 2H), 2.98 (t, 1H). m/z 145 (44) $[M]^+$, 130 (12) $[M{-}Me]^+$, 114(5) $[M{-}OMe]^+$, 112 (32), 98 (10), 88 (100) $[NHCH_2CH_2SCH]^+$, 84 (75), 61 (28), 59 (37), 45 (48), 42 (58) $[CH_2CH_2N]^+$. IR (cm^{-1}): 3210, 2930, 1650, 1610, 1450,

1300, 1280, 1180, 1170, 1050, 960, 920, 880, 820, 790. Elemental analysis (%) for $C_6H_{11}NOS$, calcd.: C 49.62, H 7.63, N 9.64, S 22.08; found: C 49.79, H 7.82, N 10.12, S 21.82.

2-Methoxy-3-(2-mercaptoethylimino)propene (**4b**). ^{1}H NMR ($CDCl_3$), δ (ppm): 7.72 (s, 1H), 4.71 (d, $^2J = 2.5$ Hz, 1H), 4.58 (d, $^2J = 2.5$ Hz, 1H), 3.80 (t, $J = 7.0$ Hz, 2H), 3.69 (s, 3H), 2.99 (t, $^3J = 7.0$ Hz, 2H). m/z 145 (2) $[M]^+$, 130 (56) $[M - Me]^+$, 114 (7) $[M - OMe]^+$, 90 (58), 88 (27) $[CH{=}NCH_2CH_2SH]^+$, 60 (58), 59 (75), 47 (43) $[CH_2SH]^+$, 45 (50), 43 (100) $[COCH_3]^+$.

2-(1-Methoxyvinyl)thiazolidine (**3b**). ^{1}H NMR (DMSO-d_6), δ (ppm): 4.91 (s, 1H), 4.24 (d, $^2J = 2.0$ Hz, 1H), 3.98 (d, $^2J = 2.0$ Hz, 1H), 3.50 (s, 3H), 3.20 (m, 1H), 2.96 (m, 1H), 2.76 (m, 2H).

2-Methoxy-3-(2-mercaptoethylimino)propene (**4b**). ^{1}H NMR (DMSO-d_6), δ (ppm): 7.75 (s, 1H), 4.71 (d, $^2J = 2.2$ Hz, 1H), 4.68 (d, $^2J = 2.2$ Hz, 1H), 3.70 (t, $^3J = 6.4$ Hz, 2H), 3.57 (s, 3H), 2.97 (t, $^3J = 6.4$ Hz, 2H).

3.5 *Process dynamics monitoring*

(a) Aminoethanethiol (0.025 g, 0.32 mmol) and 2-alkoxypropenal (0.32 mmol) were added to an NMR-ampoule with solvent ($CDCl_3$ or DMSO-d_6) (0.6 ml). The reaction mixture was then stirred and left to stand at 22 °C. Yields were determined by ^{1}H NMR. Spectra were taken at certain time intervals (table 1) after the reaction mixture was prepared.

(b) *With excess* **1a**. Aminoethanthiol (0.025 g, 0.32 mmol) and excess 2-ethoxypropenal (0.067 g, 0.80 mmol) were added to an NMR ampoule with $CDCl_3$ (0.6 ml). The reaction mixture was stirred and left to stand for 1 h at 22 °C. Yields (88%) were determined by ^{1}H NMR; the ratio **3a**:**4a** was 0:100.

(c) *With excess* **2**. Aminoethanthiol (0.018 g, 0.24 mmol) and 2-methoxypropenal (0.012 g, 0.12 mmol) were added to an NMR ampoule with $CDCl_3$ (0.6 ml). The reaction mixture was then stirred and left to stand for 1 h at 22 °C. The 100% yields of **3a** were determined by ^{1}H NMR.

(d) *With acid*. The acid CF_3SO_3H (60% mol.) was added to a mixture of **3a** and **4a** (**3a**:**4a** of 1:1.1, total yields 80%). The reaction mixture was subsequently stirred and then left to stand for 5 h at 22 °C. The ratio **3a**:**4a** (8:1) was determined by ^{1}H NMR.

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