Synthesis of N-Phenylcysteine

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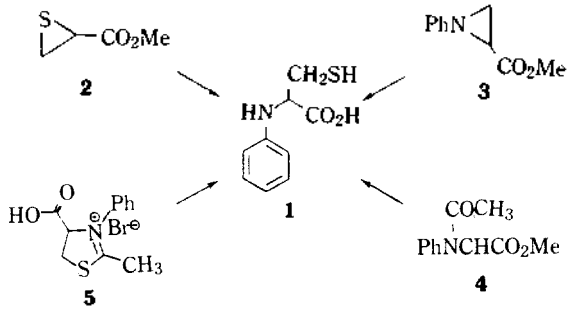
N-Phenylcysteine (**1**) was prepared as a hydrobromide in good yield from the acid hydrolysis of 4-carboxy-2-methyl-3-phenyl-Δ^2-thiazolinium bromide (**5**), which was derived from the reaction of thioacetanilide and α-bromoacrylic acid. The treatment of ethyl ester (**6**) of N-phenylcysteine with 2,2-dimethoxypropane rendered it to ethyl 2,2-dimethyl-3-phenylthiazoline-4-carboxylate (**7**).

In addition to natural amino acids, chemists have modified the most common amino acids. Various examples of applications of modified amino acids cover γ-aminobutyric acid (GABA) transaminase inhibitors, angiotensin converting enzyme (ACE) inhibitors, β-lactams, and so on.[1]

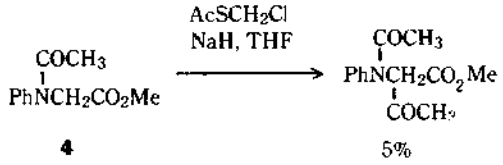
The preparation of N-phenylcysteine (**1**) came to our attention because of its potential as a starting material leading to numerous derivatives with biological activities such as antiulcer and antifulgar activities. Thus, we decided to develope its synthetic routes which allow large quantities on the preparative scale. Taking considerations of general methods for the preparation of amino acids, wide varieties of possible approaches can be adopted. However, in case of cysteine synthesis so far only few reaction routes have been known perhaps because of difficulties in the introduction of thiol group.[2]

In 1981, J. Martens *et al.* reported the successful synthesis of racemic cysteine by employing 1,3-thiazine intermediate which gives unsubstituted amine group.[3] Now that this reaction route can not provide N-substituted cysteine, the possibility of utilization of 1,3-thiazine intermediate was excluded in our synthetic plan. The reaction routes examined in our lab are shown in Scheme 1.



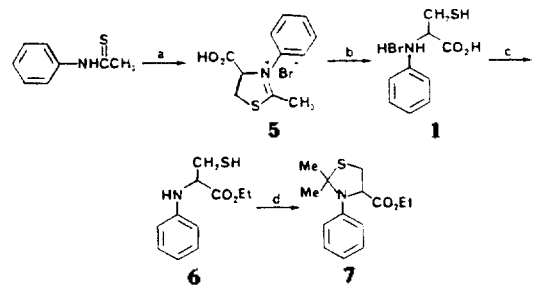
Scheme 1

First, 2-carbomethoxythiirane (**2**) was prepared from methyl acrylate[4] and was allowed to react with aniline. But instead of the desired product, we obtained β-amino acid resulted from the substitution at 3-position of thiirane ring. Similarly, opening reaction of 2-carbomethoxy-1-phenylaziridine (**3**) with hydrogen chloride was attempted. But the reaction product was originated from the attack of chloride ion at 2-position instead of expected 3-position.[5] In contrast, in case of 2-carbomethoxy-1-benzylaziridine, it was reported that chloride ion attacks at 3-position.[6] When acetyl derivative (**4**) of methyl N-phenylaminoacetate was reacted with thioacetoxymethyl chloride[7], only 5% yield of the desired product was obtained. Thus, we had to look for another method which could allow us large scale preparation.



In 1971, Å Eidem *et al.* reported the synthesis of N-substituted cysteine by hydrolysis of Δ^2-thiazolinium salt.[8] Although they briefly mentioned the progress in the synthesis of N-phenylcysteine, no details was disclosed at all even thereafter. This situation lead us to examine their methodology carefully and follow the experimental conditions.

Our reaction planning is shown in Scheme 2. α-Bromoacrylic aicd was prepared from methyl acrylate and was reacted with thioacetanilide to afford 98% yield of the desired 4-carboxy-2-methyl-3-phenyl-Δ^2-thiazolinium bromide (**5**). Consequently, the resulting thiazolinium salt was subjected to acid hydrolysis, which was found to be very critical because somewhat concentrated acid hydrolysis condition such as 6 N sulfuric acid or 6 N HCl gave the mixture of N-phenylcysteine and its acetyl derivative. However, when the thiazolium salt (**5**) was refluxed in 1.5 N HBr solution for 3 hours, a mixture of free amino acid and its HBr salt was obtained. This mixture was further treated with 48% aqueous



a) $CH_2=C(Br)CO_2H$/PhMe, Δ, 98% b) 1.5N HBr, Δ, 100% c) EtOH/H_2SO_4, $CHCl_3$, Δ, 93% d) $Me_2C(OMe)_2$/p-TsOH, Me_2CO, rt, 93%

Scheme 2

HBr solution to obtain HBr salt of N-phenylcysteine (**1**) in 96% yield. ^1H NMR spectrum of N-phenylcysteine hydrobromide in trifluoroacetic acid-d_1 exhibited the presence of

methine proton by a triplet at δ 6.84 and methylene protons by a doublet of doublet at δ 3.20. Ethyl ester of free N-phenylcysteine was obtained by esterification in chloroform solution and its ^{1}H NMR spectrum in $CDCl_3$ showed a broad singlet at δ 4.33 for PhNH, a doublet of doublet at δ 2.77 for -CH_2SH, and a triplet at δ 1.30 for -CH_2SH besides the peaks for phenyl and an ethyl ester group. IR spectrum showed a peak at 3390 cm^{-1} for NH stretching and 2560 cm^{-1} for SH stretching.

As a part of our program to utilize the N-phenylcysteine for biologically active compounds, the ethyl ester of N-phenyl cysteine (**6**) was reacted with dimethoxypropane to obtain a thiazoline derivative (**7**). Currently, further derivatization of N-phenylcysteine is being undertaken in our lab.

Experimental Section

General Comments. Melting points were determined on a Thomas-Hoover Uni-Melt apparatus in capillary tubes and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-435 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Associates EM 360 60 MHz spectrometer. The ^{1}H NMR spectra were measured in $CDCl_3$ solution, unless otherwise stated, relative to Me_4Si, as an internal standard (δ = 0.00). Mass spectra (MS) were obtained on a Shimadzu GCMS-QP 1000 at 70 ev and recorded herein (relative intensity and assignment).

Unless otherwise indicated in a specific experiment, all of the chemicals used were reagent grade and no additional purification has been done. Benzene and toluene were distilled over sodium and stored over molecular sieves. $CHCl_3$ was distilled over P_2O_5.

Thin layer chromatography (TLC) was performed on Merck 60 F-254 glass plates without activation. Column chromatography procedures utilized silica gel (Merck, Silical gel 60, 70-230 mesh).

4-Carboxy-2-methyl-3-phenyl-Δ^2-thiazolinium Bromide (5). A mixture of thioacetanilide[9] (10.0g, 66.1 mmol) and -bromoacrylic acid[10] (11.0 g, 72.9 mmol) in dry toluene (120 m*l*) was heated at 90°C for an hour. After cooling to room temperature, the precipitated pale-yellow solid was filtered off, washed with acetone (2 × 50 mL) and was dried to give **5** as a white solid (19.5 g, 98%), which was recrystallized in MeOH-EtOAc-hexane (1:1:2) to obtain pure **5**: 17.8 g (89%); mp 215-216°C; ^{1}H NMR (TFA) δ 2.47 (s, 3H), 4.18 (ddd, J = 3.0 Hz, 1.1 Hz, 0.4 Hz, 2H), 5.76 (dd, J = 1.1 Hz, 0.4 Hz, 1H), 7.37 (s, 5H); IR (KBr) 2900, 2790, 1722, 1548, 1175, 783, 692 cm^{-1}; Anal. Calcd. for $C_{11}H_{12}NBrO_2S$: C, 43.72; H, 4.00; N, 4.64. Found: C, 43.74; H, 4.10; N, 4.53.

N-Phenylcysteine (1) Hydrobromide. A solution of 4-carboxy-2-methyl-3-phenyl-Δ^2-thiazolinium bromide (10.0 g, 33.1 mmol) in 1.5N aqueous HBr (120 m*l*) was refluxed for 3 hours and then was concentrated under reduced pressure. The residue was dissolved in 48% aqueous HBr solution (50 m*l*) and was evaporated *in vacuo* to obtain a pale brown viscous material, which was dissolved in hot benzene and was cooled to obtain the hydrobromide of **1** as a pale yellow solid (9.19 g, 100%). Recrystallization from n-PrOH-benzene (1:8) afforded a white solid: 8.85 g (96%); mp 173-174°C; ^{1}H NMR (TFA) δ 3.2 (dd, J = 9.0 Hz, 4.0 Hz, 2H), 6.84 (t, J = 4.0 Hz, 1H), 7.25-7.75 (m, 5H); IR(KBr) 2900, 1735, 1535, 1490, 1440, 1190 cm^{-1}; Anal. Calcd. for $C_9H_{12}BrNO_2S$: C, 38.86; H, 4.35; N, 5.03. Found: C, 39.54; H, 4.48; N, 4.84.

Ethyl Ester of N-Phenylcysteine (6). A solution of N-phenylcysteine (5.0 g, 18.0 mmol) in absolute ethanol (40 m*l*) and dry chloroform (120 m*l*) and catalytic amount of conc. sulfuric acid were refluxed under nitrogen for 24 hours. Water was removed by aid of a Dean-Stark trap. After cooling to room temperature, solid $NaHCO_3$ was added until no more CO_2 gas evolved. The white solid formed in the reaction mixture was filtered off and the filtrate was evaporated on a rotary evaporator to yield a brown syrup. The white solid **6** was separated through silica gel column by eluting with hexane-ether(2:1): 4.47 g (93%); mp 48-48.5°C; ^{1}H NMR δ 1.1 (t, J = 8.0 Hz, 3H), 1.3 (s, J = 8.0 Hz, 1H), 2.77 (dd, J = 8.0 Hz, 5.0 Hz, 2H), 4.0 (q, J = 7.0 Hz, 2H), 4.13 (t, J = 5.0 Hz, 1H), 4.33 (brs, 1H), 6.35-7.2 (m, 5H); MS m/e 225 (M$^+$, 24.1), 178 (M$^+$-CH_3SH, 75.0), 152 (M$^+$-CO_2Et, 67.2), 118 (62.5), 104 (100); IR (KBr); 3390, 3050, 2970, 2560, 1730, 1600, 1500, 1300, 1295, 1025, 750, 690 cm^{-1}; Anal. Calcd. for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.23. Found: C, 58.09; H, 6.75; N, 6.17.

Ethyl 2,2-Dimethyl-3-phenylthiazoline-4-carboxylate (7). A solution of ethyl ester of N-phenylcysteine (4.0 g, 17.8 mmol) and 2,2-dimethoxypropane (35 m*l*, 285 mmol) in dry acetone (25 m*l*) with catalytic amount of p-toluenesulfonic acid was stirred under nitrogen for 24 hours. After concentration of the reaction mixture followed by neutralization with saturated aqueous $NaHCO_3$ solution, column chromatography on silica gel eluted with hexane-EtOAc (3:1) gave **7** as a colorless viscous liquid: 4.41 g (93%); ^{1}H NMR δ 1.07 (t, J = 7.0 Hz, 3H), 1.50 (s, 3H), 1.77 (s, 3H), 3.25 (d, J = 7.0 Hz, 2H), 4.03 (q, J = 7.0 Hz, 2H), 4.60 (t, J = 7.0 Hz, 1H), 6.60-7.30 (m, 5H); IR (neat) 3050, 2960, 2910, 1750, 1720, 1580, 1500, 1080, 1030, 745, 700 cm^{-1}; Anal. Calcd. for $C_{14}H_{19}NO_2S$: C, 63.37; H, 7.22; N, 5.28. Found: C, 63.05; H, 7.32; N, 5.17.

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5. Structural assignment of the product was based on ^{1}H NMR spectrum. ^{1}H NMR δ 3.48 (d, J = 6.0 Hz, 2H), 3.70 (s, 3H), 4.06 (brs, NH, 1H), 4.40 (t, J = 6.0 Hz, 1H), 6.35-7.35 (m, 5H).
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Surface-enhanced Raman Scattering(SERS) of Benzylcyanide in Silver Sol

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The surface-enhanced Raman scattering(SERS) of benzylcyanide in a silver sol was investigated. It was concluded that the molecule adsorbed onto the silver surface via the π system of the CN group. The molecule was assumed to coordinate with either a single atom or two silver atoms. According to the SERS selection rule, the benzene ring of the adsorbed species seemed to assume a flat stance with respect to the silver surface.

Introduction

The observation of vibrational spectra of molecules adsorbed on metal surfaces at monolayer or submonolayer coverages can be made by virtue of surface-enhanced Raman scattering (SERS)[1]. The ability to perform vibrational spectroscopy under these conditions has led to a new understanding about the chemical identity, geometry, and bonding of adsorbed material at a level previously unaccessible.

Organic cyanide(or nitrile) has a very interesting character in that several binding sites, *i.e.* π-bond of C ≡ N group, lone pair electrons of nitrogen atom, and other functional groups in the molecule, are available for the adsorption on metal surface. In the SERS study, benzonitrile appeared to adsorb on the silver surface via the nitrogen lone pair electrons[2]. It would then be worthwhile to investigate other structurally similar system in order to understand the detailed nature of the interaction between the organic cyanide(or nitrile) molecule and the metal surface. In this respect, we present here the SER spectrum of benzylcyanide adsorbed on aqueous silver sol particle.

Experimental

Details of the apparatus for Raman measurements have been described previously[3]. Preparation and spectral properties of silver sol solution have also been described. Since benzylcyanide is insoluble in water, it is difficult to introduce the material to the sol solution. Hence, a small amount of neat benzylcyanide (Merck) was dropped directly into the sol solution in this work. The color of the aqueous layer changed slowly from yellow to green. About 10 min. after the addition of benzylcyanide, the aqueous layer was sampled to record its Raman spectrum. The SER spectrum obtained in this manner hardly changed upon the amount of neat benzylcyanide initially dropped into the sol solution.

Results and Discussion

The ordinary Raman spectrum of neat benzylcyanide and its SER spectrum in a silver sol are shown in Figure 1(a) and 1(b), respectively. The latter spectrum has a broad background in the 1100-1600 cm^{-1} region. That may be due to carbon overlayers on the silver particles as reported by Cooney *et al.*[4] Nevertheless, it is rather straightforward to correlate the vibrational lines between the two spectra. For instance, the major bands associated with the benzene-ring vibrational modes[5,6] appeared at 428(ν_{6a}), 620(ν_{6b}), 701(ν_4), 748(ν_{11}), 847(ν_{10a}), 1005(ν_{12}), 1031(ν_{18a}), 1186(ν_{13}), and

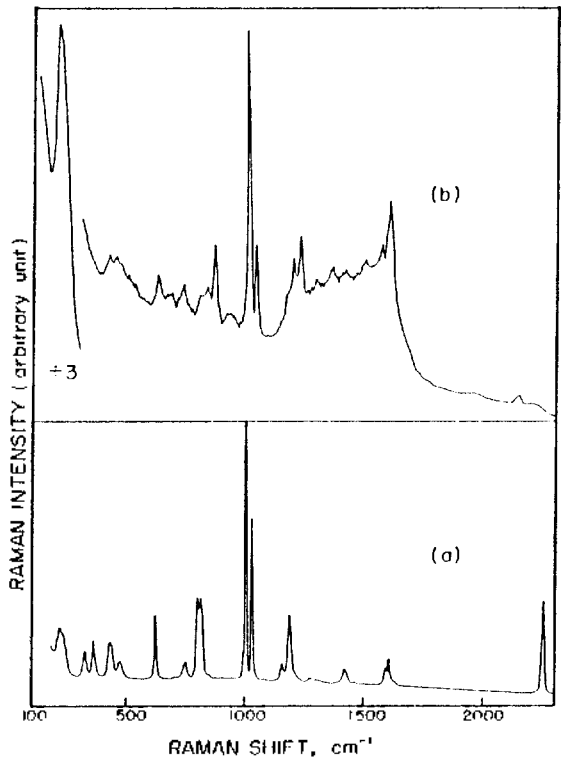

Figure 1. (a) Ordinary Raman spectrum of benzylcyanide (514.5 nm excitation at 100 mW, 4.2 cm^{-1} bandpass). (b) SER spectrum of benzylcyanide in a silver sol (514.5 nm excitation at 20 mW, 12 cm^{-1} bandpass).