UDC 547.314.07 : 547.787+547.789

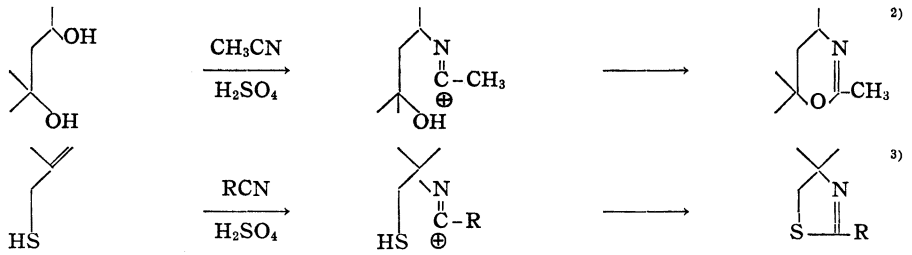
178. Yasuo Yura : Studies on Acetylenic Compounds. XXVI.*2 Ring Closure. (6). New Synthetic Method of Heterocyclic Compounds from α-Substituted Acetylenic Compounds.

(*Takamine Laboratory, Sankyo Co., Ltd.**1)

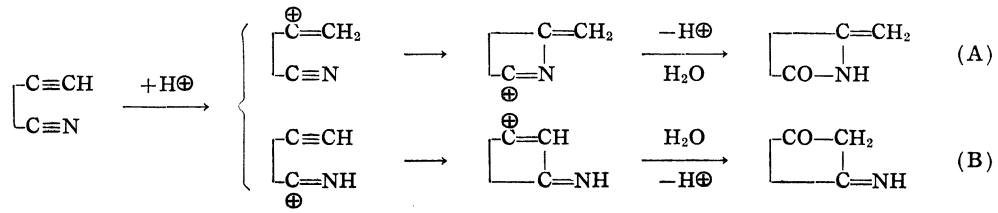
In the previous paper,*2 it has been reported that α-substituted acetylenic compounds (-CH(X)-C≡C-) such as 1-(1-methylpropynyl)urea (X= -$NHCONH_2$), 1-(1-methylpropynyl)-2-thiourea (X= -$NHCSNH_2$) and N-(1-methyl-2-propynyl)benzamide (X= -NHCOPh) internally closed their ring to give five membered heterocyclic ring compounds, 2-imidazolone, 2-imidazolethiol and 2-phenyloxazole derivatives, respectively.

In the present paper, the author intends to report that α-thiocyanatoacetylene (X= -SCN) and 2-propynyl benziminoether (X= -O-C(=NH)-R) also undergo a similar ring closure to afford heterocyclic compounds.

In 1948 Ritter *et al.*[1] reported that some alkenes catalytically reacted with nitrile to afford N-alkylamide in the presence of sulfuric acid. Since then this reaction has been investigated extensively to establish a new synthetic method of heterocyclic compounds.



The mechanism for this reaction has been considered that a nitrilium ion caused by a carbonium ion attacks the electron donating groups such as -OH or -SH to close the heterocyclic ring. These reactions were carried out in cold conc. sulfuric acid. Considering these facts, it is concluded that a nitrile group must tend to react with a carbonium ion rather than with the proton in cold conc. sulfuric acid. It seems interesting, therefore, to investigate this problem in the case of acetylenic compounds having a nitrile group, where the carbon-atoms of both radicals can form a carbonium



*1 Nishi-shinagawa, Shinagawa-ku, Tokyo (由良靖雄).

*2 Phrat XXV : This Bulletin, **10**, 1087(1962).

1) J. J. Ritter, P. P. Minieri : J. Am. Chem. Soc., **70**, 4045 (1948); J. J. Ritter, J. Kalish : *Ibid.*, **70**, 4048 (1948).

2) Emma-June Tielmanns, J. J. Ritter : J. Org. Chem., **22**, 839 (1957); A. I. Meyers, J. J. Ritter : *Ibid.*, **25**, 1147 (1960).

3) A. I. Meyers, J. J. Ritter : *Ibid.*, **23**, 1918 (1958).

ion. When acetylenic nitrile compounds are treated with sulfuric acid, if a proton adds to a triple bond, the carbonium ion formed must react with a nitrile group to give an amide, while if a proton adds to a nitrile group, the resulted nitrilium ion[2] must attack a triple bond to form a keto-ketimine.

From this standpoint, α-thiocyanatoacetylenic compounds, prepared from α-haloacetylenes and potassium rhodanate, were treated with sulfuric acid and the resulted products were investigated. 3-Bromo-1-propyne, when treated with an aqueous ethanol solution of potassium thiocyanate at room temperature, gave 2-propynylthiocyanate (I) in good yield. (I) was then dissolved in conc. sulfuric acid at 0~5° and after keeping at this temperature range for three hours under stirring, the reaction mixture was allowed to stand overnight at room temperature. Treatment as described in the experimental section gave a free base as white needles, m.p. 104°, whose elemental analysis agreed with an empirical formula C_4H_5ONS. In its infrared spectrum the absorption due to a triple bond disappeared and a strong absorption band at 1620 cm^{-1} caused by cabonyl was newly displayed. Ultraviolet spectrum showed an absorption at 241.5 mμ. These experimental data suggested that the above base is a heterocyclic compound, viz. 4-methyl-2-thiazolol (IV). This was further confirmed by admixture with an authentic sample prepared from rhodanaceton according to H. Kondo's method.[4] Infrared and ultraviolet spectra of both compounds were also identical. (Fig. 1).

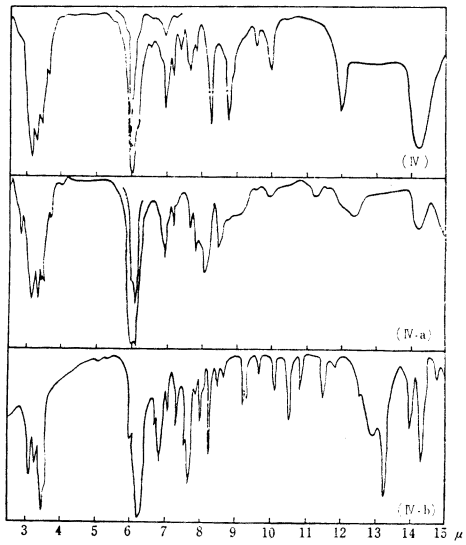


Fig. 1.
Infrared Spectra of 4-Methyl-2-thiazolol (IV; in CCl_4), 4,5-Dimethyl-2-thiazolol (IVa; in $CHCl_3$) and 4-Benzyl-2-thiazolol (IVb; Nujol)

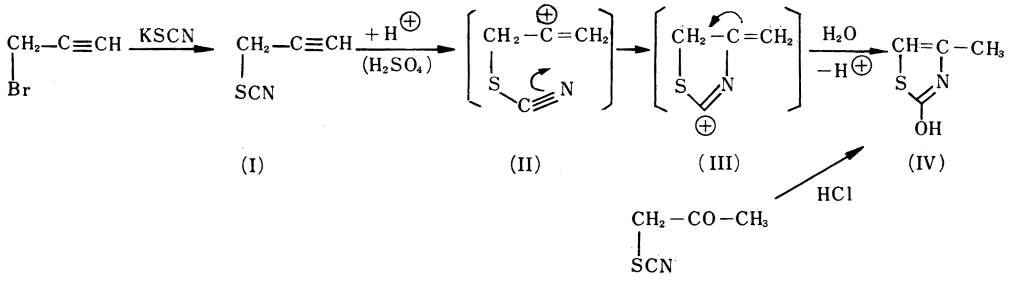
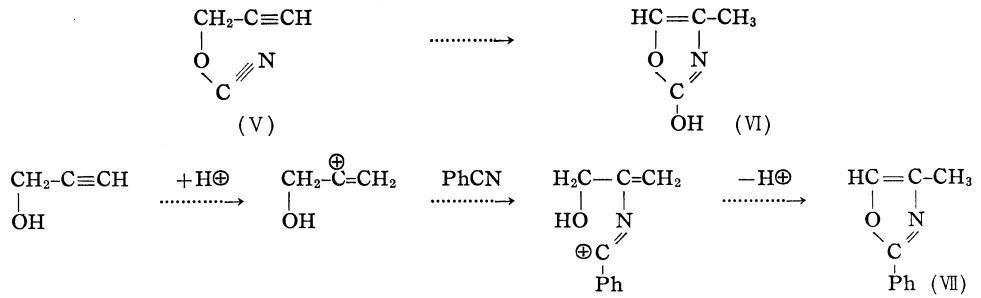


Chart 1.

4) H. Kondo, F. Nagasawa : Yakugaku Zasshi, **57**, 909 (1937).

From these results, the reaction mechanism would be considered as follows: 2-propynylthiocyanate is first transformed into carbonium cation (II), followed by ring closure to thiazole (III), and subsequent rearrangement gives (IV). Therefore, it is concluded that the ring closure of an acetylenic nitrile compound occurs according to the equation (A) in the Chart 1. By a similar way, 3-thiocyanato-1-butyne and 1-thiocyan-3-phenyl-2-propyne also gave thiazole derivatives, 4,5-dimethyl-2-thiazolol (IVa) and 4-benzyl-2-thiazolol (IVb), respectively. In acetylenic compounds, possessing a phenyl group adjacent to a triple bond, the yield of thiazoles was rather low since a considerable amount of resinous substances were produced. This might be caused by high activity of the triple bond activated by a phenyl group.

Oxazole Derivative——A new synthetic method of thiazoles from 2-propynyl thiocyanate (I) has now been discussed. If a similar ring closure takes place in the case of 2-propynyl cyanate (V) in which the sulfur atom of (I) is replaced by oxgen, 4-methyl-2-oxazolol (VI) would be obtained. However, the starting material 2-propynyl cyanate did not form 3-bromo-1-propyne and potassium cyanate. On the other hand, it has been clarified that in acetylenic nitrile compounds, protonation tends to occur at the triple bond rather than at the nitrile group. Therefore, an oxazole compound could be directly obtained from 2-propynol and nitrile compounds in the presence of sulfuric acid.



A mixture of 2-propynol and benzonitrile was treated with sulfuric acid by a similar way to give an oily product of b.p_6 100~110°(bath temperature). It formed a picrate of m.p. 97~99°, whose elementary analysis gave values corresponding to an empirical formula $C_{16}H_{12}O_8N_4$. The infrared spectrum (Fig. 2) of the oil showed an absorption at 1676 cm^{-1} (>C=O) and was very different from that an authentic sample of 2-phenyl-4-methyloxazole (IX) prepared from bromoaceton and benzamide.[5] In this case the hydroxyl group of 3-propynol would have participated in the ring closure. Therefore, benziminoether was employed as a starting material. A mixture of 2-propynol and

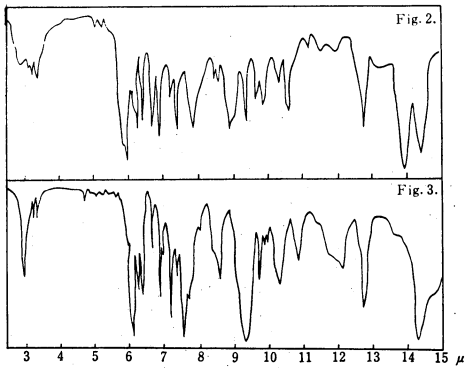


Fig. 2. Infrared Spectrum of the Base obtained from 2-Propynol and Benzonitrile (liquid film)

Fig. 3. Infrared Spectrum of 2-Propynyl Benziminoether (liquid film)

5) B. S. Friedman, M. Sparks, R. Adams: J. Am. Chem. Soc., **59**, 2262 (1937).

benzonitrile was saturated with dry hydrogen chloride under ice-cooling. After the reaction mixture was allowed to stand overnight at room temperature, (Ⅷ) was obtained as white needles, m.p. 93~94°. By treating (Ⅷ) with an aqueous solution of sodium carbonate a free base of $b.p_5$ 95° was obtained. Its analytical data agreed with an empirical formula $C_{10}H_9ON$, and absorption at 3300 and 2150 cm^{-1} (-C≡CH) were observed in infrared spectrum. Therefore, (Ⅷ) was confirmed to be formulated as 2-propynyl benziminoether hydrochloride (Fig. 3).

When (Ⅷ) was treated with conc. sulfuric acid for five days a colorless oil of $b.p_5$ 95° was obtained. The oil was confirmed to be 2-phenyl-4-methyloxazole (Ⅸ)[5] by comparing its infrared (Fig. 4) and ultraviolet spectra with those of an authentic sample (Chart 2).

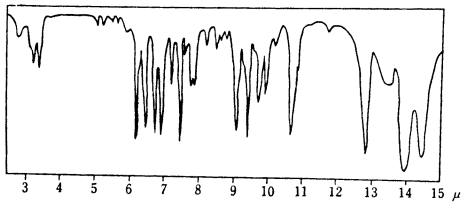


Fig. 4.
Infrared Spectrum of 2-Phenyl-4-methyloxazole (liquid film)

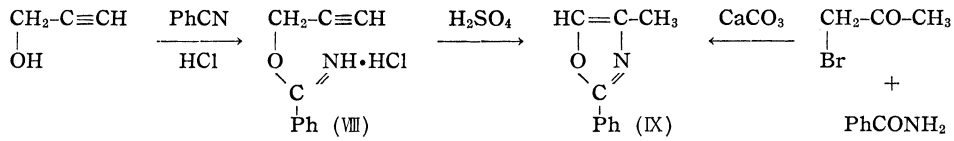


Chart 2.

Experimental

4-Methyl-2-thiazolol (IV)——To a solution of 10 g. of 3-bromo-1-propyne dissolved in 30 cc. of 70% EtOH, was added 6.65 g. of powdered KSCN. After being stirred overnight at room temperature, the reaction mixture was diluted with H_2O and extracted with Et_2O. The ethereal extract was dried over Na_2SO_4. After removal of Et_2O, the oily residue was distilled to obtain (I) as an oil, $b.p_{3.5}$ 83°. IR ν_{max}^{liquid} cm^{-1} : 3330 (≡CH), 2170 (-C≡N), 2135 (-C≡C-).

Eight grams of (I) was gradualy added to 80 cc. of conc. H_2SO_4 at 5~8° and stirring was continued for an additional 3 hr. Then the reaction mixture was allowed to stand overnight at room temperature and poured into ice-H_2O. The acidic solution was neutralized with Na_2CO_3 and extracted with Et_2O. The solid residue which was obtained from the extract by evaporating the solvent, was dissolved in benzene. After treating with Norite, the benzene solution was concentrated to give white needles, m.p. 102~103°. Yield, 7.3 g. (77%). A mixed m.p. with the authentic sample, m.p. 102~103°, prepared from rhodanaceton by the method of Kondo and Nagasawa,[4] showed no depression. *Anal.* Calcd. for C_4H_5ONS : C, 41.04; H, 4.34; N, 12.10. Found : C, 41.17; H, 4.41; N, 11.93. UV : λ_{max}^{EtOH} 241.5 mμ (log ε 3.19).

4,5-Dimethyl-2-thiazolol (IVa)——3-Thiocyanato-1-butyne (400 mg.) which was prepared from 1.7 g. of 3-bromo-1-butyne, 20 cc. of 50% EtOH and 1.01 g. of KSCN by the same procedure as in (IV), was dissolved in 5 cc. of conc. H_2SO_4 under cooling in an ice-salt bath. After being stirred for an additional 3 hr. at −5~0°, the mixture was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-H_2O. The acidic solution was neutralized with Na_2CO_3 and was extracted with Et_2O. After removal of Et_2O, the residue was crystallized from benzene to give colorless prisms, m.p. 143°, undepressed on admixture with 4,5-dimethyl-2-thiazolol (m.p. 143°), prepared by the method of Kondo and Nagasawa.[4] *Anal.* Calcd. for C_5H_7ONS : C, 46.51; H, 5.42; N, 10.85. Found : C, 46.79; H, 5.56; N, 10.76. UV : λ_{max}^{EtOH} 246.7 mμ (log ε 3.77).

4-Benzyl-2-thiazolol (IVb)——A mixture of 10 g. of 3-bromo-1-phenyl-1-propyne, 30 cc. of 70% EtOH and 4.05 g. of KSCN was stirred for 24 hr. at room temperature. The reaction mixture was diluted with H_2O and the precipitated oil was extracted with Et_2O. The ethereal solution was washed with H_2O, and dried over Na_2SO_4. After evaporation of Et_2O, the residue was distilled under reduced pressure to recover the starting material. The resulting residue (7.9 g.) was dissolved

in 70 cc. of conc. H_2SO_4 at $-10\sim-5°$. After being stirred for 3 hr. at 0°, the solution was allowed to stand overnight at room temperature and then poured on crushed ice. The acidic solution was neutralized with Na_2CO_3 and extracted with Et_2O. The ethereal extract was dried over Na_2SO_4. The residue, obtained from the extract by evaporation of Et_2O, was dissolved in benzene. After treating with Norite, the benzene solution was concentrated *in vacuo* to give white needles, m.p. 162 ~163°. Yield, 340 mg. *Anal.* Calcd. for $C_{10}H_9ONS$: N, 7.32. Found : N, 7.29. UV λ_{max}^{EtOH} mμ (log ε) : 222.0 (4.23), 273.6 (3.57).

Reaction of 2-Propynol and Benzonitrile in conc. H_2SO_4——Benzonitrile (17.1 g.) was added dropwise to 70 cc. of conc. H_2SO_4 at $0\sim3°$. To the solution was slowly added 9.3 g. of 2-propynol. The reaction mixture was kept at this temperature for 22 hr. with stirring and then poured on crushed ice. The solution was made alkaline with K_2CO_3, extracted with $CHCl_3$, and the extract was washed with a saturated aqueous solution of NaCl and dried over Na_2SO_4. After removal of $CHCl_3$, the oily residue (16 g.) was distilled to obtain a yellow oil, $b.p_6$ 100~110° (bath temperature). Yield. 8.8 g. It gave a crystalline picrate of m.p. 97~99° from EtOH. *Anal.* Calcd. for $C_{16}H_{12}O_8N_4$: C, 48.60; H, 3.01; N, 14.16. Found : C, 48.40; H, 3.13; N, 14.16. IR ν_{max}^{liquid} cm^{-1} : 1700, 1676 (>C=O), 1600, 1555, 1490, 782, 718, 695.

2-Phenyl-4-methyloxazole (XIII)——Dry HCl-gas was bubbled into an ice-cooled mixture of 5.43 g. of 2-propynol and 10 g. of benzonitrile for 3 hr. After the mixture was allowed to stand overnight at room temperature, the precipitate crystals were filtered and washed with abs. Et_2O. Yield, 15.5 g., m.p. 93~94°. Free base, $b.p_5$ 95° (bath temp.). *Anal.* Calcd. for C, 75.47; H, 5.66; N, 8.80. Found : C, 75.67; H, 5.45; N 9.02. This hydrochloride (15 g.) was slowly added to 150 cc. of conc. H_2SO_4 at $0\sim5°$. After the reaction mixture was allowed to stand for 5 days at room temperature, it was poured into ice-H_2O. The acidic solution was made alkaline with Na_2CO_3 and extracted with Et_2O. The ethereal extract was washed with H_2O, and dried over Na_2SO_4. The oily residue, obtained from the extract by evaporation of Et_2O was distilled to give a yellow oil, $b.p_5$ 95°. Yield, 4 g. *Anal.* Calcd. for $C_{10}H_9ON$: C, 75.47; H, 5.66; N, 8.80. Found : C, 75.57; H, 5.64; N, 9.02. UV : λ_{max}^{EtOH} 270.2 mμ (log ε 3.26).

The author is indebted to Prof. K. Yasuda of Tokyo University and to Mr. M. Matsui, Director of this Laboratory for encouragement during this work. Gratufull thanks are also due to Dr. I. Iwai of this Laboratory for his kind guidance and valuable suggestions throughout this work. The author also wishes to express his gratitude to Mr. T. Onoe for microanalysis and to Mr. O. Amakasu and Mr. N. Higosaki for the measurement of infrared spectra.

Summary

Treatment of α-thiocyanatoacetylenic compounds with concentrated sulfuric acid gave 2-thiazolol derivatives. 2-Phenyloxazole was also obtained in good yield by cyclization of 2-propynyl benziminoether by a similar procedure.

(Received September 26, 1961)