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RING TRANSFORMATION OF 2,3-DISUBSTITUTED 4(3H)-PYRIMIDINETHIONES WITH MALONONITRILE

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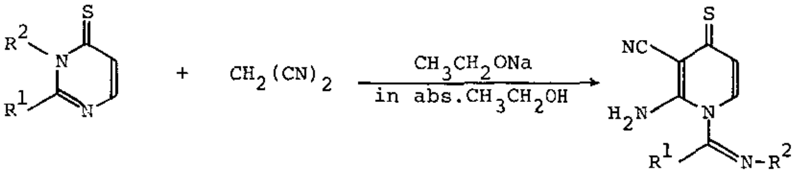
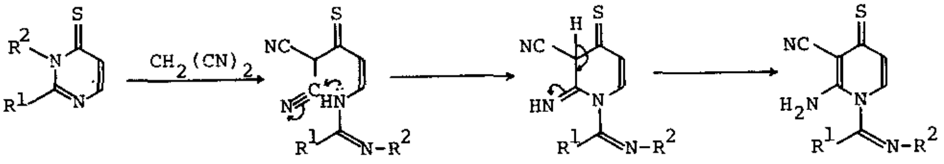
Abstract——2,3-Disubstituted 4(3H)-pyrimidinethiones (Ia-d) underwent the ring transformation with malononitrile in the presence of sodium ethoxide to give N-substituted 2-amino-3-cyano-4(1H)-pyridinethiones (IIa-d) in high yields.

The ring transformation of heterocyclic compounds has paid much attention, and many papers have been reported[1]. Previously we reported that N-substituted 2(1H)-pyrimidinones and the corresponding thiones were easily converted into isoxazoles[2], pyrimidines[2,3] by reaction with nucleophiles. As a part of study of the ring transformation of pyrimidinone derivatives, we wish to report herein the reaction of malononitrile with 2,3-disubstituted 4(3H)-pyrimidinethiones. First, 2-phenyl-3-(o-tolyl)-4(3H)-pyrimidinone, which was oxo-analogue of compound Ia, was treated with malononitrile in the presence of sodium ethoxide at room temperature, but the starting material was recovered.



a: R^1=C_6H_5- R^2=o-$CH_3C_6H_4$-　　b: R^1=C_6H_5- R^2=p-$CH_3C_6H_4$-
c: R^1=p-$CH_3C_6H_4$- R^2=o-$CH_3C_6H_4$-　　d: R^1=R^2=C_6H_5-

When 2-phenyl-3-(o-tolyl)-4(3H)-pyrimidinethione (Ia) was allowed to react similarly with malononitrile, a product, mp 153-154 °C, was obtained. The analytical data of this product gave the formula $C_{20}H_{16}N_4S$. In the ir spectrum, the strong bands appeared at 3450 and 3300, and 2235 cm^{-1} due to NH and CN stretching, respectively. Further, the ^1H-nmr spectrum shows two signals at δ 6.40 (d,1H,J=7.8 Hz) and 6.76 ppm (d,1H,J=7.8 Hz) which indicate the existence of the structure unit -CH=CH- in the product. From these data and the ^{13}C-nmr spectrum, the structure of the product was assigned to be 2-amino-3-cyano-1-[1-phenyl-1-(o-tolylimino)]methyl-4(3H)-pyridinethione (IIa). The structure was also supported by chemical reaction. Compound IIa was treated with lithium aluminum hydride to give N-benzyl-o-toluidine by the cleavage of C-N bond. The possible mechanism for ring transformation was illustrated in Figure 1. A carbanion of malononitrile attacks on C-4 position of compound I, and then the ring-opening occurs. By further attack of nitrogen of amidine moiety at cyano carbon, and proton migration, the product II can be obtained.



I

II

Figure 1

In this reaction, the C_2-N_3 portion of the pyrimidine ring was replaced by the C-C portion of malononitrile. In the reaction of N-substituted 2(1H)-pyrimidinethiones with malononitrile[4], 2-amino-3-cyanopyridines were obtained by removal of the substituents on nitrogen atom. However, in this reaction the substituent on nitrogen atom still remained in the product. It is concluded that 2,3-disubstituted 4(3H)-pyrimidinethiones are easily converted into N-substituted 4(1H)-pyridinethiones bearing cyano and amino group.

EXPERIMENTAL

General Procedure for Preparation of 4(1H)-Pyridinethiones IIa-d

A solution of 4(3H)-pyrimidinethione (I, 2 mmoles), malononitrile (8 mmoles) and sodium ethoxide (8 mmoles) in absolute ethanol (40 ml) was stirred overnight at room temperature. The solvent was evaporated off, and the residue was dissolved in water and extracted with dichloromethane. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude products were purified by column chromatography on silica gel with chloroform-benzene-ethyl acetate (2:4:1), and then recrystallization from benzene-hexane mixture.

2-Amino-3-cyano-1-[1-phenyl-1-(o-tolyl)imino]methyl-4(1H)-pyridinethione IIa
Yield 93%; mp 153-154 °C; ir(KBr) 3450, 3300, 2235 cm^{-1}; ^{1}H-nmr(δ,CDCl$_3$) 2.21 (s,3H), 5.1 (broad s,2H,D$_2$O exchangeable), 6.40 (d,1H,J=7.8 Hz), 6.76 (d,1H, J=7.8 Hz), 7.0-7.4 (m,7H), and 7.8-8.0 ppm (m,2H); ^{13}C-nmr(δ,CDCl$_3$) 17.9(q), 87.8 (s), 114.8 (d), 116.3 (s), 118.5 (d), 124.8 (d), 126.1 (d), 127.9 (s), 128.3 (d), 128.9 (d), 130.2 (d), 130.9 (d), 138.0 (s), 140.7 (d), 149.0 (s), 158.4 (s), and 161.0 ppm (s); Calcd. for $C_{20}H_{16}N_4S$: C, 69.74; H, 4.68; N, 16.26. Found: C, 69.85; H, 4.69; N 16.25.

2-Amino-3-cyano-1-[1-phenyl-1-(p-tolyl)imino]methyl-4(1H)-pyridinethione IIb
Yield 78%; mp 132-134 °C; ir(KBr) 3480, 3360, and 2220 cm^{-1}; ^{1}H-nmr(δ,CDCl$_3$) 2.32 (s,3H), 5.2 (broad s,2H), 6.42 (d,1H,J=7.8 Hz), 6.83 (d,2H,J=8.5 Hz), 7.1-7.4 (m,6H), and 7.8-8.0 ppm (m,2H); ^{13}C-nmr(δ,CDCl$_3$) 21.0 (q), 87.7 (s), 114.5 (d), 116.3 (s), 119.7 (d), 128.3 (d), 129.1 (d), 129.4 (d), 130.8 (d), 134.5 (s), 138.3 (s), 140.8 (d), 145.5 (s), 156.8 (s), 158.4 (s) and 161.2 ppm (s); Calcd. for $C_{20}H_{16}N_4S$: C, 69.74; H, 4.68; N, 16.26. Found: C, 69.70; H, 4.62; N, 16.34.

2-Amino-3-cyano-1-[1-(o-tolyl)-1-(p-tolyl)imino]methyl-4(1H)-pyridinethione IIc
Yield 85%; mp 155-156 °C; ir(KBr) 3390, 3300, and 2230 cm^{-1}; ^{1}H-nmr(δ,CDCl$_3$) 2.17 (s,3H), 2.32 (s,3H), 5.2 (broad s,2H), 6.33 (1H,d,J=7.8 Hz), 6.6-7.3 (m,7H), and 7.8 ppm (d,2H,J=9 Hz); Calcd. for $C_{21}H_{18}N_4S$: C, 70.36; H, 5.06; N, 15.63. Found: C 70.55; H, 5.10; N, 15.48.

2-Amino-3-cyano-1-(1-phenyl-1-phenylimino)methyl-4(1H)-pyridinethione IId
Yield 87%; mp 135-135.5 °C; ir(KBr) 3420, 3280, and 2210 cm^{-1}; ^{1}H-nmr(δ,CDCl$_3$) 5.35 (broad s,2H), 6.27 (d,1H,J=7.8 Hz), 6.7-7.5 (m,9H), and 7.7-8.0 ppm (m,2H); Calcd. for $C_{19}H_{14}N_4S$: C, 69.06; H, 4.27; N, 16.95. Found: C, 69.22; H, 4.34; N, 16.72.

REFERENCES

1. H. C. van der Plas, "Ring Transformation of Heterocycles", Vol 1 and 2, Academic Press, New York, 1973.
2. C. Kashima, A. Katoh, Y. Yokota, and Y. Omote, *Chem. Pharm. Bull.*, **29**, 2516(1981).
3. C. Kashima, A. Katoh, Y. Yokota, and Y. Omote, *Chem. Pharm. Bull.*, **30**, 1942(1982).
4. A. Katoh, submitted for publication in *Chem. Pharm. Bull.*

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