

SYNTHESIS AND REACTIONS OF

3-METHYLTHIOISOTHIAZOLO[3,4-d]PYRIMIDINE-4,6(5H,7H)-DIONES¹⁾

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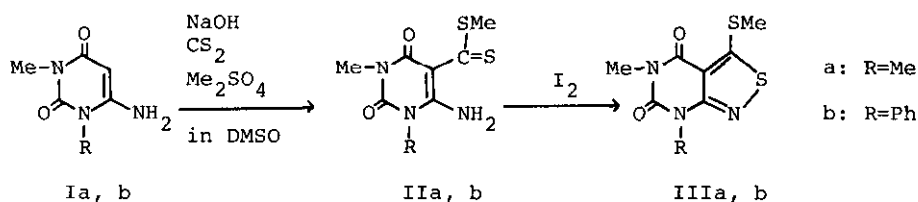
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Abstract: 3-Methylthioisothiazolo[3,4-d]pyrimidine-4,6-(5H,7H)-diones (IIIa, b) were synthesized by treatment of methyl 6-aminouracil-5-dithiocarboxylates, which were prepared by the reaction of 6-aminouracil with carbon disulfide and dimethyl sulfate in the presence of alkali, with iodine in dimethyl sulfoxide in good yields. The reaction of IIIa, b with amines, amides, and active methylene compounds gave the corresponding substituted products of methylthio group in III in good yields.

Recently Niss² and Furukawa³ have reported that the reaction of 6-aminouracils with alkyl or aryl isothiocyanates affords 5-substituted thiocarbamoyl-6-aminouracils and its subsequent oxidation with bromine or hydrogen peroxide yields 3-substituted aminoisothiazolo[3,4-d]pyrimidine-4,6(5H,7H)-diones. In our present paper, we now wish to report a new synthesis of 3-methylthioisothiazolo[3,4-d]pyrimidines and their nucleophilic displacement to give the derivatives of isothiazolo[3,4-d]pyrimidines.

Reaction of 6-amino-1,3-dimethyluracil (Ia) with carbon disulfide in the presence of sodium hydroxide in dimethyl sulfoxide, followed by methylation with dimethyl sulfate, afforded methyl 6-amino-1,3-dimethyluracil-5-dithiocarboxylate (IIa) as yellow needles, mp 262°, in 57% yield. The nuclear magnetic resonance spectrum of IIa (absence of a proton at the 5-position) demonstrated that the carbon disulfide added to the 5-position of Ia. Similarly, methyl 6-amino-3-methyl-1-phenyluracil-5-dithiocarboxylate (IIb) (yellow needles, mp 249°) was prepared by the reaction of Ib with carbon disulfide in 47% yield. Oxidation of IIa with iodine

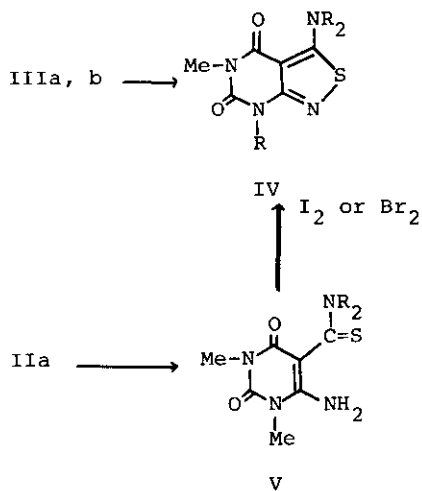
in dimethyl sulfoxide gave 5,7-dimethyl-3-methylthioisothiazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (IIIa) as colorless needles, mp 155°, in 60% yield. In a similar manner, IIIb was synthesized from compound IIb in 59% yield.








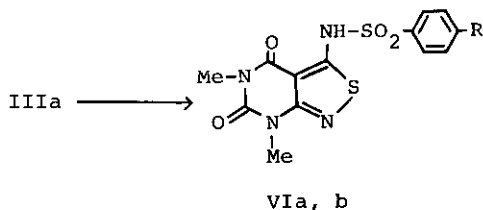
It has been well known that the methylthio group on the heterocyclic ring reacts with nucleophilic reagents to give the corresponding substituted products,⁴ but there has been no report on the substitution reaction of methylthio group on the fused isothiazole ring. We next investigated on the nucleophilic displacement of compounds IIIa, b with amines, amides, and active methylene compounds. Substitution of the methylthio group in compounds IIIa, b with amines (methylamine, benzylamine, cyclohexylamine, isopropanolamine, piperidine, morpholine, pyrrolidine) occurred easily and the corresponding 3-aminoisothiazolo[3,4-d]pyrimidine-4,6(5H,7H)-diones (IVa, b, c, d, e, f, g, h, i) were obtained in good yields. These amino derivatives IV were alternatively obtained by the oxidative cyclization of 5-substituted thiocarbonyl-6-aminouracils, which were prepared by the reaction of IIa, b with amines (methylamine, benzylamine, morpholine), with iodine or bromine in good yields.

Reaction of IIIa with *p*-toluenesulfonamide in the presence of potassium carbonate in sulforane at 150° afforded 5,7-dimethyl-3-*p*-tolylsulfonylaminoisothiazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (VIa)² (colorless needles, mp 214°) in 26.6% yield. Similarly, 3-*p*-acetylaminothiophenylsulfonylamino-5,7-dimethylisothiazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (VIb) (colorless needles, mp 264°) was obtained from IIIa and *p*-acetylaminothiophenylsulfonamide in 56% yield.

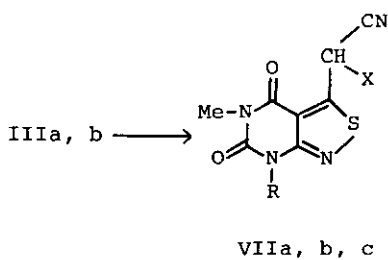
The reaction of IIIa, b with active methylene compounds (methyl cyanoacetate, phenylsulfonylacetonitrile) in the presence of potassium carbonate gave the corresponding substituted products (VIIa, b, c) in 63, 51, and 56% yields, respectively.



R	NR ₂	Yield(%)	mp(°C)
a: Me	NH-Me	75	197
b: Me	NH-CH ₂ -Ph	61	172
c: Me	NH-CH ₂ CH(OH)-Me	45	160
d: Me		63	99
e: Me		77	185
f: Me		95	187
g: Me	NH- 	56	223
h: Ph		80	235
i: Ph	NH-CH ₂ -Ph	47	212



R	Yield(%)	mp(°C)
a: Me	27	214
b: NH-Ac	56	264



R	X	Yield(%)	mp(°C)
a: Me	COOMe	62	248
b: Ph	COOMe	51	254
c: Me	SO ₂ -Ph	56	211

Yields and Physical Properties of The Main Compounds

- IIa: Yield 57%, mp 262°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3415, 3290(NH), 1710, 1692(CO). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 239(4.07), 261(4.01), 343(4.34). NMR(CF₃COOH) δ : 2.76(3H, s, SMe), 3.48(3H, s, NMe), 3.68(3H, s, NMe).
- IIb: Yield 47%, mp 249°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3300, 2860(NH), 1710, 1635(CO). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (log ϵ): 238(3.93), 262(4.11), 346(4.41).
- IIIa: Yield 60%, mp 155°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1700, 1650(CO). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm(log ϵ): 294(4.26). NMR(CF₃COOH) δ : 2.74(3H, s, SMe), 3.52(3H, s, NMe), 3.71(3H, s, NMe).
- IIIb: Yield 59%, mp 207°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1700, 1655(CO). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm(log ϵ): 293(4.32). NMR(CDCl₃) δ : 2.51(3H, s, SMe), 3.40(3H, s, NMe), 7.20 - 7.54(5H, m, Ph-H).
- VIa: Yield 51%, mp 214°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200(NH), 1700, 1645(CO). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm(log ϵ): 227(4.37), 280(4.15), 320(4.10).
- VIb: Yield 56%, mp 264°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200(NH), 1705, 1660(CO). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm: 260, 282, 316, $\lambda_{\text{min}}^{\text{EtOH}}$ nm: 227, 270, 300.
- VIIa: Yield 62%, mp 248°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2180(CN), 1715, 1620(CO). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm(log ϵ): 215(4.50), 235(4.41), 294(3.90), 354(4.46).
- VIIb: Yield 56%, mp 211°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2240(CN), 1710, 1660(CO). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm(log ϵ): 217(4.41), 258(3.92), 297(3.72).
- VIIc: Yield 51%, mp 254°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 2200(CN), 1710, 1670(CO). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm(log ϵ): 213(4.52), 235(4.44), 294(3.87).

References

- 1) This report is 'Enamino Dithiocarboxylates. II. Methyl 6-Aminouracil-5-dithiocarboxylates. 2.' Part 1: Y.Tominaga, T.Machida, H.Okuda, Y.Matsuda, and G.Kobayashi. Yakugaku Zasshi, 1979, 79, Submitted.
- 2) R.Niss and H.Eilingsfeld, Ann.Chem., 1974, 2019.
- 3) Y.Furukawa and S.Shima. Chem.Pharm.Bull.(Tokyo), 1976, 24, 979.
- 4) a) S.Ueno, Y.Tominaga, Y.Matsuda, and G.Kobayashi, Chem.Pharm.Bull.(Tokyo), 1974, 22, 2624;
b) H.Awaya, C.Maseda, Y.Tominaga, R.Natsuki, Y.Matsuda, and G.Kobayashi, Yakugaku Zasshi, 1975, 95, 13.

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