SYNTHESIS AND REACTIONS OF 3-METHYLTHIOISOTHIAZOLO[3,4-d]PYRIMIDINE-4,6(5H,7H)-DIONES[1)]

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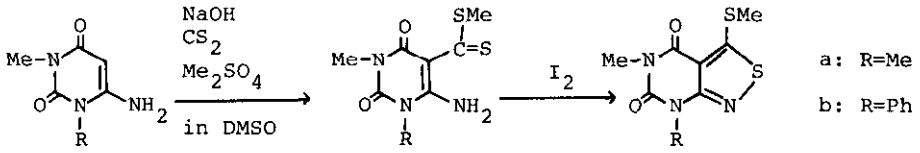
Abstract: 3-Methylthioisothiazolo[3,4-d]pyrimidine-4,6-(5H,7H)-diones (IIIa, b) were synthesized by treatment of methyl 6-aminouracil-5-dithiocarboxylates, which were prepared by the reaction of 6-aminouracil with carbon disulfide and dimethyl sulfate in the presence of alkali, with iodine in dimethyl 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 Niss[2] and Furukawa[3] 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, mp249°) was prepared by the reaction of 1b 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.

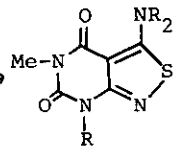


Ia, b IIa, b IIIa, b

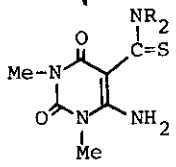
It has been well known that the methylthio group on the heterocyclic ring reacts with nucleophilic reagents to give the corresponding substituted products,[4] but there has been no report on the substitution reaction of methylthio group on the fused isothiazole ring. We next investigated on the nucleophilic 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 thiocarbamoyl-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-toluensulfonamide 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-acetylaminophenylsulfonylamino-5,7-dimethylisothiazolo[3,4-d]-pyrimidine-4,6(5H,7H)-dione (VIb)(colorless needles, mp 264°) was obtained from IIIa and p-acetylaminophenylsulfonamide 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.

IIIa, b → 

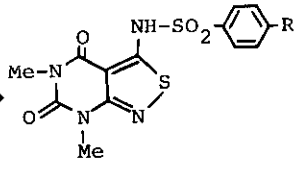
IV

IIa → 

V

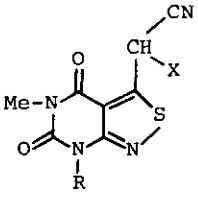
I_2 or Br_2

	R	NR_2	Yield(%)	mp(°C)
a:	Me	NH-Me	75	197
b:	Me	NH-CH_2-Ph	61	172
c:	Me	NH-CH_2CH(OH)-Me	45	160
d:	Me		63	99
e:	Me		77	185
f:	Me		95	187
g:	Me		56	223
h:	Ph		80	235
i:	Ph	NH-CH_2-Ph	47	212

IIIa → 

VIa, b

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

IIIa, b → 

VIIa, b, c

	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°. IRν_{max}^{KBr} cm^{-1}: 3415, 3290(NH), 1710, 1692(CO). UVλ_{max}^{EtOH}nm (log ε): 239(4.07), 261(4.01), 343(4.34). NMR(CF_3COOH)δ: 2.76(3H, s, SMe), 3.48(3H, s, NMe), 3.68(3H, s, NMe).

IIb: Yield 47%, mp 249°. IRν_{max}^{KBr} cm^{-1}: 3300, 2860(NH), 1710, 1635(CO). UVλ_{max}^{EtOH}nm (log ε): 238(3.93), 262(4.11), 346(4.41).

IIIa: Yield 60%,mp 155°. IRν_{max}^{KBr} cm^{-1}: 1700, 1650(CO). UVλ_{max}^{EtOH}nm(log ε): 294(4.26). NMR(CF_3COOH)δ: 2.74(3H, s, SMe), 3.52(3H, s, NMe), 3.71(3H. s, NMe).

IIIb: Yield 59%, mp 207°. IRν_{max}^{KBr} cn^{-1}: 1700, 1655(CO). UVλ_{max}^{EtOH}nm(log ε): 293(4.32). NMR($CDCl_3$)δ: 2.51(3H, s, SMe), 3.40(3H, s, NMe), 7.20 - 7.54(5H, m, Ph-H).

VIa: Yield 51%, mp 214°. IRν_{max}^{KBr} cm^{-1}: 3200(NH), 1700, 1645(CO). UVλ_{max}^{EtOH}nm(log ε): 227(4.37), 280(4.15), 320(4.10).

VIb: Yield 56%, mp 264°. IRν_{max}^{KBr} cm^{-1}: 3200(NH), 1705, 1660(CO). UVλ_{max}^{EtOH}nm: 260, 282, 316, λ_{min}^{EtOH}nm: 227, 270, 300.

VIIa: Yield 62%, mp 248°. IRν_{max}^{KBr} cm^{-1}: 2180(CN), 1715, 1620(CO). UVλ_{max}^{EtOH}nm(log ε): 215(4.50), 235(4.41), 294(3.90), 354(4.46).

VIIb: Yield 56%, mp 211°. IRν_{max}^{KBr} cm^{-1}: 2240(CN), 1710, 1660(CO). UVλ_{max}^{EtOH}nm(log ε): 217(4.41), 258(3.92), 297(3.72).

VIIc: Yield 51%, mp 254°. IRν_{max}^{KBr} cm^{-1}: 2200(CN), 1710. 1670(CO). UVλ_{max}^{EtOH}nm(log ε): 213(4.52), 235(4.44), 294(3.87).

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