A New Synthesis of 4-Hydroxythiazoles

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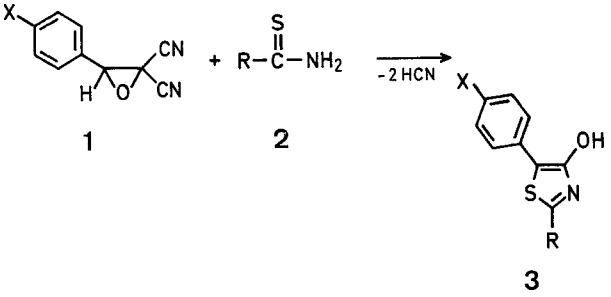
The reaction of thiourea with oxiranes is a general method for preparing thiiranes[1]. However, oxiranes substitued in the ring with functional groups often demonstrate varying reactivity depending on the nature of these substituents[2-5]. α-Chloroglycidic esters have been shown recently to react with thiourea to give 2-aminothiazoles[6,7]. In this case, the course of the reaction is linked with the presence of a leaving group at the α position of the ring. We have shown that oxiranes possessing two geminal cyanide leaving groups react with thiourea to give 2-aminothiazolinones[8].

These results suggested that the reaction of thioamides **2** with oxiranes **1** might constitute a new synthetic route to 2-alkyl-4-thiazolinones or the tautomeric 2-alkyl-4-hydroxythiazoles **3**. However, at the moment these compounds are difficultly accessible and only a few examples have been synthesized[9,11].

We now report our studies on this new reaction which proved to be a convenient method of synthesizing 4-hydroxythiazoles **3**. Thioamides **2** (R = H, CH_3, C_6H_5) react at room temperature with oxiranes **1** and give 4-hydroxythiazoles **3** in a yield of about 50%.



1 2 3

We assign the structure 4-hydroxythiazole **3** (in tri- and tetrachloromethane solution) rather than the tautomeric 4-thiazolinone form on the basis of the spectral data in shown Table 1. The I.R. spectra of these compounds show especially a band at around 3570 cm^{-1} (CCl_4) for ν_{OH}, but no band in the regions 1715 and 1680 cm^{-1} characteristic of heterocyclic >C=O[10]. The N.M.R. spectra are in agreement with the 4-hydroxythiazole **3** formula. The 4-hydroxythiazole **3** (R = CH_3, X = H) has been recently obtained using another method by Reeve and Barron[12] (yield 18%). These authors have shown too that this compound is found to exist in the 4-hydroxythiazole form. It should be mentioned that when carbon 5 is not substituted, ketoenol equilibrium

Table 1. Preparation of 4-Hydroxythiazoles **3**

3:R	X	m.p. (C_2H_5OH)	Yield (%)	I.R. (CCl_4) ν_{OH} cm^{-1}	^{1}H-N.M.R.[a] δ_R	U V (C_2H_5OH) λ nm	$\varepsilon \cdot 10^{-2}$	Empirical formula[b]
C_6H_5	H	215°	43	3572	—	363	192	$C_{15}H_{11}NOS$
						267	75	(253.2)
C_6H_5	Cl	255°	50	3561	—	364	194	$C_{15}H_{10}NOSCl$
						275	82	(287.8)
C_6H_5	H_3CO	215°	45	3567	—	270	148	$C_{16}H_{13}NO_2S$
						268	89	(283.2)
C_6H_5	NO_2	285°	55	—[c]	—	403	225	$C_{15}H_{10}N_2O_3S$
						491	39	(298.3)
						260	97.5	
CH_3	H	212°[d]	38	3573	2.82	303	124	$C_{10}H_9NOS$
								(191.2)
CH_3	Cl	232°	49	3568	2.81	306	115	$C_{10}H_8NOSCl$
								(225.5)
CH_3	H_3CO	185°	50	3574	2.88	306	126	$C_{11}H_{11}NO_2S$
								(221.3)
CH_3	NO_2	250°	36	—[c]	2.97	305	126	$C_{10}H_8N_2O_3S$
						471	330	(236.2)
						374	143	
H	H	168°	41	3566	9.15	250	49	C_9H_7NOS
						307	93	(177.2)
H	Cl	234°	46	3565	9.26	224	21.3	C_9H_6NOSCl
						247	19.5	(211.7)
						307	41	
H	H_3CO	204°	36	3572	9.00	249	36	$C_{10}H_9NO_2S$
						303	62.3	(207.2)
H	NO_2	230°[c]	41	—[c]	9.38	255	22.4	$C_9H_6N_2O_3S$
						360		(223.1)

[a] In $CDCl_3 + F_3C—COOH$.

[b] All products gave satisfactory elemental analyses (C ± 0.4%, H ± 0.2%, N ± 0.5%).

[c] Not soluble in CCl_4.

[d] Lit.[12]: m.p. 210–212°, yield: 18%.

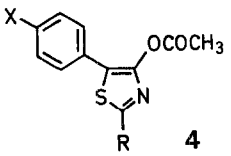
[e] Sublimation point.

Table 2. Preparation of Acetates **4**

4:R	X	m.p. (C_2H_5OH)	I.R. (Nujol) $\nu_{C=O}$ cm^{-1}	^{1}H-N.M.R. ($CDCl_3$) δ_{COCH_3}	δ_R	Empirical formula[a]
C_6H_5	Cl	143°	1770	2.26	—	$C_{17}H_{12}NO_2SCl$ (329.8)
C_6H_5	H_3CO	126°	1764	2.31	3.80[b]	$C_{18}H_{15}NO_3S$ (325.4)
CH_3	H	80°	1778	2.25	2.64	$C_{11}H_{11}NO_2S$ (221.3)
CH_3	NO_2	120°	1778	2.33	2.69	$C_{12}H_{10}N_2O_4S$ (278.3)
H	Cl	74°	1769	2.30	8.62	$C_{11}H_8NO_2SCl$ (253.7)

[a] All compounds gave satisfactory elemental analyses (C ±0.14%, H ±0.43%, N ±0.17%).
[b] δ for OCH_3.

between 4-oxo and 4-hydroxy forms was noticed[10]. In accordance with all expectations, the 4-hydroxythiazoles **3** easily react with acetic anhydride and give quantitatively the acetates **4** (Table 2).



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The *oxiranes* **1** are prepared in good yields by the action of sodium hypochlorite on corresponding α-cyanoacrylonitriles[13]. Thioacetamide (**2**, $R=CH_3$) and thiobenzamide (**2**, $R=C_6H_5$) are commercial products. Thioformamide (**2**, R = H) is prepared according to reference[14].

Preparation of 2-Substituted 4-Hydroxythiazoles (3, $R=CH_3$, C_6H_5):
The oxirane **1** (0.01 mol) and the thioamide **2** (0.01 mol) are dissolved in a mixture of water (5 ml) and dioxan (15 ml or 30 ml when $X=NO_2$). After 3–4 h at room temperature, the 4-hydroxythiazole 3 starts to precipitate. Precipitation is complete after 10 h.

Preparation of 4-Hydroxythiazoles (3, R = H):
The oxirane **1** and hydrated thioformamide (1 g) are dissolved in dioxan (10 ml, 20 ml when $X=NO_2$). A first quantity of 4-hydroxythiazole is filtered off after 2–3 h at room temperature. The remaining solution slowly deposits a further amount of product.

Preparation of Acetates 4:
The 4-hydroxythiazole (0.01 mol) is dissolved in acetic anhydride (20 ml) and heated under reflux for 24 h under nitrogen. The excess acetic anhydride is distilled off and the thiazole acetate **4** crystallizes; yield: quantitative.

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These authors prepared an 4-hydroxy thiazole **3** (X = H, $R=CH_3$) from thioacetamide and phenyl-(trichloromethyl)-carbinol. They postulate the formation (in basic conditions) of an intermediate *gem*-dichloro epoxide. This hypothesis is in perfect agreement with our results concerning the action of thioamides on *gem*-dicyano epoxides **1**.
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