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Studies on Mesoionic Compounds. V.[1] Synthesis and Cycloaddition Reaction of anhydro-5-Hydroxy-1,3-oxathiolium Hydroxide System

Katsutada Masuda, Jun Adachi and Keiichi Nomura

Faculty of Pharmaceutical Sciences, University of Toyama[2]

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Synthesis and 1,3-dipolar cycloaddition of the mesoionic ring system, anhydro-5-hydroxy-1,3-oxathiolium hydroxide, were studied. Acylthioglycolic acids (IIa, b) afforded the mesoionic products (IIIa, b) in the reaction with trifluoroacetic anhydride. In the case of α-substituted thioglycolic acids (IId, e), the mesoionic intermediates which couldn't be isolated were trapped with dimethyl acetylenedicarboxylate *in situ*.

Keywords——mesoionic compound; oxathiole ring; dehydrative cyclization; dipolar cycloaddition; acetylenedicarboxylate cycloaddition

Up to date two kinds of the five-membered mesoionic ring systems composed of carbon, sulfur and oxygen atoms have been synthesized; *i.e.*, anhydro-5-hydroxy-1,3-dithiolium hydroxide (I) and anhydro-5-hydroxy-1,3-oxathiolium hydroxide (III) systems.[3] Although there were many reports about the former,[4] the latter was mentioned in only one paper by Potts, *et al.*[5] We report the synthesis and the first example of 1,3-dipolar cycloaddition reaction of some derivatives of III.

Dehydrative cyclization of acylthioglycolic acids prepared from thiocarboxylic acids and α-bromoacetic acids were attempted. Although treatment of benzoylthioglycolic acid (IIa) with acetic anhydride under various conditions resulted in recovery of IIa, the reaction of IIa with trifluoroacetic anhydride gave orange colored mesoionic product (IIIa). Infrared (IR) spectrum of IIIa showed absorption band at 1770 and 1650 cm^{-1} assigned to stretching band of $COCF_3$ and ring CO, respectively. Its nuclear magnetic resonance (NMR) spectrum showed only a multiplet signal of the phenyl protons. The compound (IIIa) was extremely sensitive to moisture, and it gradually changed into the colorless compound (IVa) on storage. Formation of IVa would be due to hydration and subsequent decarboxylation of IIIa. Furthermore, rapid decomposition of IIIa was observed in the mass spectrometer indicative of thermal instability. Thus, on the mass spectrum of IIIa the parent ion peak at *m/e* 274 was very weak (0.1%), and ion at *m/e* 248 (13%) corresponding to IVa was observed. In the cyclization reaction of IIa the mixed acid anhydride (IIa') could be also isolated. On reffering to proposal of cyclization mechanism of sydnone,[6] it was considered that at the first stage of the above reaction C-4 unsubstituted mesoionic compound (IIIa, R'=H) would probably form, and which subsequently underwent electrophilic attack by trifluoroacetyl cation to afford IIIa.

1) Part IV: K. Masuda and T. Okutani, *Tetrahedron*, **30**, 409 (1974).
2) Location: *Gofuku, Toyama, 930, Japan.*
3) Recently, Gotthardt, *et al.* synthesized furan derivatives from thiocarbonyloxyacetic acid by trapping of anhydro-4-hydroxy-1,3-oxathiolium hydroxide (isomer of III) with alkynes; H. Gotthardt, M.C. Weisshuhn, and K. Dörhöfer, *Angew. Chem. Int. Ed. Engl.*, **14**, 422 (1975).
4) *a*) M. Ohta and M. Sugiyama, *Bull. Chem. Soc. Japan*, **36**, 1437 (1963); *idem, ibid.*, **38**, 596 (1965); H. Kato, M. Kawamura, T. Shiba and M. Ohta, *Chem. Commun.*, **1970**, 959; *b*) H. Gotthardt and B. Christl, *Tetrahedron Letters*, **1968**, 4743, 4747, 4751; H, Gotthardt, M.C. Weisshuhn, and B. Christl, *Chem. Ber.*, **109**, 740 (1976); *c*) K.T. Potts and U.P. Singh, *Chem. Commun.*, **1969**, 569.
5) K.T. Potts, J. Kane, E. Carnahan, and U.P. Singh, *Chem. Commun.*, **1975**, 417.
6) M. Ohta and H. Kato, "Nonbenzenoid Aromatics," ed. J.P. Snyder, Academic Press, New York, 1969, p. 117.

It is well known that many mesoionic compounds were characterized by reactivity with dipolarophiles. However, ability of mesoionic ring system to undergo cycloaddition will be supressed by introduction of acyl group into its ring.[7] As would be expected, the reaction of IIIa with dimethyl acetylenedicarboxylate was unsuccessful. The *p*-anisoyl derivative (IIb) could also yield the mesoionic brick-red product (IIIb), but in the case of the morpholinocarbonyl derivative (IIc) only the compound (IVc) was obtained.

On the other hand, in order to obtain the mesoionic compound which haven't trifluoroacetyl function α-substituted thioglycolic acids (IId, e) were submitted to similar cyclization reaction. The reaction of IId with trifluoroacetic anhydride gave colorless unidentified polymer by the same working up as in the cases of IIa, b. However, in this reaction it was observed as well as IIa, b that the color of the reaction mixture changed progressively from colorless to deep red. It was considered that this observation would suggest the formation of mesoionic compound (IIId) in the reaction medium. In order to trap IIId, e, the above reactions of IId and IIe in the presence of dimethyl acetylenedicarboxylate were attempted. These reactions resulted in formation of the corresponding thiphene derivatives (VIa and VIb). It was assumed that the cycloaddition reaction of III was performed and the resulting 1,3-cycloadduct (V) underwent decarboxylation to form VI. The similar reactions of IId and IIe using phenyl isocyanate or phenyl isothiocyanate as dipolarophile resulted in formation of complex material. Possibility of these reactions would depend on polarity of dipolarophiles.

On the basis of the above result, it seems that some other derivatives of III, particularly of IIId, e, will be too unstable to isolate and/or to achieve reaction except cycloaddition.

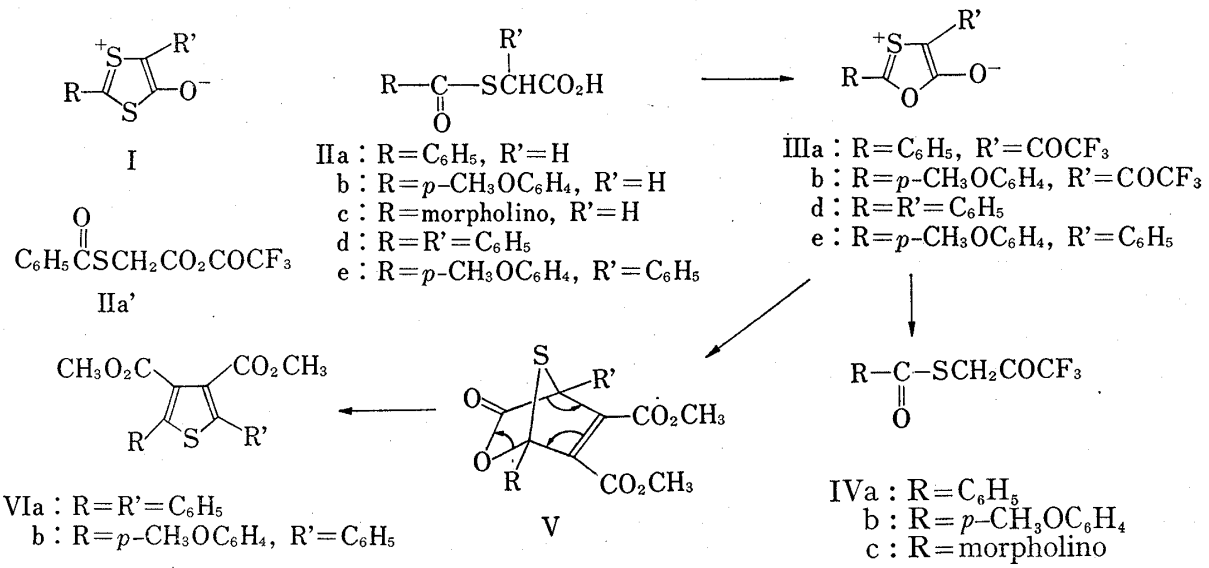

Chart 1

Experimental[8]

Benzoylthioglycolic Acid (IIa)——To a stirred solution of KOH (6.7 g) in MeOH (50 ml) and minimum amount of water was added a solution of thiobenzoic acid[9] (7 g) in MeOH (20 ml) and then a solution of bromoacetic acid (7 g) in MeOH (30 ml). The mixture was stirred at room temperature for 3 hr. After

7) K.T. Potts and D.N. Roy, *Chem. Commun.*, **1968**, 1061.
8) All melting points were determined with a Yanagimoto micro melting point apparatus, and are uncorrected. NMR spectra were taken with a JEOL PMX-60 and a Varian EM-360 spectrometers using TMS as internal standard. Mass spectra were taken on a JEOL JMS-01SG-2 instrument at 75 eV ionization potential.
9) P. Noble, Jr. and D.S. Tarbell, "Org. Syn.," Coll. Vol. 4, 1963, p. 924.

concentration *in vacuo*, the residue was dissolved in water, acidified with conc. HCl, and extracted with $CHCl_3$. The extract was worked up as usual to give 6.5 g (65%) of colorless plates of IIa, mp 107—108° (*n*-hexane–ether). IR ν_{max}^{KBr} cm^{-1}: 3000—2500, 1700 (CO_2H), 1655 (CO). NMR ($CDCl_3$) δ: 3.9 (2H, s, $-CH_2-$), 7.35—7.65 (3H, m, arom.), 7.8—8.05 (2H, m, arom.), 10.6 (1H, s, $-CO_2H$). *Anal.* Calcd. for $C_9H_8O_3S$: C, 55.09; H, 4.11. Found: C, 55.17; H, 3.83.

Benzoyl-α-phenylthioglycolic Acid (IId)——As similar as above, IId was obtained in 63% yield from α-bromophenylacetic acid. Colorless needles, mp 94—95° (lit.[5] mp 97—98°).

***p*-Anisoylthioglycolic Acid (IIb)**——A cooled solution of KOEt in EtOH (prepared from K, 1 g and abs. EtOH, 15 ml) was saturated with hydrogen sulfide. To this was added a solution of *p*-anisoyl chloride (3.4 g) in ether (10 ml), and the mixture was stirred at room temperature for 2 hr. After concentration *in vacuo*, to the residue was added MeOH (40 ml) and filtered. The filtrate was added to a mixture of bromoacetic acid (2.8 g) and KOH (1.1 g) in MeOH (30 ml) at room temperature and stirred for 3 hr. The mixture was concentrated *in vacuo*, and the residue was worked up as similar as the procedure for IIa to give 3.3 g (73%) of IIb, colorless needles, mp 134—136° (benzene) (lit.[5] mp 132—133°). *Anal.* Calcd. for $C_{10}H_{10}O_4S$: C, 53.08; H, 4.46. Found: C, 53.16; H, 4.39.

***p*-Anisoyl-α-phenylthioglycolic Acid (IIe)**——Similarly as above, IIe was prepared in 68% yield from α-bromophenylacetic acid. Colorless needles, mp 103—105° (*n*-hexane–ether). IR ν_{max}^{KBr} cm^{-1}: 3000—2500, 1700 (CO_2H), 1640 (CO). NMR ($CDCl_3$) δ: 3.8 (3H, s, $-OCH_3$), 5.4 (1H, s, >CH–), 6.7—7.0 (2H, d, J= 8 Hz, arom.), 7.1—7.5 (5H, m, arom.), 7.7—8.0 (2H, d, J=8 Hz, arom.). *Anal.* Calcd. for $C_{16}N_{14}O_4S$: C, 63.56; H, 4.67. Found: C, 63.51; H, 4.59.

Morpholinocarbonylthioglycolic Acid (IIc)——To a solution of morpholine (1.7 g) and KOH (1.4 g) in abs. EtOH (20 ml) was bubbled gaseous COS[10] (prepared from KSCN, 10 g, conc. H_2SO_4, 100 g and water, 50 ml). Colorless precipitates were collected and washed with ether. The resulting salt was treated as similar as above with bromoacetic acid to give colorless crystals of IIc, mp 157—158°. Yield, 25%. IR ν_{max}^{KBr} cm^{-1}: 3000—2500, 1700 (CO_2H), 1640 (CO). NMR ($CDCl_3$) δ: 3.5—3.9 (8H, m), 3.8 (2H, s, $-SCH_2-$), 8.2 (1H, broad peak, $-CO_2H$). Mass Spectrum *m/e*: M^+, 205. *Anal.* Calcd. for $C_7H_{11}O_4NS$: C, 40.96; H, 5.40; N, 6.83. Found: C, 40.98; H, 5.15; N, 6.57.

The Reaction of IIa with Trifluoroacetic Anhydride——A mixture of IIa (2 g) and trifluoroacetic anhydride (10 ml) was stirred in an ice bath for 3.5 hr. The orange precipitates were collected and washed with dry ether to give 1.15 g (41%) of IIIa, mp 61—62° (dec.). IR ν_{max}^{KBr} cm^{-1}: 1770 ($COCF_3$), 1650 (CO). NMR ($CDCl_3$) δ: 7.4—8.1 (m, arom.). Mass Spectrum *m/e*: M^+, 274.

On the above reaction, when the mixture was diluted with *n*-hexane after 1 hr, the mixed anhydride (IIa′) was obtained in 50% yield. Colorless needles, mp 106—107° (*n*-hexane–benzene). IR ν_{max}^{KBr} cm^{-1}: 1820, 1810 (CO_2CO), 1650 (CO). NMR ($CDCl_3$) δ: 4.0 (2H, s, $-CH_2-$), 7.3—7.65 (3H, m, arom.), 7.8—8.1 (2H, m, arom.). *Anal.* Calcd. for $C_{11}H_7O_4F_3S$: C, 45.21; H, 2.41. Found: C, 45.07; H, 2.69.

The anhydro-compound (IIIa) was progressively discolored on storage. Sublimation of it at 60—70° (0.6 mmHg) gave pure IVa, as colorless prisms, mp 68—70°. IR ν_{max}^{KBr} cm^{-1}: 1770 ($COCF_3$), 1640 (CO). NMR ($CDCl_3$) δ: 4.2 (2H, s, $-CH_2-$), 7.3—7.65 (3H, m, arom.), 7.8—8.1 (2H, m, arom.). Mass Spectrum *m/e*: M^+, 248. *Anal.* Calcd. for $C_{10}H_7O_2F_3S$: C, 48.38; H, 2.84. Found: C, 48.14; H, 3.08.

The Reaction of IIb with Trifluoroacetic Anhydride——To a solution of IIb (226 mg) in dry benzene (2 ml) was added trifluoroacetic anhydride (2 ml) at room temperature. The mixture was stirred for 1 hr, and diluted with ether. The brick-red precipitates of IIIb were collected, mp 67—70° (dec.). Yield, 210 mg (69%). IR ν_{max}^{KBr} cm^{-1}: 1800 ($COCF_3$), 1650 (CO). NMR ($CDCl_3$) δ: 3.9 (3H, s, $-OCH_3$), 6.7—7.0 (2H, d, J=9 Hz, arom.), 7.7—8.0 (2H, d, J=9 Hz, arom.).

The above product was gradually changed to pale yellow compound. Sublimation of it at 100—110° (0.6 mmHg) gave pure IVb, colorless prisms, mp 79—82°. IR ν_{max}^{KBr} cm^{-1}: 1770 ($COCF_3$), 1640 (CO). NMR ($CDCl_3$) δ: 3.85 (3H, s, $-OCH_3$), 4.15 (2H, s, $-CH_2-$), 6.75—7.05 (2H, d, J=9 Hz, arom.), 7.75—8.05 (2H, d, J=9 Hz, arom.). *Anal.* Calcd. for $C_{11}H_9O_3F_3S$: C, 47.48; H, 3.26. Found: C, 47.53; H, 3.54.

The Reaction of IIc with Trifluoroacetic Anhydride——A cooled mixture of IIc (205 mg) and trifluoroacetic anhydride (1 ml) was stirred for 4 hr. Dilution of the mixture with ether gave colorless precipitates of IVc. Yield, 180 mg (70%). mp 83—86°. Distillation gave the analytical sample, bp 60—70° (0.1 mmHg, bath temp.). IR ν_{max}^{KBr} cm^{-1}: 1780 ($COCF_3$), 1630 (CO). NMR ($CDCl_3$) δ: 3.4—3.9 (8H, m), 4.1 (2H, s, $-SCH_2-$). *Anal.* Calcd. for $C_8H_{10}O_3NF_3S$: C, 37.35; H, 3.92; N, 5.45. Found: C, 37.19; H, 4.00; N, 5.53.

Dimethyl 2,5-Diphenylthiophene-3,4-dicarboxylate (VIa)——A solution of IId (544 mg) and trifluoroacetic anhydride (420 mg) in benzene (7 ml) was stirred at room temperature for 30 min. To the resulting deep red solution was added a solution of dimethyl acetylenedicarboxylate (284 mg) in benzene (3 ml). The mixture was stirred for 3 hr, washed with water, and dried over Na_2SO_4. Evaporation of the benzene solution gave an oily residue, which crystallized on standing. The crystals were washed with a minimum amount of ether–benzene to afford 410 mg (58%) of colorless fine needles of VIa, mp 165—167° (lit.[4b] mp

10) A. Stock, W. Siecke, and E. Pohland, *Ber.*, **57**, 719 (1924).

166—167.5°). IR ν_{max}^{KBr} cm^{-1}: 1720 (CO). NMR ($CDCl_3$) δ: 3.75 (6H, s, $-OCH_3$), 7.5 (10H, s, arom.). Mass Spectrum *m/e*: M^+, 352. *Anal.* Calcd. for $C_{20}H_{16}O_4S$: C, 68.16; H, 4.58. Found: C, 67.95; H, 4.39.

Dimethyl 2-(*p*-Anisyl)-5-phenylthiophene-3,4-dicarboxylate (VIb)——To a mixture of IIe (302 mg) and dimethyl acetylenedicarboxylate (142 mg) in benzene (2 ml) was added a solution of trifluoroacetic anhydride (210 mg) in benzene (1 ml) at room temperature. The mixture was stirred for 5 hr, and then worked up as above to give 350 mg (90%) of VIb, pale yellow oil, which crystallized on standing. mp 101—108° (lit.[4b] mp 110.5—111.5°). Distillation gave the analytical sample, bp 160—165° (1×10^{-4} mmHg, bath temp.), colorless oil. Mass Spectrum *m/e*: M^+, 382. *Anal.* Calcd. for $C_{21}H_{18}O_5S$: C, 65.95; H, 4.74. Found: C, 65.98; H, 4.83.

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Fluorescence Densitometric Method for the Simultaneous Determination of Siomycins using Silicagel-Sintered Plate

KAZUMASA HIRAUCHI and SACHIKO MASUDA

Shionogi Research Laboratory, Shionogi & Co., Ltd.[1]

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A simple and rapid fluorodensitometric method for simultaneous determinations of siomycin A, siomycin B, and siomycin D_1 in siomycins was established.

The method is based on the fluorescence reaction of siomycins with sulfuric acid after separation on thin-layer chromatographic plate, and can be applied satisfactorily to simultaneous determinations in the concentration range of 5—1000 ng per spot.

Keywords——siomycins; fluorodensitometry; simultaneous determination; silicagel-sintered plate; thin-layer chromatography

Individual fluorodensitometric methods for determinations of siomycin A (A), siomycin B (B), and siomycin D_1 (D_1) have been reported previously.[2] However, the methods for A and D_1 require a troublesome, time-consuming procedure such as two-dimensional development for separation. By examining the quantitative conditions in more detail, we established a simple and rapid method for simultaneous determinations of A, B, and D_1 with one-dimensional development using a Yamato Replate-100 (Yamato Scientific Co., Ltd., Nihonbashi Hon-cho, Chuo-ku, Tokyo). This improved method is more sensitive and simple than previous methods.[2]

Experimental

Apparatus——A Hitachi MPF-2A spectrofluorometer equipped with a Hitachi thin-layer chromatogram (TLC) scanning attachment was used to measure the fluorescence of the spot on the plate. The fluorescence intensity was recorded on a Hitachi J 301 recorder and simultaneously integrated with a Hitachi J 201 integrator. We also used a Hamilton dosing syringe (10 μl), a rectangular developing chamber ($9 \times 22 \times 22$ cm), a Lapine hot plate (775 watts, 115 volts), a Toshiba Type F1-3L ultraviolet lamp, and pretreated Yamato Replate-100.

Pretreatment of Yamato Replate-100——Commercially available plate (0.2 mm, 10×20 cm) was developed with a mixture of chloroform and methanol (95: 5, v/v) for 50 min in the developing chamber saturated

1) Locations: *Sagisu, Fukushima-ku, Osaka, 553, Japan.*
2) K. Hirauchi and S. Masuda, *Bunseki Kagaku*, **25**, 689 (1976).