solution of 1.9 mL (11.0 mmol) of triflic anhydride in 15 mL of 9:1 ether–ethyl acetate was added dropwise over 15 min at 18–21 °C with ice-bath cooling to a solution of 1.51 g (10.0 mmol) of 2-(hydroxymethyl)-2-nitro-1,3-propanediol and 0.90 mL (11.0 mmol) of pyridine in 30 mL of 1:1 ether–ethyl acetate. The mixture was stirred at room temperature for 1 h, and the resulting precipitate was filtered and washed with ether. Sovent was removed, and the residue wash chromatographed on 111 g of silica gel (4:1 methylene chloride–ethyl acetate) to give 0.671 g (16.2%) of 2-(hydroxymethyl)-2-nitro-1,3-propylene ditriflate. Crystallization from methylene chloride–petroleum ether gave an analytical sample: mp 56–57 °C; ^{1}H NMR ($CDCl_3$) δ 2.70 (br s, 1 H, OH), 4.05 (s, 2 H, CH_2OH), 4.90 (s, 4 H, $CH_2OSO_2CF_3$); ^{19}F NMR ($CDCl_3$) ϕ 72.4 (s); IR (CH_2Cl_2) 3600 (OH), 1570, 1355 (NO_2), 1420, 1220, 1150, 830 (OSO_2CF_3), 980 cm^{-1} (CF).

Anal. Calcd for $C_6H_6F_6NSO_9$: C, 17.36; H, 1.70; N, 3.37. Found: C, 18.59; H, 1.75; N, 3.64.

Continued elution afforded 1.258 g (44.4%) of 3-hydroxy-2-(hydroxymethyl)-2-nitro-1-propyl triflate. Crystallization from methylene chloride–petroleum ether gave an analytical sample: mp 72–73 °C; ^{1}H NMR (acetone-d_6) δ 4.03 (s, 4 H, CH_2OH), 4.47 (s, 2 H, OH), 5.10 (s, 2 H, $CH_2OSO_2CF_3$); ^{19}F NMR (acetone-d_6) ϕ 74.8 (s); IR ($CDCl_3$) 3610, 3380 (OH), 1560, 1360 (NO_2), 1420, 1225, 1150, 870, (OSO_2CF_3), 980 cm^{-1} (CF).

Anal. Calcd for $C_5H_8F_3NSO_7$: C, 21.21; H, 2.85; N, 4.95. Found: C, 21.02; H, 2.81; N, 4.76.

Registry No. 2-Fluoro-2-nitro-1,3-propanediol, 4776-99-2; 2-fluoro-3-hydroxy-2-nitro-1-propyl triflate, 70187-43-8; 2-fluoro-2-nitro-1,3-propylene ditriflate, 75233-63-5; 3-fluoro-3-nitrooxetane, 70187-44-9; 1,3-bis(2-fluoro-2,2-dinitroethoxy)-2-fluoro-2-nitropropane, 75233-64-6; 1,3-diazido-2-fluoro-2-nitropropene, 75233-65-7; 1,3-dimethoxy-2-fluoro-2-nitropropane, 75233-66-8; 2-fluoro-3-hydroxy-2-nitro-1-propylpyridinime triflate, 75233-68-0; 3-chloro-2-fluoro-2-nitro-1-propanol, 75233-69-1; 3-bromo-2-fluoro-2-nitro-1-propanol, 75233-70-4; poly(3-fluoro-3-nitromethylene ether), 75232-62-1; 2,2-dinitro-3-hydroxy-1-propyl triflate, 75233-71-5; 2,2-dinitro-1,3-propylene ditriflate, 75233-72-6; 3-hydroxy-2-(hydroxymethyl)-2-nitro-1-propyl triflate, 75233-73-7; 2-(hydroxymethyl)-2-nitro-1,3-propylene ditriflate, 75247-60-8; diethyl fluoronitromalonate, 680-42-2; 1,3-bis(trimethylsiloxy)-2-fluoro-2-nitropropane, 75233-74-8; triflic anhydride, 358-23-6; FDNE, 17003-75-7; propiolic acid, 471-25-0; 1,3-bis[1-(4-(or 5-)-carboxy-1,2,3-triazolo)]-2-fluoro-2-nitropropane, 75232-63-2; 2-fluoro-3-methoxy-2-nitro-1-propyl triflate, 75233-75-9; 2-(hydroxymethyl)-2-nitro-1,3-propanediol, 126-11-4.

New Synthesis of Isoxazoles and Isothiazoles. A Convenient Synthesis of Thioenaminones from Enaminones

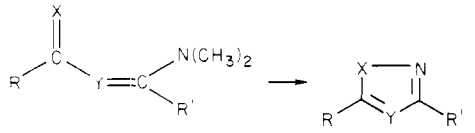
Yang-i Lin* and Stanley A. Lang, Jr.

Medical Research Division, American Cyanamid Company, Lederle Laboratories, Pearl River, New York 10965

Received July 28, 1980

The reaction of 1-aryl-3-(dimethylamino)-2-propen-1-ones (enaminones) and 1-aryl-3-(dimethylamino)-2-propene-1-thiones (thioenaminones) with hydroxylamine-*O*-sulfonic acid gave, respectively, isoxazoles in 76–84% yields and isothiazoles in 60–65% yields. The reaction of enaminones with phosphorus oxychloride, followed by treatment with sodium perchlorate and reaction with sodium sulfide, gave thioenaminones in 40–73% yields.

Recently, we described a general method[1] for the synthesis of 1,2,4-thiadiazoles **4** in which the (dimethylamino)alkylidene moiety was utilized as a masked acyl function.[1-5] This method involved the reaction of *N'*-(thioaroyl)-*N,N*-dimethylamidines **1** with an aminating agent such as *O*-mesitylenesulfonylhydroxylamine (MSH) or hydroxylamine-*O*-sulfonic acid (HSA) to give 1,2,4-thiadiazoles **4** in excellent yields.



1, X = S; Y = N
2, X = O; Y = CH
3, X = S; Y = CH

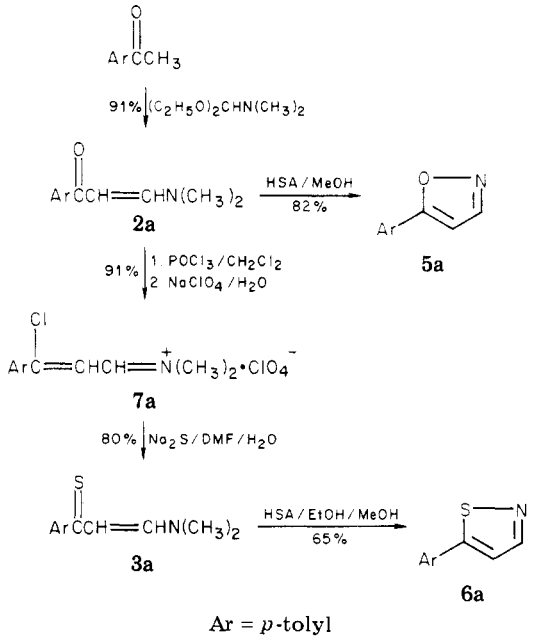
4, X = S; Y = N
5, X = O; Y = CH
6, X = S; Y = CH

We now report the extension of the method to the synthesis of isoxazoles **5** and isothiazoles **6** by the reaction of enaminones **2** and thioenaminones **3** with HSA. We also report a convenient synthesis of thioenaminones **3** from enaminones **2**.

Results and Discussion

Enaminones **2** were prepared in 87–93% yields by the reaction of acetophenones with *N,N*-dimethylalkanamide diethyl acetal or dimethyl acetal.[3,6-8] Thioenaminones **3** were prepared in 40–73% yields by the reaction of the

Scheme I

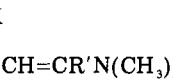


Ar = *p*-tolyl

(1) Lin, Yang-i; Lang, S. A., Jr.; Petty, S. R. *J. Org. Chem.* **1980**, *45*, 3750.
(2) Lin, Yang-i; Lang, S. A., Jr.; Lovell, M. F.; Perkinson, N. A. *J. Org. Chem.* **1979**, *44*, 4160.
(3) Lin, Yang-i; Lang, S. A., Jr. *J. Heterocycl. Chem.* **1977**, *14*, 345.
(4) Lin, Yang-i; Seifert, C. M.; Kang, S. M.; Dusza, J. D.; Lang, S. A., Jr. *J. Heterocycl. Chem.* **1979**, *16*, 1377.
(5) Lin, Yang-i; Lang, S. A., Jr. *Synthesis* **1980**, 119.
(6) Bredereck, H.; Effenberger, F.; Botsch, H. *Chem. Ber.* **1964**, *97*, 3397.
(7) Junek, H.; Schmidt, A. *Monatsh. Chem.* **1968**, *99*, 635.
(8) Junek, H.; Stolz, G. *Monatsh. Chem.* **1970**, *101*, 1234.

0022-3263/80/1945-4857$01.00/0

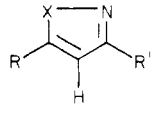
Table I. Enaminones and Thioenaminones



compd	X	R	R'	yield, %	mp, °C	formula[j]
2a	O	p-$CH_3C_6H_4$	H	91	95-96[a]	$C_{12}H_{15}NO$
2b	O	$pCH_3OC_6H_4$	H	93	92-93[b]	$C_{12}H_{15}NO_2$
2c	O	p-ClC_6H_4	H	90	84-86[c]	$C_{11}H_{12}ClNO$
2d	O	p-BrC_6H_4	H	89	75-77	$C_{11}H_{12}BrNO$
2e	O	C_6H_5	H	91	96-98[d]	$C_{11}H_{13}NO$
2f	O	C_6H_5	CH_3	87	67-69	$C_{12}H_{15}NO$
3a	S	p-$CH_3C_6H_4$	H	73	135-136[e]	$C_{12}H_{15}NS$
3b	S	p-$CH_3OC_6H_4$	H	60	108-110[f]	$C_{12}H_{15}NOS$
3c	S	p-ClC_6H_4	H	68	119-120[g]	$C_{11}H_{12}ClNS$
3d	S	p-BrC_6H_4	H	73	118-119[h]	$C_{11}H_{12}BrNS$
3e	S	C_6H_5	H	62	115-116[i]	$C_{11}H_{13}NS$
3f	S	C_6H_5	CH_3	40	118-119	$C_{12}H_{15}NS$

[a] Lit.[7] mp 90 °C. [b] Lit.[7] mp 90 °C. [c] Lit.[8] mp 86 °C. [d] Lit.[6] mp 85 °C. [e] Lit. mp 135-137 °C;[9] 133-135.[10] [f] Lit. mp 105-106 °C;[9] 108-110 °C.[10] [g] Lit.[9] mp 120-121 °C. [h] Lit. mp 109-111 °C;[9] 113-115 °C.[10] [i] Lit. mp 112-115 °C;[9] mp 116-117 °C.[10] [j] Satisfactory analytical data (±0.4% for C, H, N, S, and X, when present) were reported for all compounds in Tables I and II except those for which literature melting point values are given.

Table II. Substituted Isoxazoles and Isothiazoles



compd	X	R	R'	yield, %	mp, °C	formula
5a	O	p-$CH_3C_6H_4$	H	82	60-61[a]	$C_{10}H_9NO$
5b	O	p-$CH_3OC_6H_4$	H	84	64-65[b]	$C_{10}H_9NO_2$
5c	O	p-ClC_6H_4	H	76	84-85[c]	C_9H_6ClNO
5d	O	p-BrC_6H_4	H	77	114-116[d]	C_9H_6BrNO
6a	S	p-$CH_3C_6H_4$	H	65	83-84[e]	$C_{10}H_9NS$
6b	S	p-$CH_3OC_6H_4$	H	65	81-83[e]	$C_{10}H_9NOS$
6c	S	p-ClC_6H_4	H	60	54.5-56[e]	C_9H_6ClNS
6d	S	p-BrC_6H_4	H	61	94-96[e]	C_9H_6BrNS
6e	S	C_6H_5	H	62	46-47[f]	C_9H_7NS
6f	S	C_6H_5	CH_3	64	67-69[g]	$C_{10}H_9NS$

[a] Lit.[11] mp 58-60 °C. [b] Lit.[34] mp 58-60 °C. [c] Lit.[11] mp 82-82.5 °C. [d] Lit.[35] no melting point reported. [e] Lit.[31] no melting point reported. [f] Lit. mp 43 °C;[28] 46-47 °C;[29] 44-45 °C.[30] [g] Lit.[32] mp 69-71 °C and 67-68 °C.

enaminones **2** with phosphorus oxychloride in dichloromethane followed by treatment with sodium perchlorate in water and reaction with sodium sulfide in aqueous *N,N*-dimethylformamide. The enaminones **2** and thioenaminones **3** synthesized are listed in Table I. The reaction of the enaminones **2** and thioenaminones **3** with HSA gave, respectively, isoxazoles **5** in 76–84% yields and isothiazoles **6** in 60–65% yields. The isoxazoles **5** and isothiazoles **6** synthesized are listed in Table II.

The effectiveness of the new synthetic methods is illustrated by the following examples. Reaction of *p*-methylacetophenone with *N,N*-dimethylformamide diethyl acetal at reflux temperature gave enaminone **2a**[7] in 91% yield. Reaction of the enaminone **2a** with phosphorus oxychloride in dichloromethane at 0 °C, followed by treatment with aqueous sodium perchlorate solution at 0 °C, gave (3-chloroallylidene)dimethylammonium perchlorate **7a** in 91% yield. The perchlorate **7a** then reacted with sodium sulfide in aqueous *N,N*-dimethylformamide to give thioenaminone **3a**[9,10] in 80% yield. The enaminone **2a** reacted with HSA in methanol at 0 °C to give isoxazole **5a**[11] in 82% yield, while the thioenaminone **3a** reacted with HSA in a mixture of methanol and ethanol at room temperature to give isothiazole **6a** in 65% yield (Scheme I). The structure assignment of the isothiazole **6a** rested upon the spectral and analytical data; for example, the mass spectrum showed the molecular ion (M^+) at m/e 175 and the ^1H NMR spectrum in $CDCl_3$ showed five sets of signals at 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), and 8.42 (d, J = 2 Hz, 1 H).

The structures of the enaminones **2**, thioenaminones **3**, isoxazoles **5**, and isothiazoles **6** synthesized in this report were all supported by NMR, IR, and elemental analysis data.

Our procedure for the preparation of (3-chloroallylidene)dimethylammonium perchlorates **7** from enaminones **2** under mild reaction conditions in ~90% yield is superior to the reported method.[9b] The subsequent reaction of the (3-chloroallylidene)dimethylammonium perchlorates **7** with sodium sulfide[9] gave the thioenaminones **3** in 40–73% overall yields from the enaminones **2** (Table I). Thioenaminones **3** have been prepared by (1) reaction of acetophenones with dimethyl(chloromethylene)ammonium chloride, followed by treatment with sodium perchlorate and reaction of the resulting (3-chloroallylidene)dimethylammonium perchlorates **7** with sodium sulfide in 30–46% overall yields,[9] (2) sulfurization of enaminones **2** with phosphorus pentasulfide or hydrogen sulfide in low yields (1.4–43%),[12-14] (3) ring opening of

(9) (a) Liebscher, J.; Hartmann, H. *Z. Chem.* **1972**, *12*, 147. (b) Liebscher, J.; Hartmann, H. *J. Prakt. Chem.* **1976**, *318*, 731.

(10) Clesse, F.; Reliquet, A.; Quiniou, H. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1971**, *272*, 1049.

(11) (a) Kochetkov, N. K.; Khomutova, E. D.; Karpeysky, M. Ja.; Khorlin, A. Ja. *Zh. Obshch. Khim.* **1957**, *27*, 452; (b) *Chem. Abstr.* **1957**, *51*, 15496.

(12) Bignebat, J.; Quiniou, H.; Lozac'h, N. *Bull. Soc. Chim. Fr.* **1966**, 1699; **1969**, 127.

1,2-dithiolium salts with amines,[10,12,15-19] and (4) transamination of thioenaminones.[14,20]

The synthesis of the isoxazoles **5a–d** from the enaminones **2a–d** with HSA in methanol provides a useful alternative to literature methods.[3,11,21-23] 5-Substituted isoxazoles **5** (R′ = H) have been prepared by reaction of the enaminones **2** (R′ = H) with hydroxylamine in good yields.[3,21-23]

The chemistry of isothiazoles was reviewed by Slack and Wooldridge in 1965[24] and supplemented by the latter in 1972.[25] Since 1970, the subject has been brought up to date periodically by Kurzer[26] and Davis.[27] The synthetic routes to isothiazoles have been classified according to the nature of the fragments from which the isothiazole ring is constructed (types A to H).[26,27]

5-Phenylisothiazole (**6e**) has been synthesized by (1) the reaction of 3-phenyl-3-(thiocyanato)vinylaldehyde with ammonia (type H) in 58% yield,[28] (2) the reaction of 3-phenyl-1,2-dithiolylium perchlorate with ammonia (type H) in 49% yield,[29] (3) the catalyzed reaction of β-methylstyrene or allylbenzene with sulfur dioxide and ammonia (type C) in 30–40% yield,[30] and (4) the photolysis of 5-iodoisothiazole in benzene.[31] 3-Methyl-5-phenylisothiazole (**6f**) has been synthesized by (1) the reaction of 4-phenyl-5-(thiocyanato)-3-buten-2-one with ammonia (type H) in 40% yield,[32] (2) the reaction of 5-amino-3-methylisothiazole with isopentyl nitrite in benzene in 26% yield,[32] and (3) the photolysis of 5-iodo-3-methylisothiazole in benzene.[33] Our new synthetic method, which falls into type H, appears to be more convenient and effective than the reported methods.

Experimental Section

All melting points were taken on a Mel-Temp apparatus. Samples for elemental analyses were dried over phosphorous pentoxide under high vacuum for 3–24 h. IR spectra were measured on a Perkin-Elmer spectrophotometer (Model 21). NMR spectra were determined with a Varian Model HA-100 spectrometer; chemical shifts (δ) are in parts per million relative to internal tetramethylsilane. Mass spectra were recorded on AEI MS 902.

3-(Dimethylamino)-4′-methylacrylophenone (2a).[7] Typical Procedure for 2a–e. A solution of 100 g (0.746 mol) of *p*-methylacetophenone in 200 mL (1.17 mol) of *N,N*-dimethylformamide diethyl acetal (the dimethyl acetal was used for **2c–e**) was refluxed for 20 h during which time some ethanol was formed and removed through a reflux condenser. After cooling, the solution deposited 128.2 g (91%) of **2a** as yellow crystals: mp 95–96 °C (lit.[7] mp 90 °C); ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3 H), 3.00 (s, 6 H), 5.72 (d, J = 12 Hz, 1 H), 7.20 (d, J = 8 Hz, 2 H), 7.76 (d, J = 12 Hz, 1 H), 7.80 (d, J = 8 Hz, 2 H).

3-(Dimethylamino)crotonophenone (2f). A solution of 50.0 g (0.417 mol) of acetophenone in 100 mL (~0.62 mol) of *N,N*-dimethylacetamide dimethyl acetal (~90%) was stirred at 110 °C (oil bath temperature) under reflux for 19 h. The volatile materials were removed under reduced pressure. The residue was dissolved in ~40 mL of ether. After being cooled, the ether solution deposited 60.9 g (87%) of **2f** as tan crystals: mp 67–69 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3 H), 2.96 (s, 6 H), 5.64 (s, 1 H), 7.2–7.6 (m, 3 H), 7.6–8.0 (m, 2 H).

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.2; H, 7.99; N, 7.40. Found: C, 76.0; H, 7.95; N, 7.44.

(γ-Chloro-*p*-methylcinnamylidene)dimethylammonium Perchlorate (7a).[9b] To a solution of 22.6 g (0.120 mol) of **2a** in 80 mL of anhydrous dichloromethane at 0 °C was added a solution of 11.2 mL (0.120 mol) of phosphorus oxychloride in 30 mL of anhydrous dichloromethane over a period of 2 min. The ice–water bath was removed. After the solution was stirred at room temperature for 10 min, (γ-chloro-*p*-methylcinnamylidene)dimethylammonium phosphorodichloridate precipitated out from the reaction mixture as yellow crystals (if necessary, the reaction mixture was scratched with a spatula to induce the precipitation of the phosphorodichloridate salt). The stirring was continued at room temperature for another 10 min and then at 0 °C for 10 min. The yellow crystals were collected by filtration, washed with a small amount of ice-cold dichloromethane, and added to a stirred and ice-cold solution of 50.4 g (0.36 mol) of sodium perchlorate monohydrate in 100 mL of water. The reaction mixture was vigorously stirred at 0 °C for 20 min. The perchlorate **7a** as yellow crystals was collected by filtration, washed with an ice-cold solution of 10 g of sodium perchlorate monohydrate in 100 mL of water, dried by suction for 20 min (56.3 g), and then washed with 50 mL of cold ethanol and 50 mL of cold ether: yield 33.7 g (91%); mp 201–203 °C (lit.[9b] mp 201–203 °C).

3-(Dimethylamino)-4′-methylthioacrylophenone (3a)[9,10] from Enaminone 2a. Typical Procedure for 3a–e. The wet yellow perchlorate **7a** (56.3 g) was added over a period of 3 min to a stirred and ice-cold mixture of *N,N*-dimethylformamide (250 mL) and a solution of sodium sulfide nonahydrate (35.0 g, 0.146 mol, in 40 mL of water). The reaction mixture was stirred at room temperature for 2 h and then diluted with 600 mL of water. After being cooled in a refrigerator overnight, the solution deposited 19.8 g (81%) of reddish orange crystals, mp 130–133 °C.

The crude product was recrystallized by dissolving in 40 mL of warm chloroform and precipitating with 80 mL of hexane, giving 17.9 g (73%) of **3a** as orange crystals: mp 135–137 °C (lit. mp 135–137,[9] 133–135 °C[10]); ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3 H), 3.06 (s, 3 H), 3.00 (s, 3 H), 3.20 (s, 3 H), 6.54 (d, J = 12 Hz, 1 H), 7.12 (d, J = 8 Hz, 2 H), 7.68 (br d, 2 H), 2 H), 8.20 (br s, 1 H).

3-(Dimethylamino)thiocrotonophenone (3f). To a solution of 11.3 g (0.060 mol) of **2f** in 40 mL of anhydrous dichloromethane at 0 °C was added a solution of 5.6 mL (0.060 mol) of phosphorus oxychloride in 15 mL of anhydrous dichloromethane over a period of 2 min. The ice–water bath was removed. The reaction mixture was stirred at room temerature for 30 min. The dichloromethane was removed at room temperature under reduced pressure. To the residue was added an ice-cold solution of 25.2 g (0.18 mol) of sodium perchlorate monohydrate in 50 mL of water. The reaction mixture was vigorously stirred for 2 min. To the reaction mixture was added 35 mL of cold ether. The resulting mixture was vigorously stirred at 0 °C for 30 min. The perchlorate **7f** as off-white crystals as collected by filtration, washed with an ice-cold solution of 5 g of sodium perchlorate monohydrate in 30 mL of water, dried by suction for 15 min (yield 25.0 g), and added to a stirred and ice-cold mixture of *N,N*-dimethylformamide (125 mL) and a solution of sodium sulfide nonahydrate (15.0 g, 0.0625

(13) Clesse, F.; Quiniou, H. *Bull. Soc. Chim. Fr.* **1969**, 1940.
(14) Duguay, G.; Metayer, C.; Quinious, H. *Bull. Soc. Chim. Fr.* **1974**, 2507.
(15) Quiniou, H.; Lozac'h, N. *Bull Soc. Chim. Fr.* **1964**, 450.
(16) Duguay, G.; Quiniou, H.; Lozac'h, N. *Bull. Soc. Chim. Fr.* **1967**, 4485.
(17) Duguay, G.; Quiniou, H. *Bull Soc. Chim. Fr.* **1970**, 1918.
(18) Metayer, C.; Duguay, G. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1971**, *273*, 1457.
(19) Uhlemann, E.; Zoellner, B. *Z. Chem.* **1974**, *14*, 245.
(20) Reliquet, A.; Reliquet-Clesse, F. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1975**, *280*, 145.
(21) Kochetkov, N. K. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1954**, 47.
(22) Garcia, E. E.; Benjamin, L. E.; Fryer, R. I. *J. Heterocycl. Chem.* **1974**, *11*, 275.
(23) Kochetkov, N. K.; Sokolov, S. D. *Adv. Heterocycl. Chem.* **1963**, *2*, 365.
(24) Slack, R.; Wooldridge, K. R. H. *Adv. Heterocycl. Chem.* **1965**, *4*, 107.
(25) Wooldridge, K. R. H. *Adv. Heterocycl. Chem.* **1972**, *14*, 1.
(26) Kurzer, F. *Org. Compd. Sulphur, Selenium, Tellurium* **1970**, *1*, 369; **1973**, *2*, 556; **1975**, *3*, 541; **1977**, *4*, 339.
(27) Davis, M. *Org. Compd. Sulfur, Selenium, Tellurium* **1979**, *5*, 345.
(28) Muehlstaedt, M.; Braemer, R.; Schulze, B. *J. Prakt. Chem.* **1976**, *318*, 507.
(29) Olofson, R. A.; Landesberg, J. M.; Berry, R. O.; Leaver, D.; Robertson, W. A. H.; McKinnon, D. M. *Tetrahedron* **1966**, *22*, 2119.
(30) Hübenett, F.; Hofmann, H. D. *Angew. Chem.* **1963**, *75*, 420.
(31) Vernin, G.; Poite, J. C.; Riou, C.; Don, H. J. M.; Metzger, J. *Bull. Soc. Chim. Fr.* **1973**, 1822.
(32) Grant, M. S.; Pain, D. L.; Slack, R. *J. Chem. Soc.* **1965**, 3482.
(33) Vermin, G.; Poite, J. C.; Dou, H. J. M.; Metzger, J. *Bull Soc. Chim. Fr.* **1972**, 3157.
(34) Truerck, U.; Behringer, H. *Chem. Ber.* **1965**, *98*, 3020.
(35) Bertini, V.; Munno, A. D.; Pino, P. *Gazz. Chim. Ital.* **1967**, *97*, 173.

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.

Acknowledgment. We thank Dr. W. Gore and Mr. G. Morton and staff for the measurement and interpretation of spectral data and Mr. L. Brancone and staff for microanalysis.

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]

Gabriel Kornis,* Pamela J. Marks, and Constance G. Chidester

The Upjohn Company, Kalamazoo, Michigan 49001

Received June 17, 1980

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