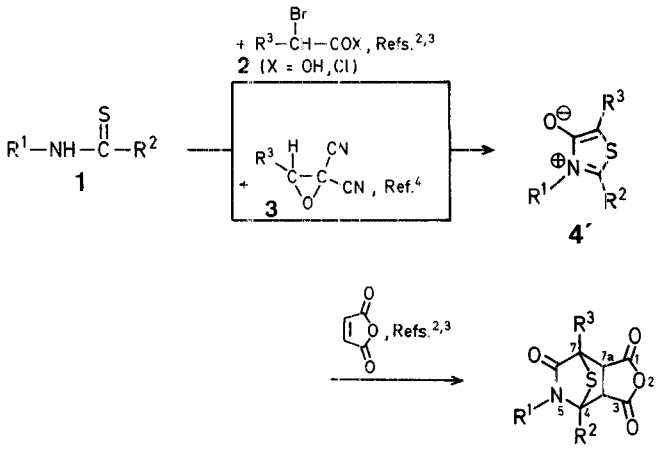
A Simple Preparation of (3aα,4α,7α,7aα)-Tetrahydro-4,7-epithiofuro[3,4-*c*]pyridine-1,3,6 (3a*H*)-triones

Toshio TAKIDO, Kunio ITABASHI

Department of Industrial Chemistry, College of Science and Technology, Nihon University, 1–8, Kanda Surugadai, Chiyoda-ku, Tokyo, 101, Japan

(3aα,4α,7α,7aα) - Tetrahydro - 4,7 - epithiofuro[3,4 - *c*]pyridine-1,3,6-(3a*H*)-triones **5** and **5'** are structurally interesting heterocyclic compounds. They are generally prepared by the cycloaddition of mesoionic 1,3-thiazolium-4-olates **4'** with maleic anhydride[1]. The mesoionic compounds **4'** are obtained by the reaction of α-bromoacetic acid (**2a**), α-bromoacetyl chloride (**2b**) or *gem*-dicyanoepoxide **3** with *N*-monosubstituted thioamides **1**[2–4] (Scheme **A**).

Now we report a one-step synthesis of the title compounds **5** using thioamides **1** with maleic anhydride in refluxing dioxan (Scheme **B**). The structure of **5** was confirmed on the basis of comparison with the spectral data of similar compounds[1] and microanalyses (Table). In the I.R. spectrum of **5**, the absorption at $\nu = \sim 1860$, 1770 cm^{-1} could be assigned to the two carbonyl groups of the five membered anhydride ring[5]. In addition, signals of the ^{13}C- and ^{1}H-N.M.R. spectra showed that compounds **5** possess an (3aα,4α,7α,7aα)tetrahydro-4,7-epithiofuro[3,4-*c*]pyridine-1,3,6(3a*H*)-trione ring system. The stereochemistry of **5** is assigned as the *endo*-configuration by analysis of the ^{1}H-N.M.R. spectrum of **5c** ($R^1 = CH_3$, $R^2 = H$). A doublet with a *cis*-coupling ($J = 6.8$ Hz) at $\delta = 3.96$ ppm is assigned to the proton at the 7a position irrespective of *endo*- or the *exo*-structure, and a doublet at $\delta = 5.55$ ppm with a small *trans*-coupling ($J = 1.9$ Hz) is assigned to the bridgehead proton at the 4 position. The proton at the 3a position appears as a doublet of doublets at $\delta = 4.29$ ppm. These data are consistent with the *endo*-structure.

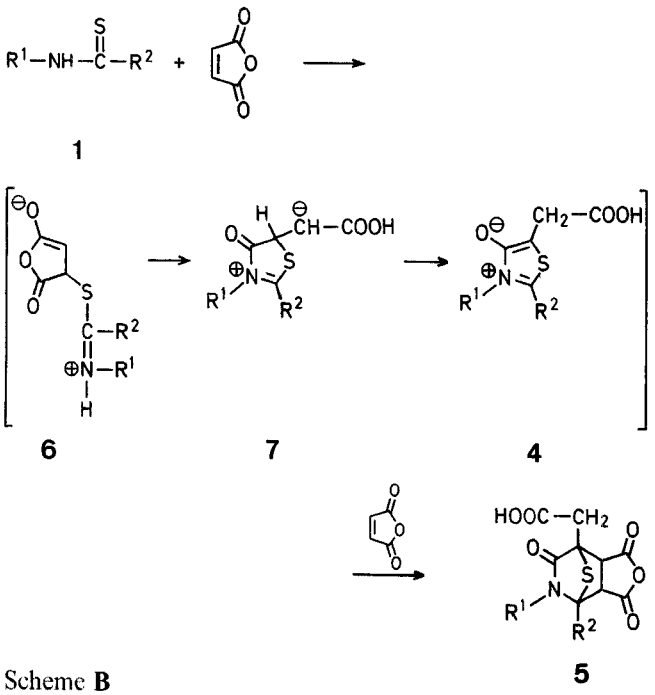


Scheme **A**

Although we have not undertaken a detailed investigation of the reaction mechanism, a possible pathway accounting for the formation of **5** is shown in Scheme **B**. In this mechanism, the mesoionic 1,3-thiazolium-4-olate **4** is generated from the reaction of thioamide **1** with maleic anhydride via intermediates **6**, **7** and undergoes cycloaddition reaction with an excess of maleic anhydride to afford **5**.

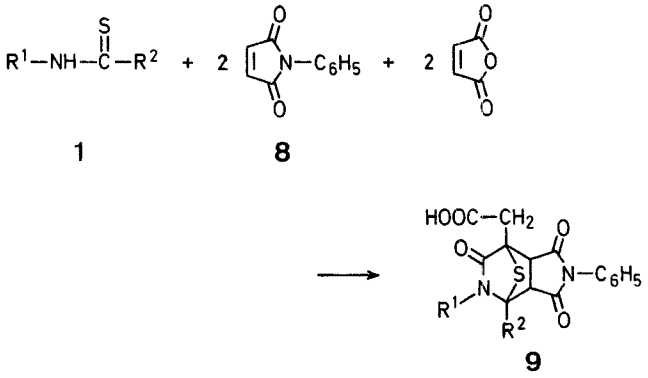
However, the reaction of thiobenzamide (**1**; $R^1 = H$, $R^2 = C_6H_5$) with maleic anhydride afforded 2-phenyl-4-hydroxy-5-thiazolacetic acid which was formed as the result of intramolecular proton rearrangement from the nitrogen atom of its mesoionic 1,3-thiazolium-4-olate (**4**; $R^1 = H$, $R^2 = C_6H_5$) to the carbonyl carbon atom. A

similar product, 2,5-diphenyl-4-hydroxythiazole, was obtained by the reaction of thiobenzamide with α-bromophenylacetyl chloride (**2**).



Scheme **B**

We also studied the reaction of thioamides with *N*-phenylmaleimide as an olefinic dipolarophile. Although *N*-phenylmaleimide (**8**) failed to react with thioamide **1**, two equivalents of *N*-phenylmaleimide (**8**) and maleic anhydride reacted with **1** to give (3aα,4α,7α,7aα)-tetrahydro-4,7-epithiopyrrolo[3,4-*c*]pyridine-1,3,6-(3a*H*)triones **9** (Scheme C). These results show that maleic anhydride reacts faster than *N*-phenylmaleimide (**8**) with thioamide **1** to form mesoionic intermediate **4**; however, *N*-phenylmaleimide (**8**) reacts faster than maleic anhydride with **4** to form **9**.



Scheme **C**

Table. Compounds **5a–e** and **9a, b** prepared

Product No.	R^1	R^2	Yield [%]	m.p. [°C, dec.]	Molecular formula[a]	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6) δ [ppm]	^{13}C-N.M.R. (DMSO-d_6) δ [ppm]
5a	CH_3	CH_3	97	204–205°	See experimental			
5b	C_6H_5	C_6H_5	45[b]	213–215°	$C_{21}H_{15}NO_6S$ (409.4)	1840, 1770	3.31 (s, 2H); 4.62 (d, J = 6.8 Hz, 1H); 5.14 (d, J = 6.8 Hz, 1H); 6.75–7.55 (m, 10H); 12.69 (br, 1H)	31.4 (t); 51.8 (d); 56.8 (d); 61.4 (s); 84.3 (s); 128.0 (d); 128.2 (d); 128.6 (d); 129.2 (s); 130.2 (d); 134.8 (s); 166.8 (s); 168.6 (s); 170.2 (s); 171.6 (s)
5c	CH_3	H	34	221–222°	$C_{10}H_9NO_6S$ (271.3)	1850, 1770	2.81 (s, 3H); 3.05 (d, J = 17.1 Hz, 1H); 3.14 (d, J = 17.1 Hz, 1H); 3.96 (d, J = 6.8 Hz, 1H); 4.29 (dd, J = 6.8 Hz, 1.9 Hz, 1H); 5.55 (d, J = 1.9 Hz, 1H); 12.57 (br, 1H)	29.4 (q); 31.3 (t); 50.0 (d); 54.0 (d); 61.9 (s); 67.1 (d); 168.6 (s); 169.0 (s); 170.1 (s); 172.3 (s)
5d	C_6H_5	H	80[b]	223–224°	$C_{15}H_{11}NO_6S$ (333.3)	1850, 1770	3.21 (s, 2H); 4.25 (d, J = 6.8 Hz, 1H); 4.36 (dd, J = 6.8 Hz, 1.9 Hz, 1H); 6.32 (d, J = 1.9 Hz, 1H); 7.20–7.48 (m, 5H); 12.65 (br, 1H)	31.4 (t); 49.8 (d); 54.7 (d); 62.9 (s); 67.0 (s); 120.2 (d); 125.4 (d); 129.1 (d); 136.6 (s); 168.1 (s); 170.1 (s); 170.4 (s)
5e	H	CH_3	82[c]	199–200°	$C_{10}H_9NO_6S$ (271.3)	1860, 1770	1.82 (s, 3H); 3.00 (d, J = 17.1 Hz, 1H); 3.09 (d, J = 17.1 Hz, 1H); 3.87 (d, J = 6.8 Hz, 1H); 4.15 (d, J = 6.8 Hz, 1H); 9.23 (s, 1H); 12.51 (br, 1H)	17.5 (q); 32.0 (t); 50.7 (d); 60.7 (d); 61.4 (s); 72.9 (s); 170.5 (s); 171.1 (s); 176.7 (s)
9a	CH_3	CH_3	63	217–219°	See experimental			
9b	C_6H_5	C_6H_5	44[b]	258–260°	$C_{27}H_{20}N_2O_5S$ (484.5)	1775, 1705	3.35 (s, 2H); 4.19 (d, J = 6.3 Hz, 1H); 4.87 (d; J = 6.3 Hz, 1H); 6.76–7.55 (m, 15H); 12.67 (br, 1H)	31.7 (t); 49.8 (d); 55.0 (d); 61.5 (s); 84.3 (s); 126.6 (d); 127.5 (d); 127.7 (d); 128.5 (d); 128.8 (d); 129.4 (d); 130.0 (s); 130.2 (s); 131.7 (s); 135.0 (s); 170.4 (s); 171.6 (s); 172.4 (s); 172.7 (s)

[a] All compounds gave satisfactory elemental analyses (C ± 0.2%, H ± 0.1%, N ± 0.2%, S ± 0.3%).

[b] Reaction time: 5h.

[c] Four-fold excess of maleic anhydride was used.

(3aα,4α,7α,7aα)-Tetrahydro-7-(carboxymethyl)-4,5-dimethyl-4,7-epithiofuro[3,4-*c*]pyridine-1,3,6-(3a*H*)-trione (5a); Typical Procedure:

N-Methylthioacetamide (**1a**; 0.89 g, 10 mmol) and maleic anhydride (1.9 g, 20 mmol) are refluxed in dioxan (50 ml) for 3 h. Removal of solvent under reduced pressure and recrystallization of the resultant yellow residue from acetone affords **5a**; yield: 2.76 g (97%); m.p. 204–205°C (dec.).

$C_{11}H_{11}NO_6S$	calc.	C 46.31	H 3.86	N 4.91	S 11.23
(285.3)	found	46.49	3.86	4.82	11.44

I.R. (KBr): ν = 1860, 1771 cm^{-1} (C=O).

^{1}H-N.M.R. (DMSO-d_6): δ = 1.89 (s, 3H, CH_3); 2.76 (s, 3H, N—CH_3); 3.05 (d, J = 17.1 Hz, 1H, H—CH—COOH); 3.15 (d, J = 17.1 Hz, 1H, H—CH—COOH); 3.96 (d, J = 6.8 Hz, 1H, CH—CH); 4.03 (d, J = 6.8 Hz, 1H, CH—CH); 12.54 ppm (br, 1H, COOH).

^{13}C-N.M.R. (DMSO-d_6): δ = 15.4 g (q); 26.1 (q); 31.3 (t); 52.4 (d); 56.9 (d); 61.5 (s); 76.1 (s); 168.2 (s); 168.9 (s); 170.1 (s); 172.6 ppm (s).

M.S. (70eV).: m/e = 285 (M^+).

(3aα,4α,7α7aα)-Tetrahydro-7-carboxymethyl)-4,5-dimethyl-*N*-phenyl-4,7-epithiopyrrolo[3,4-*c*]pyridine-1,3,6-(3a*H*)-trione (9a); Typical Procedure:

N-Methylthioacetamide (**1a**; 0.45 g, 5 mmol), *N*-phenylmaleimide (**8**; 1.74 g, 10 mmol) and maleic anhydride (0.98 g, 10 mmol) are refluxed in dioxan (50 ml) for 3 h. After evaporation of solvent under reduced pressure the residue is chromatographed on silica gel with acetone/benzene (3:7) as eluent. The unreacted *N*-methylthioacetamide (**1a**) is eluted first from the column. The product **9a** is obtained in the second fraction; yield: 1.14 g (63%); m.p. 217–219°C (dec.).

$C_{17}H_{16}N_2O_5S$	calc.	C 56.67	H 4.44	N 7.77	S 8.88
(360.4)	found	56.40	4.48	7.65	8.65

I.R. (KBr): ν = 1773, 1705 cm^{-1} (C=O).

^{1}H-N.M.R. (DMSO-d_6): δ = 2.00 (s, 3H, CH_3); 2.86 (s, 3H, CH_3); 3.31 (s, 2H, CH_2); 3.46 (d, J = 6.8 Hz, 1H, CH—CH); 3.70 (d, J = 6.8 Hz, 1H, CH—CH); 7.14–7.58 (m, 15H, ring protons); 12.38 ppm (br, 1H, COOH).

^{13}C-N.M.R. (DMSO-d_6): δ = 15.3 (q); 26.0 (q); 31.6 (t); 50.4 (d); 55.1 (d); 61.7 (s); 76.3 (s); 126.7 (d); 128.5 (s); 128.8 (s); 131.9 (s); 170.3 (s); 172.8 (s); 173.2 (s); 173.5 ppm (s).

M.S. (20eV).: m/e = 360 (M^+).

Received: July 24, 1984

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