The Formation of 2,3-Disubstituted Thiazolidin-4-ones from *S*-α'-Aminomercaptoacetic Acid Derivatives

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Variously substituted *N*-benzylidineanilines rapidly react with thioglycolic acid to generate *S*-α'-aminomercaptoacetic acid derivatives. The latter subsequently cyclize to the corresponding 2,3-diarylthiazolidin-4-ones. Kinetics for the first order cyclization reaction in the solvents toluene, carbon tetrachloride and nitrobenzene have been obtained over the temperature range 333 K to 383 K and are in accord with a neutral, but geometrically complex transition state.

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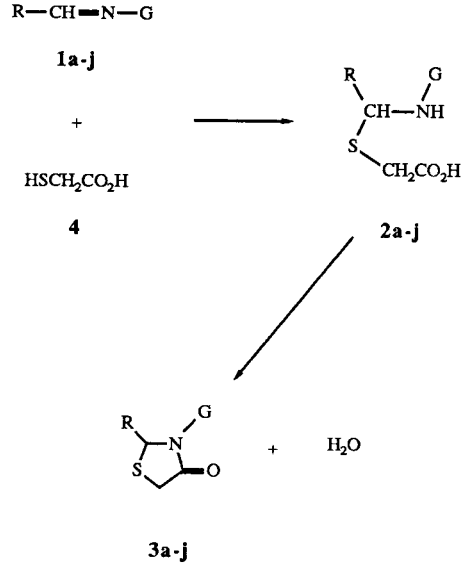
Introduction.

The reaction between *N*-benzylidineanilines **1** and thioglycolic acid **4** to yield 2,3-disubstituted thiazolidin-4-ones **3** Equation 1 (Table 1) is well known and the latter have enjoyed a history of wide ranging biological activity [1-11]. However, when imines other than *N*-benzylideneanilines are used, an apparent limit to the generality of the synthetic method is revealed [12]. Thus, as shown in Equation 2 (Table 1), imines in which the aryl group on carbon (*i.e.* that of the original aldehyde) is replaced by an alkyl group (**5k,l,m** - Equation 2) do not, under the conditions that succeed with their aryl counterparts, lead to thiazolidin-4-ones: The initial reaction between imine and **4** having apparently failed. Indeed, only one successful preparation of a 2-alkyl substituted thiazolidine-4-one by this method has hitherto been reported [13] and that one posseses an aceto group on the γ-carbon in the alkyl moiety.

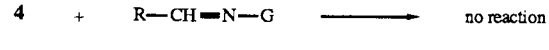
Table 1

Molecules	Groups	
from Eqns. 1 & 2	R	G
1a,2a,3a	Ph-	Ph-
1b,2b,3b	4-NO_2Ph-	Ph-
1c,2c,3c	4-MeOPh-	Ph-
1d,2d,3d	4-MePh-	Ph-
1e,2e,3e	Ph-	4-NO_2Ph-
1f,2f,3f	Ph-	3-NO_2Ph-
1g,2g,3g	Ph-	4-ClPh-
1h,2h,3h	Ph-	3-ClPh-
1i,2i,3i	Ph-	4-MeOPh-
1j,2j,3j	Cl_3C-	Ph-
5k,	Me-	Ph-
5l,	*n*-pentyl-	Ph-
5m,	*n*-heptyl-	Ph-

Based on the respective p*K*b's of the imines [14] and the observed propensity of alkyl imines to be protonated completely by strong acid and only partially so by carboxylic acids [15], this limitation is not surprising. Nonetheless, detailed examination of the presumed pathway has not been reported and to facilitate further synthesis it is clear that such would be valuable.



Equation 1

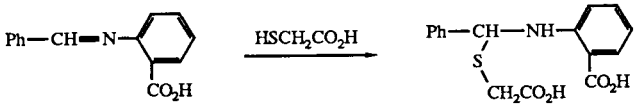


Equation 2

Results and Discussion.

Surrey, [1] obtained an addition compound **6** (Equation 3) with thioglycolic acid and imine **5** (Equation 3) formed from benzaldehyde and anthranilic acid. My results, shown in Table 2, for the ^{1}H nmr of a solution (in carbon tetrachloride) of equal volumes of equimolar thioglycolic acid and *N*-benzylideneaniline are typical of many other

thioglycolic acid and imine solutions. The observed chemical shifts obtained from this solution can be assigned to the *S*-α'-aminomercaptoacetic acid derivative **2a** (Table 2) and chemical shifts attributable to the 2,3-diphenylthiazolidin-4-one product **3a** (Table 2) or the starting compounds **1a** and **4** are not observed (Table 2 provides this comparison). The observation by Surrey that **7** (Equation 3) was the only compound that did not ring close may, initially, thought to be due to steric factors. However, it will be shown that this is probably not the case (*vide infra*).



6 7

Equation 3

The rate of ring closure for **2a-i** (Equation 1), where R and G are substituted aryl groups, was measured titrimetrically by following the disappearance of carboxylic functionality in **2a-i** and are shown in Tables 3 and 4. These results were further confirmed using gas chromatography where both disappearance of **2a-i** and formation of **3a-i** (Equation 1, Tables 3 and 4) were monitored.

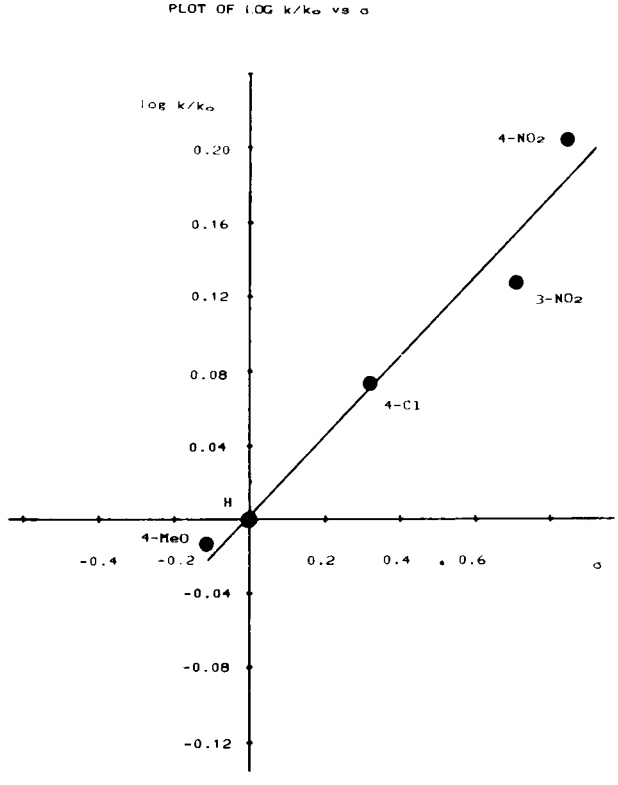


Figure 1

Table 2

^{1}H Chemical Shifts (δ ppm) for Methine and Methylene Protons Found in Compounds **1a**, **2a**, **3a** and **4**

Compound	CH	CH_2
1a	8.9 (singlet)	–
2a	6.05 (singlet)	3.15 (singlet)
3a	6.45 (singlet)	4.05 (doublet, J = 3 Hz)
4	–	3.31 (doublet, J = 8 Hz)

Table 3

Rate of Ring Closure in $M\ S^{-1} \times 10^{-6}$ for *S*-α'-Aminomercaptoacetic Acids in Toluene [a]

S-α'-Aminomercaptoacetic Acid	Initial Concentrations of *S*-α'-Aminomercaptoacetic Acid		
	Temp (° C)	0.100*M*	0.200*M*
2a	110	1.7	3.2
	80	0.7 [b]	1.5
	60	0.3	0.7
2b	110	2.1	4.0
	80	1.1 [b]	2.1
	60	0.6	1.3
2c	110	1.3	2.5
	80	0.5 [b]	1.1
	60	0.2	0.5
2d	110	1.9	4.0
	80	0.7	1.5
2e	110	2.8	5.7
	80	0.8	1.6
2f	110	2.3	4.7
2g	110	2.0	4.1
	80	0.8	1.6
2i	110	1.0	2.1

[a] All values quoted are for a minimum of 3 kinetic runs with an error of ±5%.
[b] Additional kinetic runs were carried out for these reactions with added *p*-toluenesulfonic acid. No catalysis was observed due to the added acid.

The rate of ring closure does not appear to be affected significantly by substituents on groups R or G. Linear Free Energy plots using standard σ values [16] only gave a correlation for *S*-α'-aminomercaptoacetic acids **2e-i** (Table

1), with a ρ value of 0.28 (Figure 1). The correlation does not improve when σ values (σ^+, σ^-, *etc.*) [16] are used. Neither does the correlation improve for *S*-α'-aminomercaptoacetic acids **2a-d** (Table 1), even when the varying contributions due to resonance and field effects (σ_R, σ_I)

Table 4

Rate of Ring Closure in $M\ S^{-1} \times 10^{-6}$ for *S*-α'-Aminomercaptoacetic Acids in Carbon Tetrachloride and Nitrobenzene [a]

S-α'-Aminomercaptoacetic Acid	Temp (° C)	Initial Concentrations of *S*-α'-Aminomercaptoacetic Acid		
		CCl_4 0.100*M*	0.200*M*	$PhNO_2$ 0.100*M*
2a	80	0.7	1.5	0.7
	76	1.1	1.9	
2b	80	1.1	2.1	0.8
2c	80	0.5	1.1	0.5
	76	0.9	2.0	
2d	76	1.2	2.3	
2h	76	1.0	1.9	

[a] All values are quoted for a minimum of 3 kinetic runs and have an error of ±5%.

Table 5

Arrhenius Activation Parameters

Amino-mercapto Acid	$\log_{10}k$ (temp)	E_a kJ/mol	$\Delta H^{\ddagger}$ kJ/mol	$\Delta S^{\ddagger}_{353}$ J/K/mol
2a	-4.8 (383 K)			
	-5.2 (353 K)	34.8 ±0.5	31.9 ±0.8	-255 ±1
	-5.5 (333 K)			
2b	-4.7 (383 K)			
	-5.0 (353 K)	27.9 ±1.3	25.0 ±1.1	-270 ±2
	-5.2 (333 K)			
2c	-4.9 (383 K)			
	-5.3 (353 K)	36.8 ±1.1	33.9 ±0.9	-252 ±1
	-5.7 (333 K)			

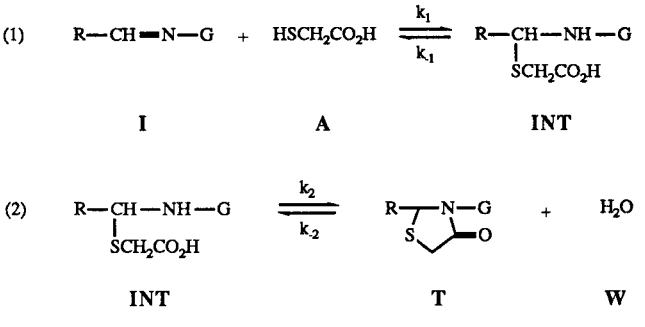
were analyzed [17], [18]. Further, the results given in Table 4 show that the rates of ring closure observed in solvents of varying dielectric constants [19a-c] did not vary drastically. Arrhenius parameters (Table 4) for apparent Ea, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}_{(353)}$ [20] can be derived from the rate data in Table 2. The large negative entropy of activation is presumably indicative of a complex transition state having little or no charge as evidenced by the small changes in rate when solvents with varying dielectric constants were employed.

Interestingly, it has been previously indicated that if R (**5k,l,m** - Equatioin 2) is alkyl no reaction ensues. However, if the group G, for imines **1a-i** in Equation 1, is replaced by an alkyl group the reaction occurs within a few seconds. This structural change leads to rates that are $10^6\ M\ S^{-1}$ faster than imines where both R and G are substituted aryl groups. This enhanced reaction rate was also found to hold where G was a cyclohexyl group. The increase bacisity of the imine and the availability of an electron lone pair is presumed to be enhanced when G is alkyl (Equation 1) [21].

Thus the observation by Surrey (*vide supra*) that **7** (Equation 3) does not ring close is probably attributable to the lack of availability of an electron lone pair on nitrogen rather than any steric effects due to the benzene ring. However, molecular models shown that hydrogen bonding between the carboxylic acid group on the benzene ring and that of the thioacid may inhibit ring closure. Surrey [1] had noted that the formation of 2,3-diarylthiazolidin-4-ones was generally slow (R and G aryl, Equation 1). He also noted that, qualitatively, the rate of product formation was increased when the water was removed. If R was alkyl (Equation 1), no reaction occurred except for one system, previously mentioned [13].

In order to test the sensitivity of the initial attack by sulfur on the imino carbon where R is alkyl (**1j** - Equation 1), *N*-2,2,2-trichloroethylideneaniline was used as the imine. This readily gave the 2-trichloromethyl-3-phenylthiazolidin-4-one, showing that an electron deficient imino carbon is favored for the initial attack by sulfur to occur.

In concert with the experimental observations and the kinetics obtained for the imine system where groups R and G are aryl the proposed mechanism is:



Equation 4

$$d[INT]/dt = k_1[I][A] - k_{-1}[INT] - k_2[INT] + k_{-2}[T][W]$$

if $k_1 >> k_{-1}$

$d[INT]/dt = k_1[I][A] - k_2[INT] + k_2/K_{2eq}[T][W]$

(where $K_{2eq} = k_2/k_{-2}$)

When the acid and imine are mixed, the intermediate forms at an immeasurably fast rate. Thus for step 1 (Equation 4) the equilibrium constant is very large and cannot be detected. Further, [T][W] = [1 - INT] then:

$d[INT]/dt = k_2[INT] + k_2/K_{2eq}[1 - INT]$

$d[INT]/dt = k_2\{[INT] - [1 - INT]/K_{2eq}\}$

and since $k_2[INT] >> [1 - INT]/K_{2eq}$

then, to a first approximation, rate = $-d[INT]/dt = k_2[INT]$.

Conclusion.

Imines, where R is aryl and G is alkyl (Equation 1) react much faster with thioglycolic acid than imines with R and G are aryl (Equation 1). Where R is alkyl the initial rapid addition to the *S*-α'-aminomercaptoacetic acid derivative does not occur (Equation 2) with the exception of a trichloromethyl group or other suitable activating system on the imino carbon. Further, the reaction can be accelerated by removing the water formed and hence continually displacing the equilibrium between the intermediate and final product.

EXPERIMENTAL

Melting points are uncorrected (Mel-Temp apparatus). The ^1H nmr spectra were obtained using a Varian EM 360A spectrometer on samples dissolved in carbon tetrachloride and using TMS as internal standard. Values are reported in ppm from TMS (δ = 0.00). Infrared spectra were obtained in nujol mulls on Perkin Elmer IR-18 and uv, in cyclohexane, on Perkin Elmer SP-124 spectrometers. Gas chromatographic analyses were carried out on a Perkin Elmer 900 Gas Chromatograph using ¼ inch by 6 feet coiled glass column of SE30A on Carbopak C at a column temperature of 120° with a helium flow rate of 2 cm^3 sec^{-1} and an FID detector. Under these conditions the *S*-α'-aminomercaptoacetic acid derivative from *N*-benzylideneaniline and thioglycolic acid had a retention time of *ca.* 3 minutes and 2,3-diphenylthiazolidin-4-one of *ca.* 8 minutes. Mass spectra were obtained on a Hitachi RMU-6H mass spectrometer and thin later chromatography (tlc) on 100 micron silica gel plates obtained from Eastman Kodak using 1:1 dichloromethane and toluene. Solvents were obtained from Fischer Scientific and dried using suitable drying agents (*e.g.* sodium wire for toluene). No further purification was carried out. Elemental analyses were performed by Galbraith Laboratories, Inc., 2323 Sycamore Drive, Knoxville, TN 37921-1750.

Various 2,3-thiazolidine-4-ones appearing in Tables 1-5 were prepared using the following general procedure. The imine (10 mmoles) was heated with a slight excess of thioglycolic acid (10-15 mmoles) in toluene (100 ml) at reflux until water collection ceased. Absence (tlc) of imine was taken to indicate that the reaction was complete. Unreacted thioglycolic acid was removed from the cool solution by extraction with saturated sodium bicarbonate and the product isolated from the organic phase by removal of the toluene at reduced pressure. The resulting solid was recrystallized from ethanol.

2,3-Diphenylthiazolidin-4-one (**3a**).

This compound was obtained in a yield of 60%, mp 131-132°, (lit mp 130-131° [1]).

2-(4-Nitrophenyl)-3-phenylthiazolidin-4-one (**3b**).

This compound was obtained in a yield of 72%, mp 138-139°, (lit mp 138.5-139° [22]).

2-(4-Methoxyphenyl)-3-phenylthiazolidin-4-one (**3c**).

This compound was obtained in a yield of 48%, mp 97-98°; ir: cm^{-1} 1690 (s) (C=O), 1170 (s) (Ar-O-C), 840, 760, 700 (s) Ar-H; ^1H nmr: 7.1-7.4 (m, 9H, aromatics), 6.7 (s, 1H, CH), 3.85-3.95 (m, 2H, CH_2) and 3.6 (s, 3H, OCH_3); uv: λ max nm 236; ms: m/e no M^+, 121, 106, 93, 92, 91, 77.

Anal. Calcd. for $C_{16}H_{15}NO_2S$: C, 67.37; H, 5.26. Found: C, 67.40; H, 5.23.

2-(4-Methylphenyl)-3-phenylthiazolidin-4-one (**3d**).

This compound was obtained in a yield of 31%, mp 112-113°; ir: cm^{-1} 1690 (s) C=O, 1600, 1490 (m) Ar C=C, 770 (m), 758 (s) Ar-H; ^1H nmr: 7.0-8.0 (m, 9H, aromatics), 6.05 (s, 1H, CH), 3.8 (m, 2H, CH_2), 2.2 (s, 3H, Ar-CH_3); uv: λ max 227.

Anal. Calcd. for $C_{16}H_{15}NOS$: C, 71.38; H, 5.58. Found: C, 71.24; H, 5.51.

2-Phenyl-3-(4-nitrophenyl)thiazolidin-4-one (**3e**).

This compound was obtained in a yield of 69%, mp 82-83° (lit mp 82-83° [23]).

2-(Phenyl)-3-(3-nitrophenyl)thiazolidin-4-one (**3f**).

This compound was obtained in a yield of 62%, mp 127-129°; ir: cm^{-1} 1670 (s) (C=O), 1600, 1520 Ar, C=C, 735 (s) Ar-H; ^1H nmr: 7.0-7.7 (m, 9H, aromatics), 6.45 (s, 1H, CH), 4.1 (m, 2H, CH_2); uv: λ max nm 240; ms: m/e M^+ 300.

Anal. Calcd. for $C_{15}H_{12}N_2O_3S$: C, 60.00; H, 4.00. Found: C, 59.95; H, 4.01.

2-Phenyl-3-(4-chlorophenyl)thiazolidin-4-one (**3g**).

This compound was obtained in a yield of 69%, mp 111.5-112°, (lit mp 110.8-112.2 [1]).

2-Phenyl-3-(3-chlorophenyl)thiazolidin-4-one (**3h**).

This compound was obtained in a yield of 53%, mp 128-129° (lit mp 128.6-129.6° [1]).

2-Phenyl-3-(4-methoxyphenyl)thiazolidin-4-one (**3i**).

This compound was obtained in a yield of 55%, mp 102.5-103.5°, ir: cm^{-1} 1675 (s) (C=O), 1600 (m), 1510 (m) Ar C=C, 840, 740 (s) Ar-H; ^1H nmr: 7.0-7.5 (m, 9H, aromatics), 6.7 (s, 1H, CH), 3.85-3.95 (m, 2H, CH_2), 3.7 (s, 3H, OCH_3); uv: λ max 230; ms: m/e 285 (M^+).

Anal. Calcd. for $C_{16}H_{15}NO_2S$: C, 67.37; H, 4.21. Found: C, 67.40; H, 4.19.

2-Trichloromethyl-3-phenylthiazolidin-4-one (**3j**).

This compound was obtained in a yield of 43%, mp 174-175°; ir: cm^{-1} 1690 (s) (C=O), 1595, 1495 (m) (arom, C=C), 780 (C-Cl); ^1H nmr: 7.3-7.5 (m, 5H, aromatics), 5.8 (s, 1H, CH), 3.95 (quartet, J = 14 Hz, 2H, CH_2); ms: m/e no M^+ peak, 178 (100), $M^+ - CCl_3$.

Anal. Calcd. for $C_{10}H_8NOCl_3$: C, 40.40; H, 2.72; N, 4.72; Cl, 35.86. Found: C, 40.60; H, 2.74; N, 4.60, Cl, 35.44.

Kinetic Studies.

Thioglycolic acid solutions were prepared in 100 ml volumetric flasks in the following concentrations: 0.100*M*, 0.200*M* and 0.400*M*. The solvents used for the thioglycolic acid solutions were toluene, carbon tetrachloride and nitrobenzene. The imine solutions were made up in the same concentrations and in the same solvents. The imine solution to be reacted was poured into a 500 ml, three necked flask. A thermometer was placed in one neck. In the middle neck was a jacketed mechanical stirrer. In the third neck a short condenser was fitted to allow the easy withdrawal of aliquots from the reaction vessel. The volumetric flask containing the thioglycolic acid solution to be reacted, was placed alongside the reaction vessel in a thermostatically controlled (±1°) water bath. The bath was used for reaction temperatures up to 80° and the surface was covered with styrofoam balls to minimize evaporation. The two flasks containing the solutions were placed in the bath for one hour prior to reaction and allowed to reach an equilibrium with the bath temperature. Thermometers (accurate to ±0.1°) were placed in the two solutions to measure the temperatures prior to mixing. To begin the reaction, the short condenser was removed from the reaction vessel and the thioglycolic acid solution was mixed rapidly with the imine solution and the short condenser replaced. Aliquots were removed at 60 minute intervals for eight hours (30 minute intervals for the first 2 hours) through the short condenser using a pipet (titration) or 10 ul syringe (gc). Aliquots (about 6 ml) withdrawn with the pipet were quenched in an ice bath. A 5 ml portion was accurately pipetted into a standard sodium hydroxide solution and this solution was titrated against a standard hydrochloric acid solution using phenolphthalein indicator. From this the concentration of *S*-α-aminomercaptoacetic acid, and hence its rate of disappearance, can be calculated. Blank titrations containing standard concentrations of each reactant and the product, along with various mixtures of reactants and products, were conducted prior to using this method of analysis. Further, other aminoacid systems were used in the blank tirations. The results showed that the concentration of a carboxylic acid containing moiety could easily be determined with an accuracy greater than 99.8% of the known concentration. The kinetic runs carried out in toluene at 110° were performed in the same reaction vessel; however, a heating mantle was used instead of the constant temperature bath.

A minimum of three runs was completed for all the compounds shown in Tables 3 and 4. The rate of dissappearance of *S*-α-aminomercaptoacetic acid was obtained by entering the measured concentration changes into a least squares program capable of computing $y = \log x$, $y = 1/x$ and $y = 1/x^2$. The "best fit" data was obtained from the log x plots with a correlation coefficient of 0.99.

Detection of Intermediates using ^{1}H NMR.

Standard 60 MHz ^{1}H nmr spectra of starting materials were in agreement with those published [24,25,26].

Equal volumes (0.5 ml) of equimolar (5*M*) thioglycolic acid and *N*-benzylideneaniline (5*M*) in carbon tetrachloride were mixed in the nmr tube. The resulting spectrum differed significantly from both the original imine and the final thiazolidin-4-one. The chemical shift changes are given in Table 1. When ethyl thioglycolate was used, under the same conditions, instead of the acid, no immediate changes in the spectrum were detected. The spectrum obtained appeared to be a mixture of ethyl thioglycolate and *N*-benzylideneaniline. On warming for two minutes at 60° dramatic changes in chemical shifts were observed in the methine proton of the imine and the methylene protons of the ester. Further, the thiol proton was not observed unless an excess volume of the acid or ester was added. *N*-Hexylideneaniline and a number of other *N*-alkylidineanilines solutions exhibited (1*M* in carbon tetrachloride) no changes in chemical shifts on addition of an equal volume of equimolar thioglycolic acid, even on heating the nmr tube.

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