mol, in 15 mL of water). The reaction mixture was stirred at 0 °C for 30 min, filtered, and diluted with 150 mL of water. The resulting mixture was filtered. The filtrate was poured onto 200 g of ice to give 5.8 g of red crystals. The crude product was recrystallized by dissolving in 12 mL of warm chloroform and precipitating with 25 mL of hexane, giving 4.9 g (40%) of **3f** as red crystals: mp 118–119 °C; ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3 H), 3.14 (s, 6 H), 6.62 (s, 1 H), 7.1–7.4 (m, 3 H), 7.5–7.8 (m, 2 H).

Anal. Calcd for $C_{12}H_{15}NS$: C, 70.2; H, 7.36; N, 6.82; S, 15.6. Found: C, 70.3; H, 7.03; N, 6.77; S, 15.4.

5-*p*-Tolylisoxazole (5a).[11] Typical Procedure for 5a–d. To a solution of 3.78 g (0.020 mol) of **2a** in 50 mL of absolute methanol at 0 °C was added a solution of 2.48 g (0.022 mol) of hydroxylamine-*O*-sulfonic acid in 20 mL of absolute methanol over a period of 2 min. After being stirred at room temperature for 20 min, the reaction mixture was poured into a mixture of cold saturated sodium bicarbonate solution (160 mL) and ice–water (140 mL). The resulting reaction mixture deposited 2.60 g (82%) of **5a** as off-white crystals: mp 60–61 °C (lit.[11] mp 58–60 °C); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3 H), 6.43 (d, J = 2 Hz, 1 H), 7.24 (d, J = 8 Hz, 2 H), 7.66 (d, J = 8 Hz, 2 H), 8.22 (d, J = 2 Hz, 1 H); IR (KBr) 3140, 3100, 1620, 1600, 1510, 1460, 1200, 1320, 1070, 1020, 940, 920, 880, 830, 800 cm^{-1}.

5-*p*-Tolylisothiazole (6a).[31] Typical Procedure for 6a–f. To a stirred suspension of 2.05 g (0.010 mol) of **3a** in a mixture of 1.6 mL (0.020 mol) of pyridine and 75 mL of absolute ethanol at room temperature was added a solution of 1.30 g (0.0115 mol) of hydroxylamine-*O*-sulfonic acid in 20 mL of absolute methanol over a period of 2 min. The temperature of the reaction was maintained with a water bath. The reaction mixture was stirred at room temperature for 0.5 h. The solvents were removed under reduced pressure at room temperature to leave a residue which was partitioned between 30 mL of water and 150 mL of ether. The aqueous layer was extracted with another 50 mL of ether. The combined ether solution was washed with 30 mL of saturated sodium bicarbonate solution and dried over Na_2SO_4 (for **6f** the reddish ether solution of the crude product was decolorized with activated carbon (Darco)). After removal of the ether, the residue (1.31 g) was recrystallized from 15 mL of hexane to give 1.14 g (65%) of **6a** as slightly tan crystals: mp 83–84 °C (lit.[31] no melting point reported); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3 H), 7.24 (d, J = 8 Hz, 2 H), 7.36 (d, J = 2 Hz, 1 H), 7.48 (d, J = 8 Hz, 2 H), 8.42 (d, J = 2 Hz, 1 H); mass spectrum, m/e 175 (M^+); IR (KBr) 1495, 1410, 1310, 1240, 1120, 1060, 840, 800, 750, 480 cm^{-1}.

Anal. Calcd for $C_{10}H_9NO$ (175.25): C, 68.5; H, 5.18; N, 7.99; S, 18.3. Found: C, 68.2; H, 5.23; N, 8.05; S, 18.6.

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Registry No. 2a, 18103-98-5; **2b**, 18096-70-3; **2c**, 28587-05-5; **2d**, 73387-60-7; **2e**, 1201-93-0; **2f**, 34523-87-0; **3a**, 31639-16-4; **3b**, 40185-70-4; **3c**, 31639-15-3; **3d**, 31639-14-2; **3e**, 24301-15-3; **3f**, 75101-71-2; **5a**, 7064-35-9; **5b**, 3672-48-8; **5c**, 7064-32-6; **5d**, 7064-31-5; **6a**, 49602-75-7; **6b**, 10514-28-0; **6c**, 49602-89-3; **6d**, 49602-97-3; **6e**, 1075-21-4; **6f**, 1732-45-2; **7a**, 7089-19-2; **7b**, 39812-29-8; **7c**, 7089-20-5; **7d**, 52117-14-3; **7e**, 39812-71-0; **7f**, 75101-73-4; *p*-methylacetophenone, 122-00-9; *p*-methoxyacetophenone, 100-06-1; *p*-chloroacetophenone, 99-91-2; *p*-bromoacetophenone, 99-90-1; acetophenone, 98-86-2; *N*,*N*-dimethylformamide dimethyl acetal, 4637-24-5; *N*,*N*-dimethylformamide diethyl acetal, 1188-33-6; *N*,*N*-dimethylacetamide dimethyl acetal, 18871-66-4; (γ-chloro-*p*-methylcinnamylidene)dimethylammonium phosphorodichloridate, 72633-12-6.

Reaction of β-Keto Esters with 2-Amino-1,3,4-thiadiazoles. A Reinvestigation[1]

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2-Amino-5-substituted-1,3,4-thiadiazoles react with ethyl acetoacetate under basic conditions to give 3-oxo-*N*-(5-substituted-1,3,4-thiadiazol-2-yl)butanamides **4**.[2] During acid cyclization, **4** rearranges to give a mixture of thiadiazolopyrimidones **3** and **5**, the ratio varying with the nature of the substituents. Under acidic conditions, the butenoic ester **2** can also be isolated; however, it does not rearrange and yields only the expected **3**. With ethyl benzoylacetate under acidic and basic conditions, only one compound is formed whose structure was determined as the enol form of **4d** by X-ray diffraction. In strong acid, it also cyclizes and rearranges to give a mixture of **3** and **5** in a 9:1 ratio.

The reactions of 2-amino-5-substituted-1,3,4-thiadiazoles **1** with β-keto esters have been previously investigated by Okabe et al.,[2] who found that in the presence of polyphosphoric acid (PPA) 2,7-substituted-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-ones **3** were obtained (Scheme I). With ethyl acetoacetate (AAE) in the presence of sodium methoxide (NaOMe) 3-oxo-*N*-(5-substituted-1,3,4-thiadiazol-2-yl)butanamides **4a** and **4b** were isolated which, on cyclization in sulfuric acid (H_2SO_4), gave 2,5-substituted-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-ones **5a** and **5b**.[3]

The reaction of **1f** with AAE in toluene[4] and a catalytic amount of *p*-toluenesulfonic acid monohydrate (TosOH) yielded a mixture of the ethyl ester of 3-[(1,3,4-thiadiazol-2-yl)amino]-2-butenoic acid **2f** and **3f**.

We now report that the H_2SO_4 cyclization of **4** gives rise to a mixture of isomers and also our new findings concerning the reactivity of ethyl benzoylacetate (BAE) with **1**.

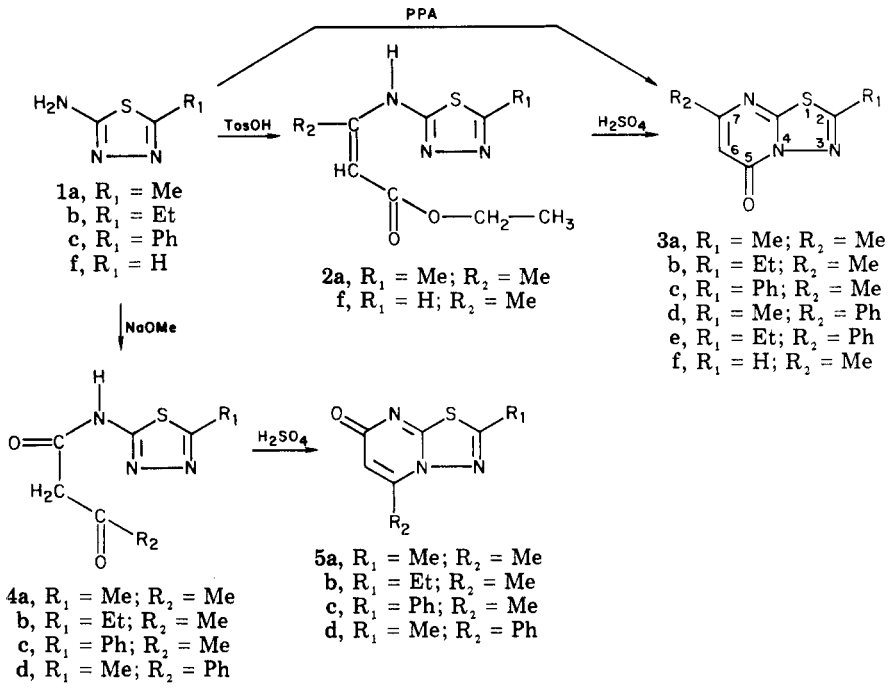
Results and Discussion

In our hands the H_2SO_4 cyclization of **4a** gave not only **5a** but also the isomeric **3a**, the latter identical in all respects with the product obtained from the PPA cyclization of **1a** with AAE. As the intermediate **4a** was rigorously

(1) Presented in part at the Second Chemical Congress of the North American Continent, Las Vegas, NV, August 1980, Abstract no. 90.
(2) Okabe, T.; Taniguchi, E.; Maekawa, K. *J. Fac. Agric., Kyushu Univ.* **1973**, *17*, 195-202.
(3) Okabe, T.; Maekawa, K.; Taniguchi, E. *Agric. Biol. Chem.* **1973**, *37*, 1197-1201.
(4) Lauer, R. F.; Zenchoff, G. *J. Heterocycl. Chem.* **1976**, *13*, 291.

0022-3263/80/1945-4860$01.00/0

Scheme I



purified and identified, the presence of intermediate **2a** which would lead to **3a** can be ruled out. It is therefore concluded that a rearrangement had taken place. To establish whether intermediate **2a** also rearranges, it was cyclized under the same conditions as for **4a**, but only the expected **3a** was obtained despite strenuous efforts to detect even a trace of **5a**. Similarly, when **1a** was reacted with AAE in the presence of TosOH in refluxing toluene, or in PPA at 135 °C, only **3a** could be isolated, identical in all respects with the product obtained from the H_2SO_4 cyclization of **2a**.

A number of analogues **4b** and **4c** were synthesized and highly purified to verify the generality of the **4** to **3** rearrangement. Cyclization under the usual conditions afforded a mixture of **5b,c** and **3b,c**. The isomer distribution was obtained by NMR analysis on the crude reaction mixtures and was as follows: **5a**, 70%; **3a**, 30%; **5b**, 80%; **3b**, 20%; **5c**, 92%; **3c**, 8%. Similar rearrangements are known to occur with aminopyridines[5] and thiadiazoles[4] to yield, however, only one isomer.

The only reaction of **1** with BAE was reported by Okabe et al.,[2] who found that in the presence of PPA **3d** and **3e** were formed. We confirmed this result but found that the reaction of **1a** with BAE in refluxing toluene in the presence of TosOH or in MeOH–NaOMe yielded a highly insoluble product which was shown by X-ray crystallography to be the enolic form of **4d** (see also Figure 1).

Cyclization of **4d** in H_2SO_4 gave a mixture of **3d** and **5d**. While the isolation of a mixture of both isomers is a further example of the rearrangement described above, there is a notable difference. With BAE, the percentage of **3d** and **5d** is 90 and 10, respectively, while with AAE the percentage of **3a** and **5a** is 30 and 70, respectively. One explanation for this reversal is the deactivating effect of the phenyl group leading to enhanced 1,3 acyl migration.

The structure proof for **5d** is based on its similarity to **5a** and dissimilarity to **3a**. Thus, compounds **5** when compared to compounds **3** have a higher melting point, are more polar on silica gel, and absorb in the IR at about 1640

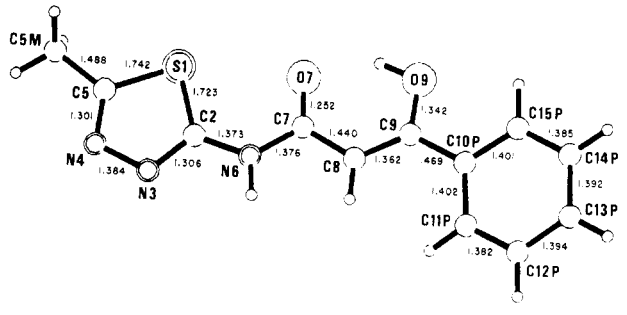


Figure 1. Numbering, conformation, and bond lengths (Å) for **4d**. Standard deviations for bond lengths are 0.002–0.004 Å.

cm^{-1} (**3** absorb at about 1680 cm^{-1}),[6] and in the NMR spectrum the 5-Me group and 6-H are more shielded. From the limited number of compounds synthesized in this series, it also appears that when R_2 is phenyl, the aromatic region for **5** is a very narrow multiplet centered at about δ 7.6, while for **3** the aromatic region shows two distinct broad multiplets centered at δ 7.4 and 7.9.

It is therefore concluded that in the presence of TosOH **1a** reacts with AAE on the ketonic function to give **2a** which, on treatment with H_2SO_4, cyclizes exclusively to **3a**. In the presence of NaOMe, however, nucleophilic attack on the carboethoxy group yields the intermediate **4a** which cyclizes through partial rearrangement to a mixture of mainly **5a** and **3a**. In contrast, the reaction of **1a** with BAE occurs exclusively on the carboethoxy group, with TosOH or NaOMe, to give the inter- and intramolecularly hydrogen-bonded intermediate **4d**. **4d** on acid cyclization also partially rearranges to a mixture of **5d** and **3d**; the major constituent, however, is the rearranged **3d**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were

(5) Kato, T.; Yamanaka, H.; Niitsuma, T.; Wagatsuma, K.; Oizumi, M. *Chem. Pharm. Bull.* **1964**, *12*, 910.

(6) Okabe, T.; Taniguchi, E.; Maekawa, K. *J. Fac. Agric., Kyushu Univ.* **1975**, *20*, 7.

(7) We have no explanation for the discrepancy in melting point. In our hands, three procedures furnished the same product with a melting range between 193 and 200 °C.

recorded on a Perkin-Elmer 137 or 299B instrument. ^1H NMR spectra were recorded on a Varian A-60D or HFT-80 spectrometer, using tetramethylsilane as an internal standard. Mass spectra were obtained with a Varian MAT CHF mass spectrometer. GC was done on a Hewlett-Packard Model 5830A linked to a Model 18850A terminal, using a 4-ft glass column with 3% UCW 982 on Chromosorb WHP (100–120 mesh). Chromatography was on gravity columns or two in series Merck Lobar size C high-pressure LC columns. Organic phases were dried over sodium sulfate and evaporated under reduced pressure. The following starting thiadiazoles were made by literature procedures: **1a**,[8,9] **1b**,[8] **1c**,[8,10] **1d**.[4]

Ethyl 3-[(5-Methyl-1,3,4-thiadiazol-2-yl)amino]-2-butenoate (2a). To a vigorously stirred suspension of 2-amino-5-methyl-1,3,4-thiadiazole (**1a**, 5.75 g, 0.05 mol) in benzene (400 mL) were added ethyl acetoacetate (13.0 g, 0.1 mol) and TosOH (0.38 g, 0.002 mol). The reaction vessel was equipped with a Dean–Stark trap and the mixture heated under reflux for 26 h. The white solid (4.4 g) was filtered and identified as starting material by its melting point and mixture melting point of 210–213 °C, identical TLC behavior in three solvent systems, and same retention time on GC. The filtrate was evaporated and chromatographed on silica gel in ethyl acetate. The least polar fractions were combined to yield **2a** (1.6 g, 60%) which was recrystallized twice from ethyl acetate–Skelly B and once from methylene chloride–Skelly B, mp 50–52 °C. The absence of **1a**, **3a**, **4a**, and **5a** was ascertained by TLC and GC: IR ($CHCl_3$) 2980, 1625, 1480, 1270, 1145 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, 3, CH_3CH_2), 2.42 (s, 3, CH_3), 2.67 (s, 3, CH_3), 4.20 (q, 2, CH_2CH_3), 4.95 (s, 1, C=CH).

Anal. Calcd for $C_9H_{13}N_3O_2S$: C, 47.56; H, 5.76; N, 18.49; S, 14.11. Found: C, 47.86; H, 5.54; N, 18.41; S, 14.02.

2,5-Dimethyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (5a) and 2,7-Dimethyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3a). Procedure A. 3-Oxo-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)butanamide (**4a**,[2] 4.6 g, 0.023 mol) in concentrated sulfuric acid (15 mL) was kept at 60 °C for 5.5 h, cooled, poured on ice (200 mL), basified with sodium carbonate, and extracted with chloroform (4 × 60 mL). The combined extracts were washed with brine and dried and the solvent was removed to yield a solid (3.6 g, 99%). This consisted of a mixture of **5a** (70%) and **3a** (30%) (NMR), which upon recrystallization from methanol, then toluene, and finally Skellysolve B yielded **5a** (1.2 g, 33%): mp 191–194 °C (lit.[3] mp 189.5 °C); IR ($CHCl_3$) 2990, 1635, 1505, 1450, 1416, 1235, 1173, 950, 860, 830, 660, 620 cm^{-1}; NMR ($CDCl_3$) δ 2.53 (sh s, 3, CH_3), 2.68 (s, 3, CH_3), 6.15 (sh s, 1, CH).

Anal. Calcd for $C_7H_7N_3OS$: C, 46.39; H, 3.89; N, 23.23. Found: C, 46.65; H, 3.82; N, 23.34.

The combined mother liquors were chromatographed (high-pressure LC). Elution with toluene–ethanol (6:1) yielded **3a** (0.6 g, 16.6%) which, after crystallization from ethyl acetate–hexane, had mp 155–158 °C (lit.[3] mp 153–154 °C): IR ($CHCl_3$) 2990, 1685, 1565, 1495, 1430, 1392, 1360, 1185, 1131, 1000, 905, 839, 588 cm^{-1}; NMR ($CDCl_3$) δ 2.37 (s, 3, CH_3), 2.73 (s, 3, CH_3), 6.30 (s, 1, CH).

Anal. Calcd for $C_7H_7N_3OS$: C, 46.39; H, 3.89; N, 23.23. Found: C, 46.53; H, 3.59; N, 23.56.

Further elution with the same solvent system yielded **5a** (0.8 g, 22%) which, after recrystallization from toluene, had a melting point and mixture melting point of 190–193 °C with the **5a** isolated above by crystallization.

2,7-Dimethyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3a). A suspension of **2a** in concentrated sulfuric acid was reacted according to procedure A to give **3a** in an 80% yield, identical in all respects with the **3a** obtained from the H_2SO_4 cyclization of **4a**, or of **1a** with PPA.[2] The absence of **5a** in the crude product was ascertained by GC and TLC.

2-Ethyl-5-methyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (5b) and 2-Ethyl-7-methyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]-pyrimidin-5-one (3b). 3-Oxo-*N*-(5-ethyl-1,3,4-thiadiazol-2-yl)-butanamide (**4b**)[3] in concentrated sulfuric acid was reacted according to procedure A to give a 96% yield of a mixture of **5b** (80%) and **3b** (20%). Chromatography on silica gel and elution with ethyl acetate yielded **3b** which, after crystallization from toluene–hexane, had mp 110–113 °C (lit.[3] mp 112 °C): IR ($CHCl_3$) 2970, 1675, 1558, 1548, 1490, 1385, 1352, 1170, 1125, 895, 830 cm^{-1}; NMR ($CDCl_3$) δ 1.45 (t, 3, CH_2CH_3), 2.37 (s, 3, CH_3), 3.11 (q, 2, CH_2CH_3), 6.32 (m, 1, CH).

Anal. Calcd for $C_8H_9N_3OS$: C, 49.21; H, 4.65; N, 21.52; S, 16.42. Found: C, 49.02; H, 4.66; N, 21.42; S, 16.33.

Further elution with ethyl acetate–methanol (2:1) yielded **5b** which, after crystallization from ethyl acetate, had mp 158–160 °C (lit.[3] melting point not stated): IR ($CHCl_3$) 2965, 1625, 1495, 1440, 1405, 1185, 1123, 930, 850, 819, 650 cm^{-1}; NMR ($CDCl_3$) δ 1.42 (t, 3, CH_2CH_3), 2.53 (sh s, 3, CH_3), 3.02 (q, 2, CH_2CH_3), 6.18 (sh s, 1, CH).

Anal. Calcd for $C_8H_9N_3OS$: C, 49.21; H, 4.65; N, 21.52, S, 16.42. Found: C, 49.30; H, 4.97; N, 21.39; S, 16.24.

5-Methyl-2-phenyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (5c) and 7-Methyl-2-phenyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3c). Concentrated sulfuric acid and **4c** were reacted according to procedure A to give a 95% yield of a mixture of **5c** (92%) and **3c** (8%). Chromatography on silica gel and elution with ethyl acetate gave **3c** which, after crystallization from ethanol–water, had mp 193–196 °C (lit.[3] mp 169–172 °C[7]): IR ($CHCl_3$) 3000, 1703, 1692, 1575, 1505, 1490, 1450, 1400, 1366, 1270, 1132, 1100, 902, 840, 683 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3, CH_3), 6.35 (s, 1, CH), 7.50–7.80 (m, 3, Ar H), 7.85–8.17 (m, 2, Ar H).

Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.18. Found: C, 59.18; H, 3.60; N, 17.38; S, 13.45.

Further elution with the same solvent yielded **5c** which, after crystallization from ethanol, had mp 237–238 °C: IR ($CHCl_3$) 2973, 1630, 1621, 1500, 1480, 1438, 1405, 1273, 1186, 1172, 1125, 1090, 995, 989, 930, 850, 678, 650, 591 cm^{-1}; NMR ($CDCl_3$) δ 2.64 (sh s, 3, CH_3), 6.23 (sh s, 1, CH), 7.50–7.77 (m, 3, Ar H), 7.77–8.05 (m, 2, Ar H).

3-Hydroxy-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)-3-phenyl-2-propenamide (4d, Enol Form). Procedure B (TosOH Method). To a vigorously stirred suspension of **1a** (8.16 g, 0.075 mol) in toluene (200 mL) was added $PhCOCH_2COOEt$ (21.6 g, 0.112 mol) followed by TosOH (0.25 g, 0.00131 mol). The reaction vessel was equipped with a Dean–Stark head and the mixture was heated under reflux for 23 h. The mixture was cooled, and the precipitate was filtered (10.78 g, 55%) and recrystallized from DMF to give **4d** (3.6 g, 22%): mp 255–256 °C; IR (Nujol) 2900, 2705, 1610, 1560, 1455, 1400, 1373, 1310, 1270, 1210, 1195, 1080, 1005, 993, 973, 870, 827, 770, 749, 690, 629 cm^{-1}; NMR (Me_2SO) δ 2.67 (s, 3, CH_3), 4.38 (s, 2, CH_2), 7.50–7.87 (m, 3, Ar H), 7.87–8.22 (m, 2, Ar H), 12.33–12.66 (br s, 1, NH); mass spectrum, *m/e* (relative intensity) 105 (100), 77 (38), 115 (38), 142 (31), 147 (20), 69 (9), 233 (8), 191 (7), 51 (7), 74 (7).

Anal. Calcd for $C_{12}H_{11}N_3O_2S$: C, 55.15; H, 4.24; N, 16.08; S, 12.27. Found: C, 54.88; H, 4.50; N, 16.11; S, 12.16.

Procedure C (NaOMe Method). To a suspension of **1a** (8.7 g, 0.075 mol) in dry methanol (130 mL) was added sodium methoxide (4.46 g, 0.0825 mol) followed by $PhCOCH_2COOEt$ (15.86 g, 0.0825 mol) and the mixture was heated under reflux for 5 h. The reaction mixture was cooled, concentrated under reduced pressure, and acidified with 6 N HCl and the precipitate was filtered off to give **4d** (13.6 g, 70%) which, after recrystallization from DMF–H_2O, was shown to be identical by melting point, TLC, IR, mass spectra, and elemental analysis with the **4d** sample prepared above.

2-Methyl-7-phenyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3d) and 2-Methyl-5-phenyl-7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one (5d). (a) Concentrated H_2SO_4 and **4d**, made by the TosOH method, were reacted according to procedure A to give, in a 78% yield, a complex mixture which contained **3d** and **5d** in a ratio of 9 to 1. Chromatography over silica gel and elution with ethyl acetate gave **3d** which was crystallized from ethanol: mp 196–198 °C (lit.[3] mp 195.5 °C); IR ($CHCl_3$) 3000, 1685, 1587, 1557, 1515, 1487, 1449, 1382, 1372, 1243, 1183, 1130, 1100, 1027, 1010, 865, 845 cm^{-1}; NMR ($CDCl_3$) δ 2.75 (s, 3, CH_3), 6.87 (s, 1, CH), 7.28–7.62 (m, 3, Ar H), 7.78–8.12 (m, 2, Ar H).

Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.18. Found: C, 58.99; H, 3.56; N, 17.57; S, 13.29.

Further elution with toluene–ethanol (4:1) yielded **5d** which was crystallized from methylene chloride–Skellysolve B: mp 209–211 °C; IR ($CHCl_3$) 3010, 1640, 1581, 1520, 1496, 1455, 1421, 1269, 1238, 1195, 1182, 1140, 1112, 1068, 874, 700 cm^{-1}; NMR

(8) Bambas, L. L. *Chem. Heterocycl. Compd.* **1952**, *4*, 110–1.
(9) Freund, M.; Meinecke, C. *Chem. Ber.* **1896**, *29*, 2511.
(10) Hoggarth, E. *J. Chem. Soc.* **1949**, 1165.

Table I. Final Atomic Coordinates (× 10^4) and Standard Deviations for Compound 4d

	X	Y	Z
S (1)	7176 (1)	4180 (1)	206 (1)
C (2)	8298 (3)	2173 (4)	83 (1)
N (3)	9906 (2)	2194 (3)	408 (1)
N (4)	10364 (3)	3866 (3)	783 (1)
C (5)	9089 (3)	5031 (4)	725 (1)
C (5M)	9247 (3)	6917 (5)	1084 (1)
N (6)	7648 (2)	616 (3)	−317 (1)
C (7)	5966 (3)	293 (4)	−642 (1)
O (7)	4866 (2)	1485 (3)	−594 (1)
C (8)	5635 (3)	−1462 (4)	−1030 (1)
C (9)	4037 (3)	−1929 (4)	−1400 (1)
O (9)	2718 (2)	−772 (3)	−1417 (1)
C (10P)	3597 (3)	−3684 (4)	−1810 (1)
C (11P)	4706 (3)	−5280 (4)	−1721 (1)
C (12P)	4294 (3)	−6913 (4)	−2115 (1)
C (13P)	2756 (3)	−6989 (4)	−2610 (1)
C (14P)	1643 (3)	−5415 (5)	−2704 (1)
C (15P)	2049 (3)	−3785 (4)	−2305 (1)

($CDCl_3$) δ 2.63 (s, 3, CH_3), 6.42 (br s, 1, CH), 7.45–7.82 (m, 5, Ar H).

Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.18. Found: C, 58.43; H, 3.61; N, 17.35; S, 13.13.

(b) The above experiment was repeated, using **4d** prepared by the NaOMe method (procedure C); the isolated products **3d** and **5d** were identical in all respects with the **3d** and **5d** samples described above.

3-Oxo-*N*-(5-phenyl-1,3,4-thiadiazol-2-yl)butanamide (4c). By procedure C, **1c** was reacted with $AcCH_2COOEt$ to give **4c** (60%) which, after recrystallization from DMF–H_2O, had mp 239–241 °C: IR (Nujol) 3182, 2910, 2845, 1717, 1690, 1565, 1459, 1372, 1318, 1152, 684 cm^{-1}; NMR (Me_2SO) δ 2.26 (s, 3, CH_3), 3.85 (s, 2, CH_2), 7.52–7.77 (m, 3, Ar H), 7.92–8.17 (m, 2, Ar H).

Anal. Calcd for $C_{12}H_{11}N_3O_2S$: C, 55.15; H, 4.24; N, 16.08; S, 12.27. Found: C, 55.02; H, 4.26; N, 16.06; S, 12.47.

7-Methyl-2-phenyl-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-5-one (3c). To a suspension of **1c** (7.08 g, 0.04 mol) in polyphosphoric acid (30.0 g, 0.0887 mol) was added $AcCH_2COOEt$ (6.0 g, 0.0461 mol) and the mixture was placed in an oil bath at 135–140 °C for 1 h. The cooled reaction mixture was treated with ice water, stirred at room temperature for 1 h, and filtered. The precipitate was thoroughly washed with water, dried (6.4 g, 66%), and recrystallized twice from ethanol, mp 199–201 °C (lit.[3] mp 169–172 °C[7]). It was identical by melting point, IR, TLC, NMR, and elemental analysis with the **3c** sample prepared above from **4c**. The aqueous filtrate was extracted several times with chloroform, but only a negligible amount of oil was obtained which was discarded.

X-ray Crystallography. Crystal data for compound **4d** ($C_{12}H_{11}N_3O_2S$) were as follows: monoclinic, space group $P2_1/c$; $z = 4$; $a = 8.310$ (1) Å $b = 6.828$ (1) Å; $c = 21.611$ (3) Å; $\beta = 107.79$ (1)°; $D_{obsd} = 1.47$ g cm^{-3}; $D_{calcd} = 1.49$ g cm^{-3}; μ(CuK) = 23.3 cm^{-1}; 2011 reflections (1883 reflections with intensities greater than one standard deviation).

Intensity data for all reflections with $2\theta < 145°$ were collected by using the step-scan technique[11] at low temperature (about −155 °C) on a Syntex P$\bar{1}$ diffractometer controlled by an IBM 1800 computer using graphite monochromatized Cu Kα radiation (λ = 1.5418 Å). The data were corrected for systematic errors, including absorption.[12a] All calculations were carried out on an IBM 370 computer, using the CRYM system of crystallographic programs.[12b] The structure was solved by direct methods. Coordinates, except hydrogen coordinates, and anisotropic thermal parameters were refined by multiple-matrix crystallographic least squares, minimizing the function $\sum\omega(F_o^2 - F_c^{*2})^2$, where weights ω were taken as the reciprocals of the variances $\sigma^2(F_o^2)$ and where F_c^* was as defined by Larson.[13] A difference Fourier map clearly showed that all the hydrogens were very close to positions which could be generated by using standard geometry. Subsequently, hydrogens were included in the calculations at generated positions but were not refined. Atomic form factors are from "International Tables for X-ray Crystallography",[14] except for hydrogen form factors which are taken from Stewart, Davidson, and Simpson.[15] The final agreement index $R[R = \sum||F_o| - |F_c||/\sum|F_o|]$ was 0.051, and the standard deviation of fit was 2.68. The final value of the secondary extinction parameter g was 2.5 (2) × 10^{-6}.

Table II

atom	related atom	distance, Å	symmetry relation
O7	O9	2.605 (3)	internal hydrogen bond
O7	HO9	1.72 (2)	internal hydrogen bond
N3	N6	2.846 (3)	$2 - x, -y, -z$
N3	H6	1.85 (2)	$2 - x, -y, -z$
S1	C9	3.409 (3)	$1 - x, -y, -z$
S1	O9	3.483 (3)	$1 - x, -y, -z$
N3	C5	3.400 (3)	$2 - x, 1 - y, -z$
O9	C5M	3.291 (3)	$1 - x, 1 - y, -z$
O9	C2	3.380 (3)	$1 - x, -y, -z$
O7	C7	3.196 (3)	$1 - x, -y, -z$
O7	C11P	3.261 (3)	$x, y + 1, z$

Figure 1 shows the conformation of the molecule, the numbering, and bond distances not involving hydrogen. Final coordinates and standard deviations are listed in Table I. There is an intramolecular hydrogen bond between the hydroxyl and the carbonyl, and there is one intermolecular hydrogen bond between N6 in the chain and N3 in the thiadiazole ring of molecules related by a center of symmetry. Hydrogen-bond parameters and other intermolecular distances which are close to van der Waals separations are listed in Table II. The thiadiazole ring is planar; the propenamide chain atoms are in a plane tilted about 7° from the plane of the thiadiazole ring, and the plane of the phenyl ring is inclined 17.5° to the chain atoms and 10° to the thiadiazole ring. Distances in the thiadiazole ring and along the chain show shorter than normal lengths for single bonds and longer than normal double bond lengths, as would be expected in a highly conjugated system. Bond lengths in the thiadiazole ring are similar to those reported for other 1,3,4-thiadiazoles.[16-18]

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Registry No. 1a, 108-33-8; **1c**, 2002-03-1; **2a**, 75045-88-4; **3a**, 41914-67-4; **3b**, 41837-55-2; **3c**, 42484-83-3; **3d**, 42484-76-4; **4a**, 42484-67-3; **4b**, 42484-93-5; **4c**, 75045-89-5; **4d**, 75045-90-8; **5a**, 41837-62-1; **5b**, 55276-13-6; **5c**, 75045-91-9; **5d**, 65528-25-8; ethyl acetoacetate, 141-97-9; ethyl β-oxobenzenepropanoate, 94-02-0.

Supplementary Material Available: Table III (hydrogen coordinates), Table IV (anisotropic thermal parameters), and Table V (bond angles) (3 pages). Ordering information is given on any current masthead page.

(11) Duchamp, D. J. *ACS Symp. Ser., No. 46* **1977**, 98–121.
(12) (a) Busing, W. R.; Levy, H. A. *Acta Crystallogr.* **1957**, *10*, 180. (b) The CRYM system of crystallographic programs was written by David J. Duchamp, The Upjohn Company, Kalamazoo, MI.
(13) Larson, A. C. *Acta Crystallogr.* **1967**, *23*, 664–665.
(14) "International Tables for X-ray Crystallography"; Macgillavry, C. H., Rieck, G. D., Eds., Kynoch Press: Birmingham, 1962; Vol. III, pp 202–205.
(15) Stewart, R. F.; Davidson, E. R.; Simpson W. T. *J. Chem. Phys.* **1965**, *42*, 3175.
(16) Mathew, M.; Palenik, G. J. *J. Chem. Soc., Perkin Trans. 2* **1974**, 532–536.
(17) Flippen, J. L. *Acta Crystallogr., Sect. B* **1972**, *28*, 2749–2753.
(18) Downie, T. C.; Harrison, W.; Raper, E. S. *Acta Crystallogr., Sect. B.* **1972**, *28*, 1584–1590.