

transition is a matter of attractive forces, while the liquid properties are dominantly affected by repulsive forces. The hard sphere system without attractive forces never distinguishes its liquid and gas states. It is worth pursuing to formulate an approximation of integral equation which provides a satisfactory phase transition by selecting some of nodal group and/or E group.

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Synthesis of Nucleophilic Adducts of Thiols (VII). Addition of Thioglycolic Acid to α -Cyano- β -phenylacrylic Acid Derivatives

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Reaction of α -cyano- β -phenylacrylic acid derivatives (I) with thioglycolic acid in the molar ratio of 1:2 in saturated sodium bicarbonate solution yielded 3-(4'-oxo-2'-thiazolin-2'-yl)-2-phenyl-4-oxotetrahydrothiophene derivatives (V). Thioglycolic acid was found to be added not only to carbon-carbon double bond but also to carbon-nitrogen triple bond and those adducts were cyclized to V.

Introduction

As a part of continuous investigation on the syntheses of thiol derivatives by nucleophilic addition, the reactions of thiol with β -nitrostyrene^{1,2} and ω,ω -diacetylstyrene³ have been reported recently. Much information has been appeared in the literature concerning the anticancer and antimicrobial activities of these thiol adducts.⁴⁻⁷

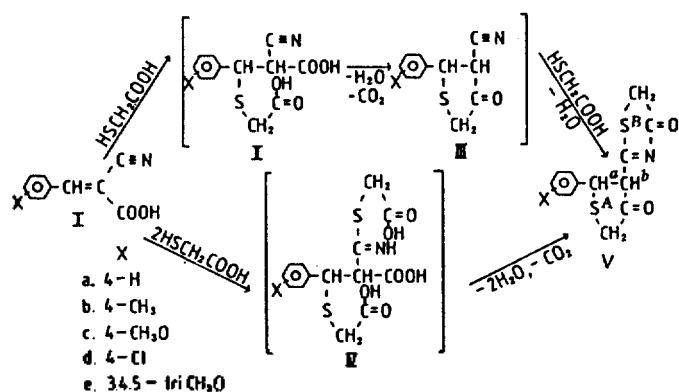
Elnagdi, *et al.*,⁸ prepared 3,3-dicyano-2-phenyl-4-oxotetrahydrothiophene and 2-(4-oxo-2-thiazolin-2-yl) cinnamionitrile by the addition of thioglycolic acid to benzyliden-malononitrile in refluxing pyridine. This paper presents our study of the addition of thioglycolic acid to α -cyano- β -

phenylacrylic acid derivatives.

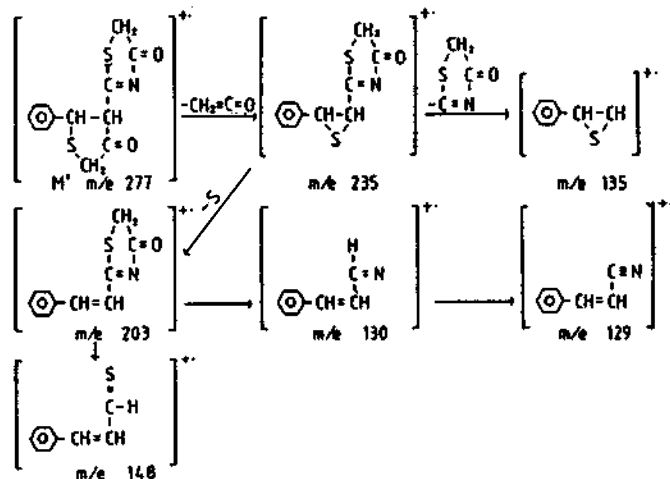
Results and Discussion

When α -cyano- β -phenylacrylic acid (Ia) was treated with thioglycolic acid in the molar ratio of 1:2 in saturated sodium bicarbonate solution, a product of molecular formula $C_{11}H_{11}NS_2O_2$ was formed. The IR spectrum of the product revealed absorption band at 1780 cm^{-1} , which is attributable for C=O group in cyclic ketone. The mass spectrum shows the molecular ion of m/e 277. Intensity ratio of $M+2$ peak vs. M^+ peak is 11.43% : 100%, which represents the presence of two sulfur atoms (calculated for $C_{11}H_{11}NS_2O_2$: 10.25%).

Based on these data structure Va was suggested for this product.



The NMR spectrum is also consistent with this structure. The doublet at δ 4.85 ppm and the singlet at δ 4.07 ppm are assigned to CH^a and CH_2 in the ring B, respectively. The multiplet centered at δ 3.82 ppm is attributable for the protons in CH^a and CH_2 in ring A. The following scheme presents a rationale for the major fragmentations in the mass spectrum.



Two probable mechanisms for the formation of the product are shown in scheme 1. However, exact mechanism will not be clarified until the intermediates are isolated and their structures are established.

Experimental

All melting points are uncorrected. Infrared spectra were obtained on a Beckman Accu Lab 4 spectrophotometer. Proton NMR spectra were obtained on a Bruker WP80CW(80 MHz) using TMS as the internal standard and chemical shifts are expressed in ppm unit. Ultraviolet spectra were recorded on a Gilford Spectronic 2600 spectrophotometer. Mass spectrum was determined with Hewlett Packard 5985 mass spectrometer and elemental analyses were performed on Perkin-Elmer Model 240 CHN analyzer. α -Cyano- β -phenylacrylic acid and its derivatives were prepared according to Lapworth.⁹

3-(4'-Oxo-2'-thiazolin-2'-yl)-2-phenyl-4-oxotetrahydrothiophene(Va).

A mixture of α -cyano- β -phenylacrylic acid (1.73g, 10 mmol) and thioglycolic acid (1.84g, 20 mmol) in saturated sodium bicarbonate solution (20 ml) was stirred at room temperature for 2 hours and allowed to stand overnight. The white precipitate was collected by filtration and recrystallized from methanol, which gave 1.8g(65.0%) of white crystal of Va melting at 198–202°C. IR(KBr): 1780 cm^{-1} (C=O). NMR (acetone- d_6): δ 3.82(*m*, 3H), 4.07(*s*, 2H), 4.85(*d*, 1H), 7.54(*m*, 5H). MS: *m/e* 277(*M*⁺, 79.6%), 235(3.6), 203(3.6), 148(43.3), 135(38.2), 130(57.5), 129(40.0), 122(100), 121(26.5). Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{NS}_2\text{O}_2$: C,56.31; H,3.97; N,5.05%. Found: C,55.77; H, 3.74; N,4.79%.

3-(4'-Oxo-2'-thiazolin-2'-yl)-2-(*p*-methylphenyl)-4-oxotetrahydrothiophene(Vb).

A mixture of α -cyano- β -(*p*-methylphenyl)acrylic acid (1.87g, 10 mmol) and thioglycolic acid(1.84g, 20 mmol) in saturated sodium bicarbonate solution (20 ml) was stirred at room temperature for 3 hours and allowed to stand overnight. The white precipitate was collected by filtration and recrystallized from methanol, which gave 2.15g(73.9%) of white crystal of Vb melting at 188–189°C. IR(KBr): 1770 cm^{-1} (C=O). NMR: δ 2.35(*s*,3H), 3.82(*m*,3H), 4.15(*s*,2H), 4.85(*d*,1H), 7.52(*m*,4H). Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{NS}_2\text{O}_2$: C,57.73; H,4.47; N,4.81%. Found: C,57.17; H,4.30; N,4.63%.

3-(4'-Oxo-2'-thiazolin-2'-yl)-2-(*p*-methoxyphenyl)-4-oxotetrahydrothiophene(Vc).

A mixture of α -cyano- β -(*p*-methoxyphenyl) acrylic acid(2.03g, 10 mmol) and thioglycolic acid(1.84g, 20 mmol) in saturated sodium bicarbonate solution (20 ml) was stirred at room temperature for 3 hours and allowed to stand overnight. The pale yellow precipitate was collected by filtration and recrystallized from methanol, which gave 1.3g(42.3%) of pale yellow crystal of Vc melting at 186–189°C. IR(KBr): 1765 cm^{-1} (C=O). NMR(acetone- d_6): δ 3.83 (*m*,3H), 3.84(*s*,3H), 4.15(*s*,2H), 4.85(*d*,1H), 7.53(*m*,4H). Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{NS}_2\text{O}_2$: C,54.72; H,4.23; N,4.56%. Found: C,54.18; H,4.01; N,4.34%.

3-(4'-Oxo-2'-thiazolin-2'-yl)-2-(*p*-chlorophenyl)-4-oxotetrahydrothiophene(Vd).

A mixture of α -cyano- β -(*p*-chlorophenyl) acrylic acid (1.50g, 8 mmol) and thioglycolic acid(1.84g, 20 mmol) in saturated sodium bicarbonate solution (20 ml) was stirred at room temperature for 3 hours and allowed to stand for 2 days. The white precipitate was collected by filtration and recrystallized from methanol, which gave 1.5g(60.2%) of white crystal of Vd melting at 184–188°C. IR(KBr): 1779 cm^{-1} (C=O). NMR(acetone- d_6): δ 3.75(*m*,3H), 4.15(*s*,2H), 4.85(*d*,1H), 7.53(*m*,4H). Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{NS}_2\text{O}_2\text{Cl}$: C,50.13; H,3.21; N,4.49%. Found: C,49.55; H,3.05; N,4.30%.

3-(4'-Oxo-2'-thiazolin-2'-yl)-2-(3,4,5-trimethoxyphenyl)-4-oxotetrahydrothiophene(Ve).

A mixture of α -cyano- β -(3,4,5-trimethoxyphenyl)acrylic acid (1.33g, 5 mmol) and thioglycolic acid(0.92g, 10 mmol) in saturated sodium bicarbonate solution (20 ml) was stirred at room temperature for 3 hours and allowed to stand overnight. The white precipitate was collected by filtration and recrystallized from methanol, which gave 1.05g(57.2%) of white crystal of Ve melting at 198–200°C. IR(KBr): 1772 cm^{-1} (C=O). NMR(acetone- d_6): δ 3.75 (*m*,3H), 3.80(*s*,9H), 4.15(*s*,2H), 4.85(*d*,1H), 7.12(*s*,2H). Anal. Calcd. for

$C_{16}H_{17}NS_2O_5$: C,44.04; H,4.63; N,3.81%. Found: C,43.68; H,4.45; N,3.66%.

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Kinetics and Thermodynamic Studies on the Reaction of Cysteine with Cinnamaldehyde

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The reaction of cysteine with cinnamaldehyde have been studied kinetically and thermodynamically. It was found that the reaction proceeds in two steps; formation of the monoadduct by a Michael type addition followed by the nucleophilic attack of the second cysteine to the carbonyl carbon of the monoadduct to afford the thiazolidine derivative. A reaction profile for the reaction of cysteine with cinnamaldehyde was constructed based on the thermodynamic parameters analyzed for the forward and the reverse reactions. It was assumed that the second step of this reaction accompanies an intermediate, a Schiff base.

Introduction

Michael obtained the addition product of ethyl malonate with ethyl cinnamate in sodium ethoxide solution, and Ingold formulated the mechanism of Michael addition in an alkaline solution.¹

Strong nucleophiles having sulfhydryl groups can be added to benzalaceto-phenone or acrylonitril without acid or base catalyst.² The formation of thiazolidine-4-carboxylic acid from formaldehyde and cysteine was explained by Ratner.³ The mechanism of the reaction of sulfhydryl compounds with α,β -unsaturated carbonyl compounds has been studied by Esterbauer.⁴⁻⁶ In this work, we have studied the mechanism of the reaction between cinnamaldehyde and cysteine. Spectroscopic and polarographic techniques have been employed to follow the rate of the reaction. The concentrations of the cinnamaldehyde and the cysteine were determined by the polarographic wave heights corresponding to the oxidation and the reduction of the respective substrates.

Experimental

General procedure

A. Perkin Elmer UV spectrophotometer and a Shimadzu RP-50 polarograph were used. All chemicals were commercially available reagent grade and were used as received. Ionic strength of the solution was maintained at 0.1 by adding appropriate amount of sodium chloride.

Kinetic Studies

The rate of the reaction was determined by spectroscopic and polarographic methods.

Spectrophotometric method: 98 ml of buffer solution in 100 ml volumetric flasks were immersed into the thermostat at 25°C, and 1 ml of 2×10^{-3} M cinnamaldehyde alcohol solution and 1 ml of cysteine solution of several different concentrations (10^{-2} ~ 10^{-1} M) were added. In order to prevent the oxidation of cysteine by oxygen in the solution, they had to be in nitrogen environment. Initial concentration of cinnamaldehyde was 2×10^{-5} M and that of cysteine were from 10×10^{-5} M to 100×10^{-5} M. The concentration of cinnamaldehyde in each reaction mixture were determined at 293 nm.

Polarographic method: 5 ml of 1×10^{-3} M solution of cinnamaldehyde in buffer and 10 ml 1×10^{-3} M solution of cysteine in buffer were mixed in the polarographic cell. Every procedure was carried out in nitrogen environment in order to prevent the oxidation of cysteine and 25°C water was passed around the reaction vessel to keep the temperature constant. Dropping mercury electrode and saturated calomel electrode were applied. The initial concentration of cinnamaldehyde and cysteine were 3.3×10^{-4} M and 6.6×10^{-4} M, respectively. The wave height, current -0.25 V v.s. S.C.E for the cysteine and at -1.40 V v.s. S.C.E for the cinnamaldehyde were recorded against time. Thermodynamic parameters: The rate constants at temperature of 13°C, 25°C, 32°C and 38°C were determined, respectively.