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Synthesis and Reaction of Biheterocyclic Thiazolo[3,2-a]pyrimidinium-betaines

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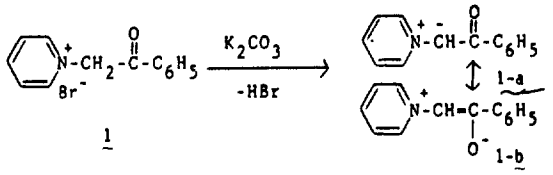
Various new kinds of biheterocyclic betaines were prepared by the reaction of 3-substituted-6, 7-dihydro-5H-thiazolo[3,2-a] pyrimidine with electrophiles such as isothiocyanates, isocyanates in aprotic solvents, respectively. The biheterocyclic betaines containing methyl group at 3-position of thiazole ring were obtained particularly in good yields at room temperature. These betaines were also reacted with alkyl halide to give quarternary ammonium salts. It was found that these betaines are dissociated in polar organic solvents depending on temperature. And new biheterocyclic compounds via ring transformation were prepared by the reaction of 8-phenyl (thiocarbamoyl)-3-phenyl-6, 7-dihydro-5H-thiazolo[3, 2-a]pyrimidinium-betaine with α-halo kester α-halo ester and γ-halo keto ester.

Introduction

The first compound N-ylid structure may be assigned was prepared in 1933 by Krollpferiffer and Müller[1] by treating an aqueous solution of N-(2-ethyl-mercapto-5-ethyl-phenacyl)-pyridinium bromide with sodium hydroxide. Two years later, Kröhnke[2] isolated a crystalline product by elimination of hydrogen bromide from phenacylpyridinium bromide and he assigned to it an "enol-betaine" structure **1-b**.



The betaines with N-ylid are highly reactive organic compounds. Owing to the presence of the carbanion they appear to be strong nucleophiles and react therefore with a large variety of organic compounds; in most cases a new c-c bond is formed in such reactions, which are very important for organic synthesis.

Some thiazolo[3,2-a]pyrimidines reported[3-6] earlier have shown fairly good antibacterial activity and a variety of pharmaceutical activities, including an anti-inflammatory effect. And it was known that certain 8-substituted-6,7-dihydro-5H-thiazolo[3, 2-a]pyrimidinium salts had useful pesticidal and acaricidal properties[7]. The N-bridged thiazolo compounds, isolated as the hydrobromides or hydrochlorides, were prepared by reacting the cyclic thioureas with α-halo ketone or α-halo ester by following the general procedure reported previously[5, 8-10].

It was known[11-13] that 8-substituted-3-phenyl-6,7-dihydro-5H-thiazolo[3,2-a] pyrimidinium-betaines with pyrimidinium—ylid structure are obtained from reaction of 3-pheny-6,7-dihydro-5H-thiazolo [3,2-a] pyrimidine with phenyl isothiocyanate, phenyl isocyanate or carbon disulfide. And it was also reported[14, 15] that the reaction of phenacyl bromide with the bicyclic zwitterionic thiazole, which result from a three-component reaction of cyclic thioureas, mercury bis(phenylacetylide), and phenyl isothiocyanate, does not yield the bromide; instead ring opening and renewed cyclization af-

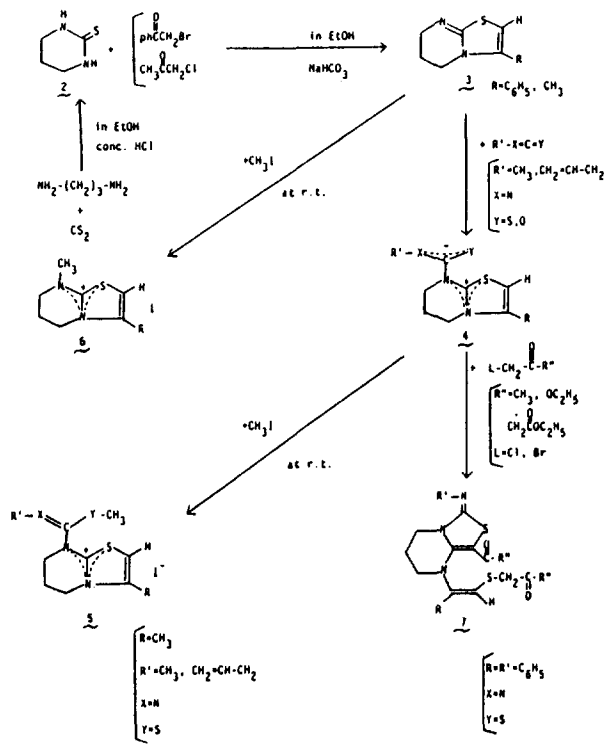
fords the new bicyclic thiazole 2-[2-(8-benzoyl-6-phenylimino-1,2,3,4-tetrahydro thiazolo[3,2-a]pyrimidin-1-yl)-2-phenyl-vinylthio]acetophenone.

In this work, various new kinds of biheterocyclic 8-substituted-3-phenyl (or methyl)-6, 7-dihydro-5H-thiazolo[3, 2—a]pyrimidinium-betaines were prepared by the reaction of 3-phenyl (ormethyl)-6, 7-dihydro-5H-thiazolo [3, 2-a]pyrimidine with electrophiles such as allyl isothiocyanate, methyl isothiocyanate, methyl isocyanate in aprotic solvents like acetonitrile and toluene, respectively. These betaines were also reacted with alkyl halide to give quarternary ammonium salts. In addition the stabilities of betaine compounds and quarternary ammonium salts according to temperature and polarity of solvents were examined. And new biheterocyclic compounds via ring transformation were prepared by reaction of 8-phenyl (thiocarbamoyl)-3-phenyl-6,7-dihydro-5H-thiazolo[3,2-a] pyrimidinium-betaine with α-chloroacetone, ethyl bromoacetate and ethyl 4-chloroacetoacetate such as α-halo ketone, α-halo ester and γ-halo keto ester.

Experimental

Melting points were determined on a Thomas-Hoover melting point apparatus and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 267 spectrophotometer using NaCl or pressed KBr pellet. Only selected adsorptions are reported. ^{1}H NMR spectra were obtained on JEOL JNM-PMX 60$_{SI}$ nmr spectrometer and Brucker 90 MHz nmr spectrometer, using tetramethylsilane as internal standard. Chemical shift values from TMS were reported on the scale.

All of the electrophiles such as allyl isothiocyanate, methyl isothiocyanate, methyl isocyanate were used without further purification. But phenacyl bromide (Aldrich Chem. Co.) was purified by recrystallization with ethanol. And acetone was dried over anhydrous M_gSO_4. Kieselgel 60 (70-230 mesh ASTM, MERCK) was used for column chromatography.



Scheme 1.

Cyclic thiourea consisting of six-membered ring system[16-18] **2** and 3-phenyl (or methyl)-6,7-dihydro-5H-thiazolo[3, 2-a] pyrimidine[8-10] **3** were prepared by methods described in the literatures.

A. Preparation of betaine compounds. In a round bottomed flask equipped with a dropping funnel, 0.0046 mole (1.0g) of 3-phenyl-6, 7-dihydro-5H-thiazolo[3, 2-a]pyrimidine was dissolved in 30 ml of acetonirile. To this solution was added an equimolar amount of electrophile slowly through the dropping funnel with constant stirring at room temperature. The precipitate was formed at once and filtered.

8-Allyl(thiocarbamoyl)-3-phenyl-6,7-dihydro-5H-thiazolo [3, 2-a]pyrimidinium-betaine (**4-a**). Allyl isothiocyanate (0.46g) as electrophile was used and yield was 0.91g (62.6%) of pale yellow solid, mp 113-116°C.

^{1}H NMR(CF_3CO_2D): δ(ppm) 2.9-2.4(2H,*m*, $-CH_2-$), 5.1-4.2(6H, *m*, $=C-CH_2$, CH_2N, NCH_2), 5.7-5.3 (2H, *m*, $CH_2=$), 6.1-5.7 (1H, *m*, $=CH-C$), 7.1(1H, *s*, $=CH$), 7.8-7.4(5H, *s*, ArH).

8-Methyl(thiocarbamoyl)-3-phenyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidinium-betaine **(4-b).** Methyl isothiocyanate (0.34g) as electrophile was used and yield was 1.14g (85.8%) of yellow solid, mp 141-143°C.

^{1}H NMR(CF_3CO_2D): δ(ppm) 2.3-1.9(2H, *m*, $-CH_2-$), 2.9(3H, *s*, $-CH_3$), 4.1-3.6(4H, *m*, CH_2N, NCH_2), 6.5(1H, *s*, $=CH$), 7.2(5H, *s*, ArH).

8-Methylcarbamoyl-3-phenyl-6,7-dihydro-5H-thiazolo [3,2-a]pyrimidinium-betaine **(4-c).** Methyl isocyanate (0.26g) as electrophile was used and yield was 0.20g (16.0%) of white solid, 139.5-141.5°C.

^{1}H NMR(CF_3CO_2D): δ(ppm) 2.4-2.0(2H, *m*,$-CH_2-$), 3.1(3H, *s*, $-CH_3$), 4.3-3.8(4H, *m*, CH_2N, NCH_2), 6.7(1H, *s*, $=CH$), 7.3(5H, *s*, ArH)

In this case, 0.0065mole (1.0g) of 3-methyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidine was used. And toluene in place of acetonitrile was used as solvents. Other conditions were the same above.

8-Allyl (thiocarbamoyl)-3-methyl-6,7-dihydro-5H-thiazolo [3,2-a]pyrimidinium-betaine **(4-d).** Allyl isothiocyanate (0.65g) as electrophile was used and yield was 1.34g (81.5%) of yellow solid, mp 101-103°C.

^{1}H NMR(CF_3CO_2D): δ(ppm) 2.9-2.3(5H, *m*, CH_3, $-CH_2-$), 4.7-3.6(6H, *m*, $=C-CH_2$, CH_2N, NCH_2), 5.5-5.1(2H, *m*, $CH_2=$), 6.0-5.5(1H, *m*, $=CH-C$), 6.8(1H, *s*, $=CH$).

8-Methyl(thiocarbamoyl)-3-methyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidinium-betaine **(4-e).** Methyl isothiocyanate (0.48g) as electrophile was used and yield was 1.27g (86.1%) of yellow solid, mp 124-126°C.

^{1}H NMR(CF_3CO_2D): δ(ppm) 2.8-2.4(5H, *m*, CH_3,$-CH_2-$), 3.1(3H, *s*, CH_3-N), 4.5-4.0(4H, *m*, CH_2N, NCH_2), 6.9(1H, *s*, $=CH$).

8-Methylcarbamoyl-3-methyl-6,7-dihydro-5H-thiazolo [3,2-a]pyrimidinium-betaine **(4-f).** Methyl isocyanate (0.37g) as electrophile was used and yield was 0.29g(21.2%) of white solid, mp 115-117°C.

^{1}H NMR(CF_3CO_2D): δ(ppm) 2.8-2.4(5H, *m*, CH_3, $-CH_2-$), 3.3(3H, *s*, CH_3-N), 4.6-4.1(4H, *m*, CH_2N, NCH_2), 6.8(1H, *s*,

=CH).

B. Reaction of betaine compounds with alkyl halide. In acetonitrile biheterocyclic betaines were dissolved. An equimolar amount of methyl iodide was added slowly through dropping funnel at room temperature.

8-(C-Methylthio-N-allylformimidoyl)-3-methyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidinium iodide **(5-a).** In acetonitrile 0.0039 mole(1.0g) of 8-allyl(thiocarbamoyl)-3-methyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidinium-betaine was dissolved. In a few minutes while colored solid was formed. The precipitate was filtered to yield 0.89g(58.0%), mp 110-112°C.

^{1}H NMR($CDCl_3$): δ(ppm) 2.8-2.2(5H, *m*, CH_3, $-CH_2-$), 3.3(3H, *s*, S-CH_3), 4.7-3.7(6H, *m*, $=C-CH_2$, CH_2N, NCH_2), 5.5-5.0(2H, *m*, $CH_2=$), 6.2-5.7(1H, *m*, =CH-C), 7.1(1H, *s*, =CH).

8-(C-Methylthio-N-methylformimidoyl)-3-methyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidinium iodide **(5-b)**. In acetonitrile 0.0044 mole(1.0g) of 8-methyl(thiocarbamoyl)-3-methyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidinium-betaine was dissolved. In a few minutes white colored solid was formed. The precipitate was filtered to yield 1.11g(68.5%), mp 134-136°C.

^{1}H NMR(DMSO-d_6): δ (ppm) 2.6-2.1(5H, *m*, $-CH_2-$), 2.9(3H, *s*, S-CH_3), 3.5(3H, *s*, CH_3-N), 4.7-4.3(4H, *t*, CH_2H, NCH_2), 7.0(1H, *s*, =CH).

C. Reaction of N-bridged thiazolo compounds with alkyl halide. To a 50 *ml* round bottomed flask containing starting material dissolved in solvents was added an equimolar amount of methyl iodide through dropping funnel at room temperature. The precipitate was collected and dried.

8-Methyl-3-phenyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidinium iodide **(6-a).** In acetonitrile 0.0046mole (1.0g) of 3-phenyl-6,7-dihydro-5H-thiazolo[3,2-a] pyrimidine was dissolved and the precipitate was filtered to yield 1.49(90.5%) of yellow solid, mp 184-186°C.

^{1}H NMR(DMSO-d_6): δ(ppm) 2.5-2.1(2H, *m*, $-CH_2-$), 3.3(3H, *s*, CH_3), 4.2-3.7 (4H, *m*, CH_2N, NCH_2), 6.9(1H, *s*, =CH), 7.4(5H, *s*, ArH).

8-Methyl-3-methyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidinium iodide **(6-b).** In toluene 0.0065mole(1.0g) of 3-methyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidine was used and the precipitate was filtered to yield 1.32g(68.6%) of white solid, mp 181-183°C.

^{1}H NMR($CDCl_3$): δ(ppm) 2.4-1.9(5H, *m*, CH_3, $-CH_2-$), 3.2(3H, *s*, CH_3-N), 3.8-3.4(2H, *t*, CH_2N), 4.2-3.8(2H, *t*, NCH_2), 6.8(1H, *s*, =CH).

D. Preparation of biheterocyclic compounds via ring transformation. In acetone 0.00285mole (1.0g) of 8-phenyl (thiocarbamoyl)-3-phenyl-6,7-dihydro-5H-thiazolo[3,2-a] pyrimidinium-betaine was dissolved at room temperature. The α-halo ketone, α-halo ester and γ-halo keto ester dissolved in acetone was added slowly to this solution through dropping funnel, respectively. During the reaction was developing, salt precipitated. When the reaction was completed, solution was concentrated under reduced pressure and cooled. The salt was filtered. And the filtrate was distilled off in rotary evaporator and solidified with methanol. In case that the solid was not formed or a small amount of salt remained, it was separated by column chromatography(Kieselgel 60, Merck, eluting solvent; n-hexane: ethyl acetate = 2.5:1). The combined solutions containing product were distilled off and resulting solid was dried in vacuo.

2-[2-(8-Acetyl-6-phenylimino-1,2,3,4-tetrahydro-thiazolo [3,4-a] pyrimidin-1-yl)-2-phenylvinylthio]acetone **(7-a).** It was reacted with an equimolar amount of α-chloro acetone. The dark yellow crystalline was obtained by recrystallization with ethanol, mp 145-146.5°C.

IR(KBr):ν_{max} (cm^{-1}) 3050(*m*), 1715(*s*), 1600(*vs*), 1200(*s*), 770(*vs*), ^{1}H NMR ($CDCl_3$): δ(ppm) 2.3-1.7 (8H, *m*, 2*s*, $-CH_2-$, $2COCH_3$), 3.5-3.1(4H, *m*, CH_2CO, CH_2N), 4.2-3.8(2H, *t*, NCH_2), 5.9(1H, *s*, =CH), 7.6-7.0(10H, *m*, 2ArH).

2-[2-(8-Ethoxycarbonyl-6-phenylimino-1,2,3,4-tetrahydro-thiazolo[3,4-a]pyrimidin-1-yl)-2-phenylvinylthio]ethyl acetate **(7-b).** It was reacted with an equimolar amount of ethyl bromoacetate. The yellow crystalline was obtained by recrystallization with ethanol, mp 155-157°C.

IR(KBr)ν_{max} (cm^{-1}) 3050(*m*), 1735(*s*), 1650(*s*), 1600(*vs*), 1210(*vs*), 750(*vs*) ^{1}H NMR($CDCl_3$): δ(ppm) 1.4-0.9(6H, *m*, $2CH_3$), 2.3-1.9(2H, *m*, $-CH_2-$), 3.5-3.2(4H, *m*, CH_2CO, CH_2N), 4.4-3.8(6H,*m*,$2COOCH_2$,NCH_2), 6.1(1H, *s*, =CH), 7.6-6.9(10H, *m*, 2ArH).

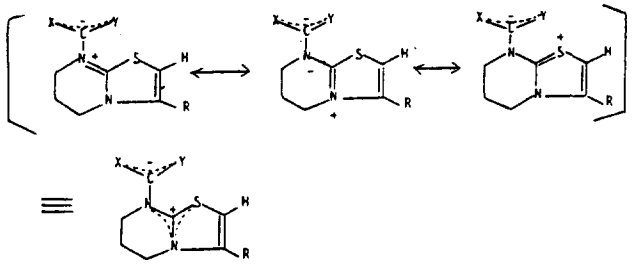
2-[2-(8-Ethoxycarbonylacetyl-6-phenylimino-1,2,3,4-tetrahydro-thiazolo[3,4-a]pyrimidin-1-yl)-2-phenylvinylthio] ethyl acetoacetate **(7-c).** It was reacted with an equimolar amount of ethyl 4-chloro acetoacetate. The palle yellow crystalline was obtained by recrystallization with ethanol. mp. 58-60°C.

IR(KBr):ν_{max} (cm^{-1}) 3050(*m*), 1735(*s*), 1630(*s*), 1600(*vs*), 1200(*s*), 780(*vs*) ^{1}H NMR($CDCl_3$): δ(ppm) 1.4-1.0(6H, *m*, $2CH_3$), 2.3-1.9(2H, *m*, $-CH_2-$), 3.6-3.2(8H, 3*s*, *t*, $2CH_2COO$, CH_2CO, CH_2N), 4.3-3.8(6H, *m*, $2COOCH_2$, NCH_2), 5.8(1H, *s*, =CH), 7.5-6.9(10H, *m*, 2ArH)

Results and Discussion

Many synthetic methods of 3-substituted-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidine were developed[5,8-10] and pharmacological activities of some of these compounds were reported[3-7].

The compounds of formula **3** are used as strong nucleophiles because of non-bonding electrons of nitrogen atom at 8-position. Therefore the reaction with electrophiles containing electron deficient center carbon due to great electronegativities of heteroatom, O, N, S, resulted in the corresponding betaines **4.** These betaines **4** were stabilized by a series of resonance structures as follows:



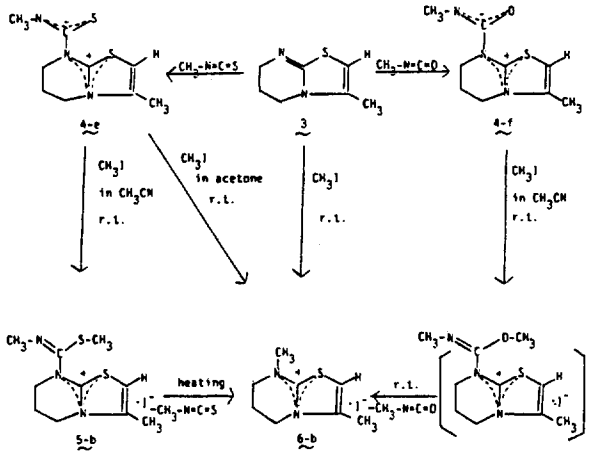
It is expected that the first structure of quarternary ammonium salt form contributes mainly.

In this work, the reactivities according to electrophiles and substituents at 3-position of thiazole ring were examined. The difference of reactivities between electrophiles is detected by comparison of phenyl isothiocyanate, phenyl isocyanate with methyl isothiocyanate and methyl isocyanate. Generally, in case of phenyl group it was obtained in high yields than that of methyl group. It is likely that deloc ılization of the π-electron extended to phenyl ring contributes to stabilization. It was known that delocalization of the π-electron is very important in determining the N-ylid stability. On the other hand, it is assumed that substituent at 3-position of thiazole ring may be effected to nucleophilicity of non-bonding electrons belong to nitrogen. In case that methyl substituent to donate electrons is attached, the corresponding betaines are obtained in high yields at room temperature because nucleophilicity is enhanced by methyl group. The 3-phenyl-6,7-dihydro-5H-thiazolo [3,2-a] pyrimidine with electrophiles led to the corresponding betaines in good yields, but was not so good as methyl group is.

The stabilities of betaine compounds is remarkably influenced by the temperature and polarity of solvents. Judging from ^{1}H NMR spectra of 8-phenyl(thiocarbamoyl)-3-phenyl-6,7-dihydro-5H-thiazolo[3,2-a] pyrimidinium-betaine as shown Figure 1, it is found that is more dissociated according as temperature is increased. At 273°K degree of dissociation is about half, but it is completely dissociated at 330°K. This dissociation occurs in $CDCl_3$, but don't occur in $C_2D_2Cl_4$ that is less polar solvents than $CDCl_3$.

The biheterocyclic betaines also can be used as nucleophile by virtue of negative charge. Accordingly, quarternary ammonium salt is formed from reaction with alkyl halide.

In this reaction S-or O-alkylation in compared with N-alkylation occurs exclusively because of steric hindrance and inductive effect by neighbouring group. The biheterocyclic betaine of methyl isothiocyanate **4-e** reacted with methyl iodide to give S-alkylated quarternary ammonium salt **5-b** at room temperature. However 8-methylcarbamoyl-3-methyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidinium-betaine **4-f** with methyl iodide led to 8-methyl-3-methyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidinium iodide **6-b** via bond cleavage instead of O-alkylation as shown Scheme **2**.



Scheme 2.

This dissociation of bond was detected in polar solvents as acetone even though room temperature. When the reaction of compound **4-e** with methyl iodide was carried out in acetonitrile, which is less polar than acetone, S-alkylated quarternary ammonium salt 8-(C-methylthio-N-methyl-formimidoyl)-3-methyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidinium iodide **5-b** was obtained. At that time ^{1}H NMR spectrum indicates that the dissociation takes place in polar nmr solvents DMSO-d_6 as shown Figure 2.

As a result, it was found that temperature and polarity solvents have influence on stabilities of betaine compounds and quarternary ammonium salt formed by treatment of biheterocyclic betaines with alkyl halide.

In 1976 it was reported[14,15] that the reaction of phenacyl bromide **8** with the bicyclic zwitterionic thiazole does not yield the bromide **9**, instead ring opening and renewed cyclization affords the biheterocyclic compound **7'** via ring transformation.

In this work, for the purpose of indirect indentification the reaction of biheterocyclic betaine **4'** with p-methoxy-phenacyl

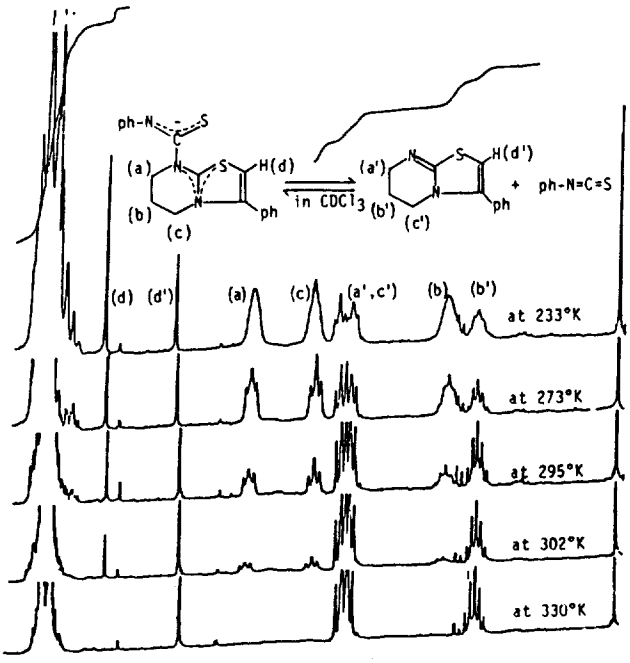


Figure 1. ^{1}H NMR spectra of 8-phenyl (thiocarbamoyl)-3-phenyl-6,7-dihydro-5H-thiazolo[3,2-a] pyrimidinium-betaine.

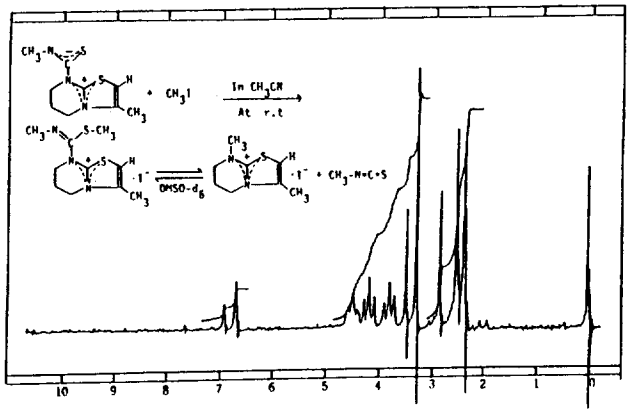
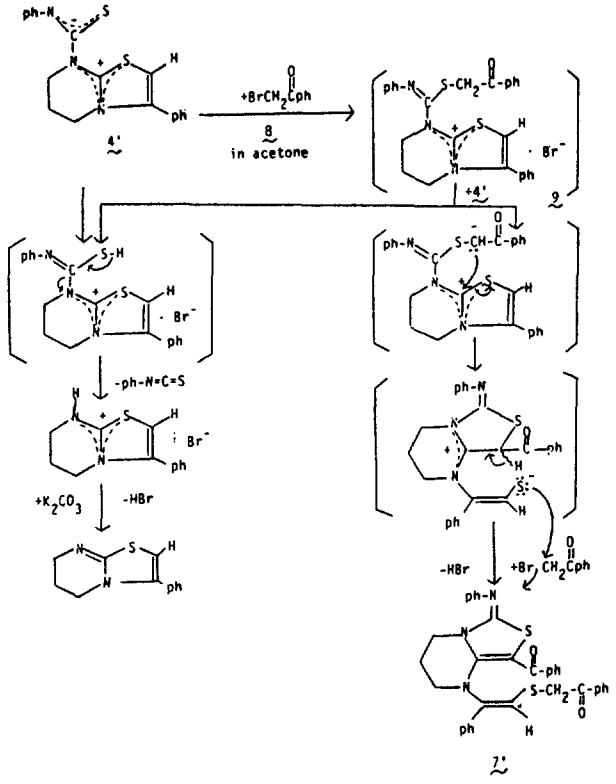
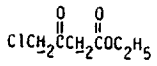


Figure 2. ^{1}H NMR spectrum of 8-(C-methylthio-N-methyl-formimidoyl)-3-methyl-6,7-dihydro-5H-thiazolo [3,2-a] pyrimidinium iodide (5-b).



bromide in place of phenacyl bromide was carried out. In ^1H NMR spectrum two of singlet at δ 3.73 (3H, s, OCH_3) and δ 3.87 (3H, s, OCH_3) suggest that reaction is carried out via ring transformation above.

Furthermore to extend the reaction, 8-phenyl(thiocarbamoyl)-3-phenyl-6,7-dihydro-5H-thiazolo[3,2-a]pyrimidinium-betaine was reacted with α-chloroacetone, ethyl bromoacetate and ethyl 4-chloro acetoacetate such as α-haloketone, α-haloester and γ-halo keto ester to give new biheterocyclic compounds via ring transformation. On the occasion of ethyl 4-chloro acetoacetate **10**, it was accomplished reaction not by the more acidic hydrogen abstract of C_2 but by the hydrogen abstract of C_4 because of steric hindrance same as the before.



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These biheterocylic compounds were characterized by spectrometric methods.

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