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# SELECTIVE CYCLIZATION OF 2-PROPARGYLTHIO-6-METHYL-PYRIMIDIN-4(1H)-ONE TO THIAZOLO [3,2-a] PYRIMIDIN-7-ONE

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**Abstract**

Selective transformation of 2-propargylthio-6-methyl-pyrimidin-4(1H) one (**2**) to 3,5-dimethyl-7H-thiazolo [3,2-a] pyrimidin-7-one (**3**) is performed under the condition of base catalysis. For elucidation of structure, palladium catalyzed cyclization reaction of (**2**) was carried out and the structures of the products were assigned (**5**) and (**6**). These compounds underwent isomerization to (**3**) and (**4**) respectively. From this result, regioselectivity by base catalysis was concluded.

## Introduction

Up until now, the general method for synthesizing thiazolo [3,2-a] pyrimidines has been basically dependent on starting from 2-aminothiazoles [1,2]. Many thiazolo [3,2-a] pyrimidines have been synthesized to evaluate their biological activities from 2-thiopyrimidines [3-7]. However, these synthetic methods have the disadvantages of giving another regioisomer, thiazolo [2,3-b] pyrimidines. All attempts made so far to reach either the pure regioisomeric thiazolo [3,2-a] pyrimidine or thiazolo [2,3-b] pyrimidine have invariably led to failure or poor yield [3-5]. Recently, we studied the regioselective cyclization of propargylthio [8-11] and propargylseleno 1,2,4-triazines [12,13]. In the present work, we wish to report the regioselective cyclization of 2-propargylthio-6-methyl-pyrimidin-4(1H)-one (**2**) to 3,5-dimethyl-thiazolo [3,2-a] pyrimidin-7-one (**3**) by base catalysis.

## Results and Discussion

6-Methyl-2 thiouracil (1) [14] was condensed with propargyl bromide in the presence of sodium methoxide at room temperature to afford 2-propargylthio-6-methylpyrimidin-4(1H)-one(**2**). When (**2**) was refluxed in sodium methoxide for a long period of time, a single (TLC) pure compound was obtained in good yield. From spectral data, the elucidation of the structure was quite straightforward. $^1$H NMR showed one aromatic proton at $\delta$ 6.45, characteristic of fused thiazole ring [8,9], and mass spectrum showed $M^+$ at m/z 180. These data suggested a base catalyzed cyclization of (**2**) to an intermediate (**5**) or (**6**) and simultaneous isomerization of these to either (**3**) or (**4**). The cyclization and isomerization are reminiscent of the cyclization and isomerization of propargylthio and propargylseleno-1,2,4-triazines to the corresponding thiazolo and selenazolo triazines [8-13]. The spectral data, however, were not much help in deciding in favour of either angular product (**3**) or the linear product (**4**).

For exact determination of structure, we were going to refer to the preferentiality of N-methylation of pyrimidine [15,16], but we found out that methylation of 2-methylthio 6-methyl-pyrimidin-4(1)-one with $CH_3I$ and $Me_2SO_4$ under basic conditions produces a mixture of N-1 and N-3 in a ratio of 3:1. (The latest report in this field by A.R. Katritzky and his group [17] confirmed this finding).

**Keywords:** Base catalyzed; Selective cyclization; Thiazolo pyrimidine

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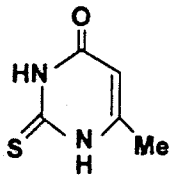

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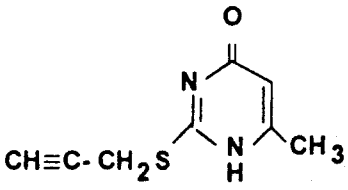

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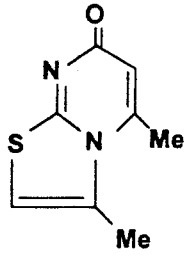

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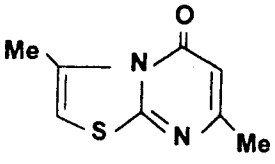

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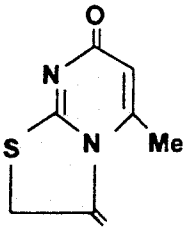

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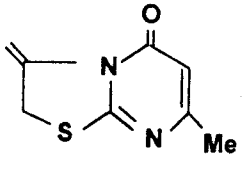

(6)

Pd-catalyzed reaction enjoys widespread application in organic synthesis [18]. Pd-catalyzed intramolecular functionalization of acetylenes has been one of our laboratory interests [9,11,13,19-22] and many cyclization reactions have been catalyzed by Pd(II) salt leading to heterocyclic systems [22-24].

When (2) was refluxed in a mixture of $CH_3CN$ and MeOH with catalytic amount of $[PdCl_2(PhCN)_2]$ a mixture was obtained. Without palladium, no reaction took place either with aprotic or protic solvent at their refluxing temperature and starting material was recovered. The Pd-catalyzed reaction provided two isomeric cyclized compounds (5 and 6) together with small amounts of a depropargylated product (1).

The formation of (5) and (6) clearly indicates that palladium-catalyzed cyclization of (2) to (5) and (6) proceeds via a direct attack of N-3 and N-1 on the acetylenic triple bond activated by the coordination of Pd(II). Structures (5) and (6) were recognised from their physical spectral data. In the UV spectra, (6), with a dienone structure, shows the absorption maxima at the longer wavelength compared to (5) with a quinone structure. In the $^1H$ NMR spectra of (6), the *exo* methylene proton *syn* to the C-4 amide carbonyl appeared downfield by ca 1.4 ppm compared with the *anti* proton, while the methylene protons in (5) appeared approximately in the same region.

When (5) or (6) was refluxed in NaOH-MeOH, a single compound was isolated in each case. These compounds were identified as: 3,5-dimethyl-7H-thiazolo [3,2-a] pyrimidin-7-one (9) and 3,7-dimethyl-5H-thiazolo [2,3-b] pyrimidin-5-one (4). The mechanism of this type of isomerization has been suggested elsewhere [8 and 9].

Comparison of the spectral data of the product obtained by base catalysis cyclization and isomerization of (2) with those of (3) showed that they are identical. Hence, we were able to conclude that in the base catalysis of cyclization of (2), compound (3) is obtained exclusively and the reaction is therefore regioselective.

## Experimental Section

The melting points are uncorrected and were obtained by a Kofler Heizbank Richert type 7841 melting point apparatus. IR spectra were obtained on a 4300 Shimadzu spectrometer. The $^1H$ NMR spectra were recorded on a Varian 60 A spectrometer using TMS as internal reference and mass spectra were scanned on a Varian Mat CH-7 instrument at 70 eV.

**2-Propargylthio-6-methyl-pyrimidin-4(1H)-one (2)**

Sodium (1 g) was dissolved in methanol (100 ml) and compound 1 (4.97 g, 0.035 mol) was dissolved in this solution. Propargyl bromide (4.65 ml of 80% solution in toluene) was added dropwise at room temperature. The reaction mixture was stirred at ambient temperature for 24 h. The solution was acidified using acetic acid. The solid was filtered off, washed with water and crystallized from EtOH to afford (2) as white crystals, (4.53 g, 72%), m.p. 160-162, IR, $\nu$ (KBr disk), 1630 (amide carbonyl), 3300, (C≡ C-H), $cm^{-1}$, UV ($CHCl_3$), $\lambda$ max 284 nm. $^1H$ NMR $\delta$ ($CDCl_3$), 2.3 (s, 3H, $CH_3$), 2.35 (t, 1H, CH), 4.05 (d, 2H, $CH_2$), 6.16 (s, 1H, CH). M.S. m/z (rel. intensity) 180 ($M^+$, 20), 177(106), 139(89), 83(49), 67(80), 28(81).

**3,5-Dimethyl-7H-thiazolo [3,2-a] pyrimidin-7-one (3)**

Compound 2 (0.6 g, 0.033 mol) was dissolved in a solution of MeOH (35 ml) containing sodium hydroxide (0.06 g). The reaction mixture was refluxed for 8 h and the

solvent evaporated. To this crude, water (50 ml) was added and extracted with $CHCl_3$. Chloroform was dried over $Na_2SO_4$ and evaporated to dryness under reduced pressure to afford the title compound as yellow needles (0.36 g; 60%), m.p. 116-118 (s, 1H, CH). M.S. m/z (rel. intensity), 180(15, $M^+$), 177(100), 150(95), 149(68), 69(52), 65(53), 38(95), 27(26).

**Pd(II) Catalyzed Reaction of 2**

A solution of compound **2** (1.8 g, 0.01 mol) in a mixture of acetonitrile and methanol (80 ml and 20 ml) and [$PdCl_2$(PhCN) (0.23 g, 0.06 ml) was refluxed for 2 h. After evaporation of solvent, the residue was directly subjected to a column chromatography (silica gel, $CHCl_3$, $CH_3OH$, 90:10). The first fraction of column was indentified as depropargylated product (1) (0.05 g). The second fraction was identified as 2,3-dihydro-3-methylene-5-methyl-7H-thiazolo [3,2-a] pyrimidin-7-one (5) (0.11 g, 9%), m.p. 190-192°C, IR, ν(KBr disk), 3100, 1630 (amide carbonyl), 1670, (C= C), 1460, 770 $cm^{-1}$, UV ($CHCl_3$), λ max 239, ABS= 0.669 g, $^1H$ NMR, δ ($CDCl_3$), 2.45 (s, 3H, $CH_3$), 4.1 (s, 2H, $CH_2$), 5.2 (s, 2H, *exo* methylene), 6.03 (s, 1H, CH). M.S, m/z (rel. intensity), 180 ($M^+$, 10), 177(65), 149(38), 70(35), 67(100), 52(41), 38(84). The third fraction was eluted from column and identified as 2,3-dihydro-3-methylene-7-methyl 5H-thiazolo [2,3-b] pyrimidin-5-one (**6**) (0.83 g, 66%), m.p. 180-181°C, IR, ν (KBr disk), 3100, 1630, (amide carbonyl), 1615, (C= C), 850, 770 $cm^{-1}$, UV ($CHCl_3$), λ max 245, ABS, 2.253, $^1H$ NMR, δ ($CDCl_3$), 2.35 (s, 3H, $CH_3$), 4.2 (s, 2H, $CH_2$), 5.27 (d, 1H= $CH_a$), 6.16 (s, 1H, CH), 6.7 (d, 1H = $CH_b$). M.S., m/z (rel. intensity), 180($M^+$, 25), 177(100), 149(40), 67(28), 66(23).

**3,7-Dimethyl-5H-thiazolo[2,3-b] pyrimidin-5-one (4)**

Compound **6** (0.05 g, 0.27 mmol) was refluxed in a solution of MeOH (20 ml) containing sodium hydroxide (0.04 g) for 6 h. The solvent was evaporated under reduced pressure, water was added to the residue which was then extracted with $CHCl_3$. Chloroform was dried over $Na_2SO_4$ and evaporated to dryness to afford the title compound (0.02 g, 40%) m.p. 136-137°C, IR, ν(KBr disk), 3100, 2900, 1695 (amide carbonyl), 1660, 1500 $cm^{-1}$, UV ($CHCl_3$), λ max 275, ABS= 1.57, $^1H$ NMR, δ ($CDCl_3$), 2.25 (s, 3H, $CH_3$), 2.75 (s, 3H, $CH_3$), 6.05 (s, 1H, CH), 6.4 (s, 1H, CH thiazolo ring). M.S. (rel. intensity), 180($M^+$.25), 176(100), 80(19), 72(56), 71(49), 27(30).

**3,5-Dimethyl-7H-thiazolo [3,2-a] pyrimidin-7-one (3)**

Compound (**5**) (0.04 g; 0.22 mmol) was refluxed in a solution of MeOH (20 ml) containing sodium hydroxide (0.04 g) for 4 h. The solvent was evaporated under reduced pressure. The residue was dissolved in water and extracted with $CHCl_3$. The chloroform was dried over $Na_2SO_4$ and evaporated to dryness to afford the title compound (0.02 g, 50%), m.p. 116-118°C. Its spectroscopic data has already been given.

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