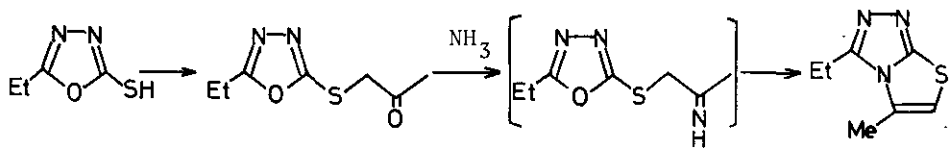
S-PHENACYLATION OF 6-METHYL-4-OXO-2-THIO-2,3-DIHYDRO-4H-1,3-OXAZINE AND THE RING TRANSFORMATION OF THE S-PHENACYLATED COMPOUND

Tadashi Sasaki,* Eikoh Ito, and Koji Asai
Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464, Japan

Abstract 1,3-Oxazine 1 reacted with phenacyl bromide in water using sodium hydroxide as a base to give S-phenacylated derivative 2, but the homogeneous conditions such as NaH in THF or NaOMe in methanol caused the base-induced cycloreversion of 1, resulting in the formation of thiocyanate 3. For the purpose of the intramolecular transformation to pyrimidine-fused heterocycle 11, 2 was treated with ammonia in refluxing ethanol, but gave amidamine 6 while 8 was obtained with ammonium acetate in refluxing acetic acid. Although the direct ring closure failed, the target 11 was finally synthesized by the cyclodehydration of ketamide 7 with phosphorus pentoxide at 250°C.

Previously we have demonstrated the intramolecular displacement of oxygen in the 1,3,4-oxadiazole ring with the imine nitrogen derived from the reaction of S-connected side chain



eq 1

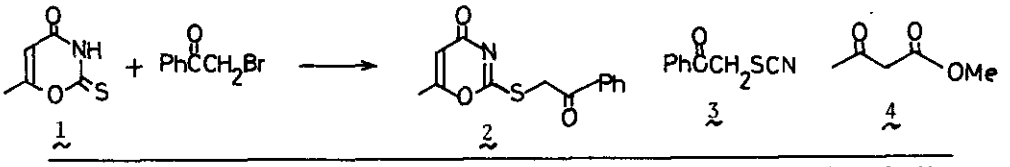
ketone and ammonia as shown in eq 1.[1] To explore such a transformation systematically, we have turned our attention to six membered ring, 6-methyl-4-oxo-2-thio-2,3-dihydro-4H-1,3-oxazine (1), which possesses cyclic vinyl imino-ether moiety for the desired ring transformation and which, in fact, was reported to be converted into 6-methyl-2-thiouracil on treatment with ammonia as the intermolecular case.[2] For this purpose we here report at first S-phenacylation of 1, and secondly the reaction of S-phenacyl derivative 2 with amines in

which the direct ring closure was not realized. It was finally performed by cyclodehydration of the intermediate ketamide with phosphorus pentoxide

RESULTS AND DISCUSSION

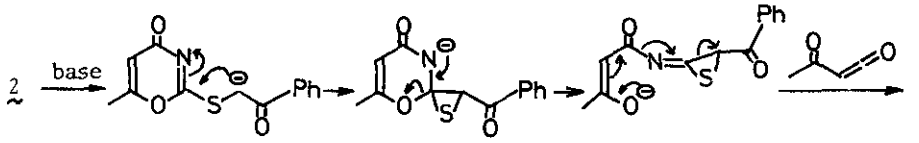
S-Phenacylation of 1 The reaction of 1 with phenacyl bromide under various conditions was examined as shown in Table. When phenacyl bromide was added to a suspension of 1 and NaH in THF, it gave both 34% of thiocyanate 3 and 17% of desired S-phenacylated product 2 after the

Table. The reaction of 1 with phenacyl bromide



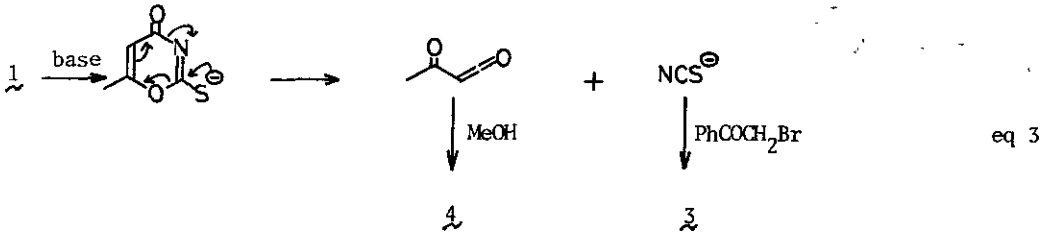
run	base	solvent	conditions	isolated product (yield, %)
1	NaH	THF	rt 1 day	2 (17), 3(34)
2	NaOMe	MeOH	rt 12 h	3 (87), 4(29)
3	NaOH	H_2O	rt 1 day	2 (69)

separation by recrystallization (run 1). The reaction carried out in methanol containing NaOMe afforded none of 2, but only undesired 3 and 4 in 87 and 29% yields respectively (run 2). At first we assumed that 3 was derived by the Eschenmoser type reaction with a base after S-phenacylation as shown in eq 2.[3] However, this pathway was neglected because the parent



eq 2

oxazine 1 itself was found to give 4 in 57% yield when 1 was subjected to 1 equiv of NaOMe in methanol in the absence of phenacyl bromide. This result suggests that 3 and 4 were produced from the reaction of thiocyanate anion and phenacyl bromide and that of acetylketene and



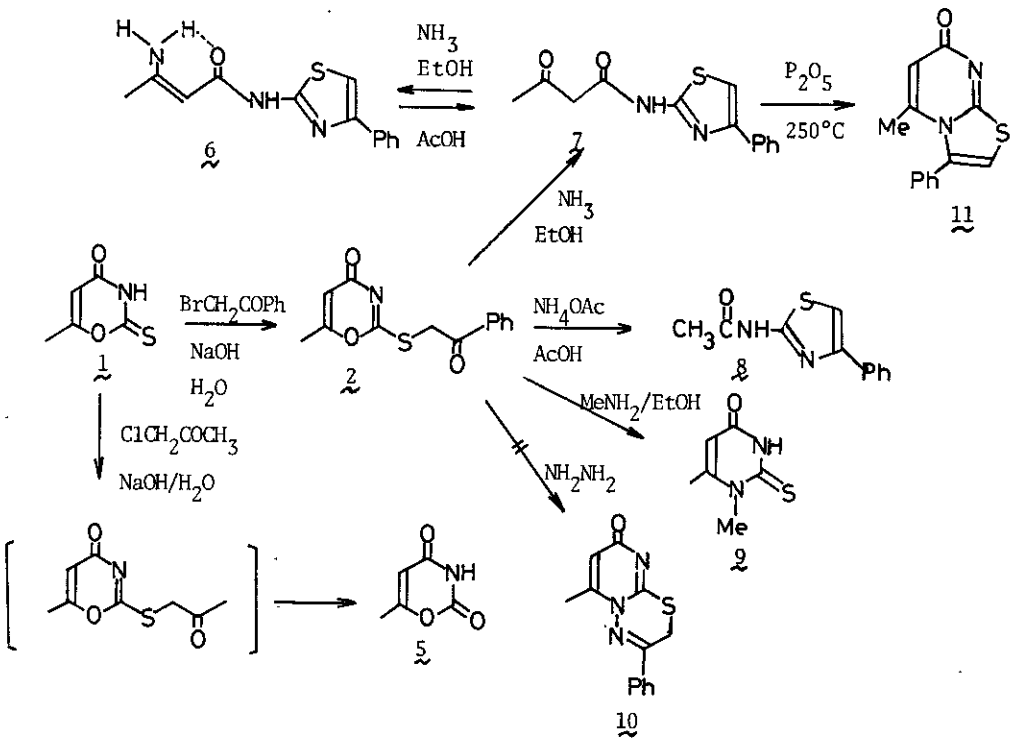
eq 3

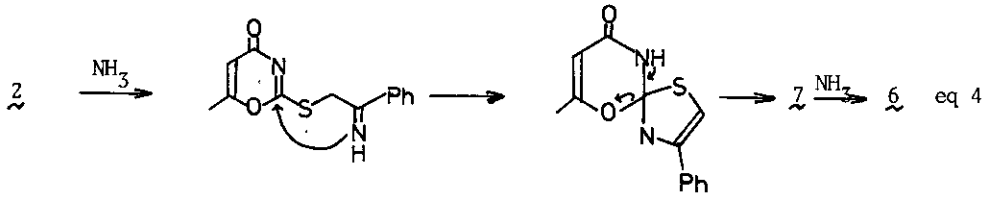
methanol, respectively as shown in eq 3. It is interesting to compare the present base-induced cycloreversion of 1 to acetylketene with the thermal one of related ring system, 4-oxo-1,3-dioxin.[4] After examining several bases such as triethylamine and pyridine, we could firmly

achieve successful S-phenacylation under the heterogeneous conditions (run 3): Phenacyl bromide was added soon after a mixture of 1 and 1 equiv of NaOH in water became a clear solution, and the product was recrystallized from chloroform - n-hexane to give pure 2 in 69% yield. However, addition of phenacyl bromide must not be delayed since the cycloreversion occurs slowly even in water. Structural assignment of 2 was based on elemental analysis and spectral data; The IR spectrum showed two strong carbonyl absorptions at 1690 and 1670 cm^{-1}. The ^1H NMR spectrum exhibited methylene and phenyl protons at δ 4.87 and 7.40-8.02, respectively. Selective S-phenacylation instead of N- or O-phenacylation was supported by further transformation of 2 to other heterocyles (vide infra). In contrast, S-acetonylation resulted in the formation of 2,4-dione derivative 5 in 86% yield (Scheme).[5] Presumably the homogeneous conditions throughout the reaction might be responsible for the hydrolysis of once formed S-acetonylated derivative to 5.

The Reaction of 2 with Amines Reaction of 2 with 5 equiv of ammonia in refluxing aqueous ethanol for 6 h, followed by the removal of the solvent afforded an oil, which on recrystallization from ethanol gave yellow crystals of mp 187-190°C in 50% yield. The structure of this compound was determined to be N-(4-phenylthiazol-2-yl)-3-aminocrotonamide (6) on the basis of spectral data and elemental analysis; The IR spectrum showed N-H absorption at 3450 and 3330 cm^{-1} and carbonyl absorption at 1620 cm^{-1}. The ^1H NMR spectrum exhibited three D_2O-exchangeable N-H protons at δ 4.70, 7.40, and 11.31. These three distinguishable N-H proton signals imply that 6 has a chelated amidamine structure due to the hydrogen-bonding as reported in the case of a ketamine.[7] Mechanism for the ring transformation of 2 to 6 is the same as proposed for the transformation of α-(oxadiazol-2-yl)thio or α-(oxazol-2-yl)thio ketones to s-triazole- or imidazole-fused heterocycles:[1,8] The initial condensation of the ketone function with ammonia gives imine. A subsequent attack of the imine nitrogen on the carbon-nitrogen double bond of the oxazine ring affords a spiro derivative, which collapses to ketamide 7. Finally 7 produces 6 on reacting with excess ammonia (eq 4). Thus, condensation of ketone function of ketamide 7 proceeded with excess ammonia intermolecularly rather than with the expected N-3 nitrogen of the thiazole ring arranged for the intramolecular cyclization. Treatment of 6 with acetic acid gave ketamide 7 in 80% yield, which was identified by a comparison of the IR spectrum with that of an authentic sample.[9] Next we examined the reaction with ammonium acetate in acetic acid which successfully converted α-(1,3,4-oxadiazol-2-yl)thioketone into thiazolo-s-triazole as indicated in eq 1.[1] However, treatment of 2 with 10 equiv of ammonium acetate in refluxing

Scheme





eq 4

acetic acid resulted in the formation of acetylaminothiazole 8 in 78% yield, which was identified by a comparison of its spectral data with those of the authentic sample.[10] The comparative experiment suggested that 8 was derived from the reaction of 7 with ammonium acetate in acetic acid.

With an expectation that methylamine also reacts with 2 to give a similar ketamide as 7, 2 was treated with methylamine in refluxing aqueous ethanol for 4 h. However, the product obtained was identified as 1,6-dimethyl-2-thiouracil (9).[11] In this case more basic methylamine promoted the C-S bond cleavage giving the parent oxazine 1, which subsequently reacted with excess methylamine to produce 9. Actually this pathway was supported by the fact that the reaction of the assumed intermediate 1 with methylamine in refluxing ethanol afforded 9 in 58% yield in the same manner as known transformation of 1 to 6-methyl-2-thiouracil with ammonia.[2]

Finally, we examined the transformation of 2 into pyrimidothiadiazine 10 with hydrazine. Unfortunately treatment of 2 with hydrazine hydrate in ethanol or in acetic acid resulted in the formation of complex mixtures in contrast to the successful converstion of α-(1,3,4-oxadiazol-2-yl)thio or α-(oxazol-2-yl)thioketones into s-triazole- or imidazole-fused thiadiazines with hydrazine.[1,8]

7H-Thiazolo[3,2-a]pyrimidin-7-one ring system, which is known as a useful antifungal, amebicidal, and antiinflammatory agent,[12] has been synthesized in two ways; one involves the condensation of 2-thiouracil with α-haloketone[13] and the other consists of the reaction of 2-aminothiazole and propiolic ester.[14] Although as mentioned above, the direct one step transformation of 2 to these pyrimidine-fused heterocycles was unsuccessful, it is worth to attempt the further cyclization of 7 to 11. As the preceding result, Ohta reported that the cyclodehydration of 7 to thiazolopyrimidine 11 was unsuccessful on heating or acid treatment.[9] We have also examined various acidic (conc. H_2SO_4, PPA, P_2O_5 in benzene, CF_3COOH), basic (KOH in aqueous ethanol, n-BuLi in THF), and neutral (DCC or otherwise simple heating) conditions, but these efforts were in vain. After all heating a mixture of 7 and phosphorus pentoxide without solvent at 250°C for 2 h gave the desired 11 in 24% yield. The structure of 11 was confirmed by its spectral data and elemental analysis; The IR spectrum showed a new single carbonyl absorption at 1685 cm^{-1}, and ^1H NMR spectrum exhibited methyl protons at δ 2.29, two olefinic protons at δ 6.05 and 7.31, and phenyl protons at δ 7.30-8.20. These data are in good agreement with those of 7H-thiazolo[3,2-a]pyrimidin-7-one ring system

reported by Dunwell and Evans.[14] Notably, the present cyclization of 7 to 11 complements the condensation reaction of 6-methyl-2-thiouracil and phenacyl bromide, in which methyl substituent sterically obliged the cyclization at N-3 nitrogen to isomeric 7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one derivative rather than at N-1 nitrogen to 11.[13]

EXPERIMENTAL

Melting points were measured with a Yanagimoto micro-melting-point apparatus and are uncorrected. Microanalyses were performed with a Perkin-Elmer 240 B elemental analyzer. The ^{1}H NMR spectra were taken at room temperature with a JEOL C-60-HL spectrometer with tetramethylsilane as an internal standard. The IR spectra were taken with JASCO-A-100 spectrometer.

The reaction of 1 with phenacyl bromide (A) In the presence of NaH A suspension of 1 (290 mg, 2 mM) and NaH (80 mg, 2 mM) in dry THF (15 ml) was stirred for 20 min, to which was added phenacyl bromide (400 mg, 2 mM) in one portion at room temperature. After stirring at room temperature for 1 day, the solvent was removed under reduced pressure to give a yellow oil, which solidified by adding saturated sodium bicarbonate. Fractional recrystallization of the collected products from chloroform - n-hexane gave 90 mg (17%) of 2 and 120 mg (34%) of 3: 2, mp 185-187°C; IR (KBr) 1690, 1670 (C=O) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 2.22 (s, 3H, CH_3), 4.78 (s, 2H, CH_2), 5.19 (s, 1H, =CH-), 7.40-8.20 (m, 5H, Ph). Anal. Calcd for $C_{13}H_{11}NO_2S$: C, 59.76; H, 4.24; N, 5.36. Found: C, 59.71; H, 4.26; N, 5.39.

(B) In the presence of NaOMe A solution of 1 (430 mg, 3 mM) and NaOMe (170 mg, 3 mM) in dry methanol (15 ml) was stirred for 20 min, and then to this solution was added phenacyl bromide (600 mg, 3 mM) in dry methanol (15 ml) dropwise at room temperature. After stirring for 12 h, the solvent was removed under reduced pressure. To the residue was added 30 ml of saturated brine and the products were extracted with chloroform (30 ml). The organic layer was dried over anhydrous magnesium sulfate and concentrated to give a yellow oil, which was chromatographed on silica gel column using $CHCl_3$/EtOH = 30/1 as the eluent to afford 460 mg (87%) of 3 and 100 mg (29%) of 4. Under the same conditions except for the absence of phenacyl bromide and stirring for 30 min, 4 was obtained in 57% yield.

(C) In the presence of NaOH A mixture of 1 (3.0 g, 21 mM) and NaOH (890 mg, 21 mM) in water (50 ml) was stirred at room temperature until 1 was dissolved. To this solution was added phenacyl bromide (4.2 g, 21 mM) in one portion. After stirring at room temperature for 1 day, the product was separated by filtration and recrystallized from chloroform -

n-hexane to give 3.8 g (69%) of 2.

The reaction of 1 with chloroacetone A mixture of 1 (330 mg, 2.1 mM) and NaOH (90 mg, 2.1 mM) in water (20 ml) was stirred at room temperature until 1 was dissolved. To this solution was added chloroacetone (0.17 ml, 2.1 mM) and stirring was continued at room temperature for 1 day. Then the products were extracted with chloroform (30 ml). The organic layer was dried over anhydrous magnesium sulfate and concentrated to give 230 mg (87%) of 5: mp 228-232°C[15] (lit.[6] 237-238°C).

N-(4-Phenylthiazol-2-yl)-3-aminocrotonamide (6) A solution of 2 (200 mg, 0.77 mM) and 28% aqueous ammonia (0.26 ml, 3.9 mM) in ethanol (10 ml) was refluxed for 3 h. The solvent was removed under reduced pressure to leave an oil, which was recrystallized from ethanol affording 100 mg (50%) of 6: mp 187-190°C; IR (KBr) 3450, 3330 (N-H), 1620 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.83 (s, 3H, CH_3), 4.70 (br s, 1H, NH, D_2O-exchangeable), 7.20-8.10 (m, 7H, Ph and 2 ✕ =CH-), 7.40 (br s, 1H, NH, D_2O-exchangeable), 11.31 (br s, 1H, NH, D_2O-exchangeable). Anal. Calcd for $C_{13}H_{13}N_3OS \cdot 1/5\ C_2H_5OH$:[16] C, 59.93; H, 5.33; N, 15.65. Found: C, 59.99; H, 5.46; N, 15.49.

2-Acetylamino-4-phenylthiazole (8) from 2 A solution of 2 (260 mg, 1 mM) and ammonium acetate (770 mg, 10 mM) in acetic acid (2 ml) was refluxed for 9 h. After cooling to room temperature, the reaction mixture was poured into 40 ml of water. Filtration of the precipitates gave 170 mg (78%) of crude 8: mp 215-217°C[15] (EtOH) (lit.[10] 213°C).

2-Acetylamino-4-phenylthiazole (8) from 7 A solution of 7 (150 mg, 0.6 mM) and ammonium acetate (440 mg, 5.7 mM) in acetic acid (4 ml) was refluxed for 4 h. After cooling to room temperature, the reaction mixture was poured into 40 ml of saturated brine and allowed to stand at room temperature overnight. The precipitates were separated by filtration to give 120 mg (100%) of 8.

2-Acetoacetylamino-4-phenylthiazole (7) A solution of 6 (90 mg, 0.34 mM) in acetic acid (1 ml) was heated at 85°C for 2 min and poured into 20 ml of water after cooling to room temperature. Filtration of the resulting precipitates gave 70 mg (80%) of 7: mp 180-182°C[15] (EtOH) (lit.[9] 172°C). Compound 7 was also obtained by the direct treatment of the crude oil of 6 with acetic acid in 80% overall yield from 2.

1,6-Dimethyl-2-thiouracil (9) A solution of 2 (300 mg, 1.1 mM) and 40% aqueous methylamine (0.5 ml, 5.5 mM) in ethanol (20 ml) was refluxed for 4 h. After removal of the solvent 20 ml of water was added to the residue and the product was extracted with chloroform (30 ml).

The organic layer was dried over anhydrous magnesium sulfate and concentrated to give a brown oil, which was washed with ether to afford 80 mg (45%) of crude 9: mp 225-230°C[17] (lit. 235-245°C,[18] 258-260°C[11]). The reaction of 1 with methylamine under the same conditions as above gave 9 in 58% yield.

3-Phenyl-5-methyl-7H-thiazolo[3,2-a]pyrimidin-7-one (11) A mixture of 7 (500 mg, 1.9 mM) and phosphorus pentoxide (660 mg, 4.6 mM) was heated at 250°C for 1.5 h. After cooling to room temperature, 30 ml of water was added to the reaction mixture and stirring was continued for 30 min. The insoluble products were separated by filtration and extracted with hot ethanol (20 ml × 3). Removal of the ethanol gave 110 mg (24%) of 11. An analytical sample was obtained by recrystallization from ethanol: mp 199-203°C; IR (KBr) 1685 (C=O) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.29 (s, 3H, CH_3), 6.05 (s, 1H, =CH-), 7.31 (s, 1H, =CH-), 7.15-8.20 (m, 5H, Ph). Anal. Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.24; H, 4.41; N, 11.50.

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15. Its spectral data are in good agreement with those of the authentic sample prepared according to the procedure described in the literature.

16. Compound 6 invariably crystallized with inclusion of 1/5 mol of ethanol, which was also observed by ^{1}H NMR.

17. Its spectral data are in good agreement with those reported in the literature.

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Received, 13th February, 1983