(CO); NMR δ 1.2–2.1 (complex signal, 7 H), 2.20 (s, 3 H, NCH_3), 2.6–3.1 (complex signal, 2 H), 3.46 (s, 2 H, $NCOCH_2$), 3.54 (d, 2 H, $CONCH_2$), 6.6–7.4 (m, 4 H, Ar). For the hydrochloride: mp 244–246 °C (EtOH). Anal. Calcd for $C_{15}H_{21}ClN_2O$: C, 64.16; H, 7.54; N, 9.98; Cl, 12.62. Found: C, 64.23; H, 7.60; N, 9.82; C, 12.60.

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Registry No. 1, 3731-53-1; 2, 87451-35-2; 3, 87451-36-3; 4, 87451-37-4; 5, 80077-92-5; 6, 87451-38-5; 7, 87451-39-6; 8, 87451-40-9; 9, 87451-41-0; 10, 83348-32-7; 11, 5275-07-0; 12, 87451-42-1; 13, 87451-43-2; 16, 82485-24-3; 17, 82485-29-8; 18, 82485-25-4; 19, 87451-44-3; 20, 87451-45-4; 21, 87451-46-5; 2,5-diethoxytetrahydrofuran, 3320-90-9; 4-cyanopyridine, 100-48-1; 1-methylpyrrole, 96-54-8; indole, 120-72-9; mercuric acetate, 1600-27-7; 4-chloromethylpyridine hydrochloride, 1822-51-1.

Synthesis of 2,4-Disubstituted Pyrimidines, Polypyrimidinediyls, and Annulated Pyrimidines[1]

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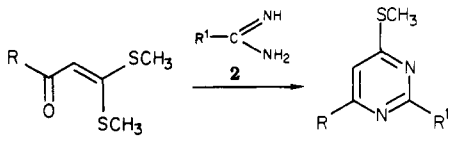
Carboxamidines reacted with α-oxoketene dithioacetals in benzene/DMF solution in the presence of sodium hydride, giving 2,4-disubstituted-6-(methylthio)pyrimidines containing a variety of alkyl, aryl, and heteryl substituents in the 2 and 4 positions. Bis(α-oxoketene dithioacetals) and 2 equiv of carboxamidine allowed the introduction of several pyrimidine nuclei into the polyheteryl system. Thiourea also reacted with bis(α-oxoketene dithioacetals), giving the corresponding bis(pyrimidinethione).

α-Oxoketene dithioacetals have been shown[2] to be versatile synthons for 1,5-enediones, intermediates in the synthesis of 2,6-disubstituted pyridines, polypyridindiyls, and annulated pyridines. In this publication we describe the application of these α-oxoketene dithioacetals to the synthesis of a variety of 2,4-disubstituted pyrimidines and related derivatives. Numerous syntheses of pyrimidines have been described[3] in the literature. Ketene acetals and amidines readily form pyrimidines,[4] and *S*-methylisothiourea and guanidine derivatives also react readily with α-oxoketene dithioacetals to form the appropriately substituted pyrimidines.[5] This present procedure is characterized by the variety of substituents (alkyl, aryl, and heteryl) which may be introduced into the 2,4-positions and by the 6-methylthio substituent which may be converted into other groups. It is particularly suited to the synthesis of heterocyclic systems with considerable potential for behaving as ligands.

Reaction of the α-oxoketene dithioacetal **1** with a carboxamidine **2** in benzene–DMF solution in the presence of sodium hydride resulted in the formation of the 2,4-disubstituted-6-(methylthio)pyrimidine **3** in moderate yields (Table I). The carboxamidine was usually used as its salt, an additional quantity of sodium hydride being added to generate the free amidine.



1 **3**

Spectral and analytical data for the products described in Table I were consistent with the assigned structures. Thus 2,4-di-2-thienyl-6-(methylthio)pyrimidine (**3**, R = R^1 = 2-C_4H_3S) was prepared from 3,3-bis(methylthio)-1-(2-thienyl)-2-propen-1-one (**1**, R = C_4H_3S) and 2-thiophenecarboxamidine[6] (**2**, R^1 = C_4H_3S). Its seven aromatic protons were distinguishable as a singlet for the new pyrimidine proton and multiplets for the six thiophene protons, together with the SCH_3 protons at δ 2.66. The 13 line ^{13}C NMR spectrum was also consistent with this structure.

The pyridinecarboxamidines, prepared conveniently from their nitriles, sodium methoxide, and ammonium chloride,[7] underwent ready pyrimidine formation with the 3- and 4-substituted pyridines. 2-Pyridinecarboxamidine, however, resulted in a poor yield of the corresponding pyrimidine. Solvent variation or the use of potassium hydride had little influence on the reaction, and we tentatively attribute this poor yield to an intramolecular stabilization of the amidine anion with the pyridine nitrogen and the counter ion.

Use of heterocyclic bis(ketene dithioacetals) provides an opportunity of appreciably extending the number of heterocyclic units in a particular system. Thus reacton of 2,6-bis[3,3-bis(*n*-propylthio)-1-oxo-2-propen-1-yl]pyridine (**4**) with 2 equiv of 2-thiophenecarboxamidine (**2**, R = 2-C_4H_3S) in benzene/sodium hydride resulted in **5** (R =

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(3) For summaries see Brown, D. J. "The Pyrimidines"; Weissberger, A., Taylor, E. C., Eds.; Wiley-Interscience: New York, 1970; Supplement I and earlier parts in this series.

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(5) Chauhan, S. M. S.; Junjappa, H. *Tetrahedron* **1976**, *32*, 1779, 1911. Rudorf, W. D., Augustin, M. *J. Prakt. Chem.* **1978**, *320*, 576. Rudorf, W. D.; Schierhorn, A.; Augustin, M. *Tetrahedron* **1979**, *35*, 551.

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(7) 2- and 4-Pyridinecarboxamidine hydrochlorides were prepared according to Singh, B.; Lesher, G. Y. *J. Heterocycl. Chem.* **1977**, *14*, 1413. 3-Pyridinecarboxamidine hydrochloride was prepared by a modification of the procedure of Gronowitz (ref 6).

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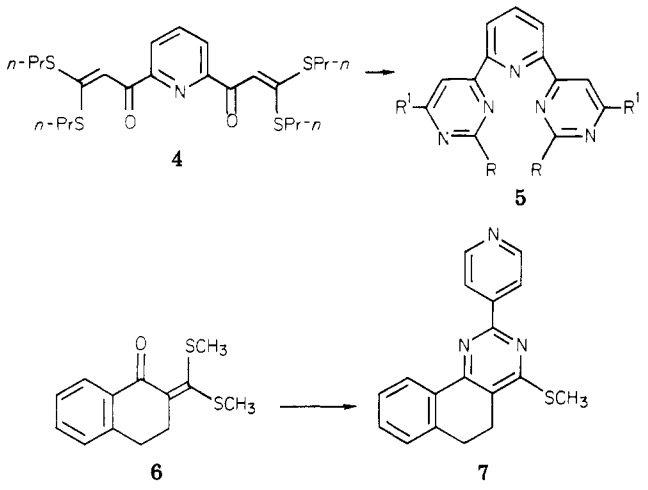
2-C_4H_3S; R^1 = S-*n*-Pr) in moderate yield. Ring-annulated



pyrimidines may also be obtained by this procedure. Thus reaction of **6** with 4-pyridinecarboxamidine gave **7** in good yield.

The reaction conditions used above provide for retention of the methylthio substituent in the final product. Use of sodium ethoxide as base in ethanol, however, results in a 6-ethoxy substituent in the final pyrimidine. Reaction of the bis(ketene dithioacetal) **4** with acetamidine hydrochloride in the presence of sodium ethoxide (>4 equiv) in boiling ethanol resulted in the formation of **5** (R = CH_3; R^1 = OEt). Benzamidine hydrochloride and **4** gave the corresponding **5** (R = Ph; R^1 = OEt). When exactly 4 equiv of sodium ethoxide were used, a mixture of products was obtained with partial retention of an S-*n*-Pr group. This could be completely displaced by the ethoxy group on reflux of the mixture with sodium ethoxide in ethanol. These products containing ethoxyl substituents were appreciably less soluble in organic solvents than pyrimidines containing methylthio or *n*-propylthio substituents.

Thiourea also underwent reaction with **4** in refluxing ethanol in the presence of sodium ethoxide. The product obtained was identified as the pyrimidinethione **5** (R = SH; R^1 = OEt) by its conversion into the methylthio compound **5** (R = SCH_3; R^1 = OEt) with NaH/DMF followed by methyl iodide. Spectral data in support of these structures are described in the Experimental Section.

Experimental Section[8]

The following reactions illustrate the conditions used in the preparation of the pyrimidines.

2,4-Di-2-thienyl-6-(methylthio)pyrimidine (3, R = 2-C_4H_3S). Sodium hydride (1.21 g, 59.6% oil suspension, 0.03 mol) was added to a solution of 2-thiophenecarboxamidine hydrochloride (**2**, R = 2-C_4H_3S) (2.44 g, 0.15 mol) in benzene (50 mL) followed by DMF (10 mL). 3,3-Bis(methylthio)-1-(2-thienyl)-2-propen-1-one (**1**, R = 2-C_4H_3S) (3.45 g, 0.15 mol) was added and the mixture stirred under reflux for 29 h. The reaction solution was concentrated on a steam bath and after dilution with water was extracted with CH_2Cl_2. After the combined extracts were washed with water and dried (Na_2SO_4), the solvent was removed and the resulting oil partially crystallized after standing several days. This residue was diluted with a small volume of cold methanol (5 mL), and the solid material was collected and then dissolved in hot ethanol (charcoal) from which it separated on cooling as colorless prisms: 1.38 g (32%); mp 90–91 °C (Table I).

2,4-Di-2-pyridinyl-6-(methylthio)pyrimidine (3, R = R^1 = 2-C_5H_4N). A mixture of 2-pyridinecarboxamidine hydrochloride (3.8 g, 0.024 mol) and NaH (2.3 g, 0.0479 mol, 50% oil suspension) in benzene (100 mL) was treated with DMF (5 mL) followed by 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one (**1**, R = 2-C_5H_5N) (5.0 g, 0.022 mol). The mixture was stirred at 60 °C for ca. 36 h. After a long induction period a sudden evolution of methanethiol occurred accompanied by an appreciable darkening of the reaction mixture. Addition of iced water (100 mL), extraction with $CHCl_3$ (3 × 30 mL), drying of the $CHCl_3$ extract (Na_2SO_4), and final evaporation of the solvent left a dark oil. This was dissolved in EtOAc and on HPLC separation (Prep 500; EtOAc, silica) gave unreacted ketene dithioacetal as the first eluate, followed by the pyrimidine. The pyrimidine crystallized from petroleum ether (bp 60–80 °C) to afford colorless prisms: 0.7 g (12%); mp 116–118 °C (Table I).

4-(Methylthio)-6-(2-pyridinyl)-2-(4-pyridinyl)pyrimidine (3, R = 2-C_5H_4N; R^1 = 4-C_5H_4N). A mixture of 4-pyridinecarboxamidine hydrochloride (12.52 g, 0.016 mol), 3,3-bis(methylthio)-1-(2-pyridinyl)-2-propen-1-one (3.38 g, 0.015 mol), and NaH (1.54 g, 0.032 mol, 50% oil suspension) in benzene (100 mL) was treated with DMF (10 mL), and the reaction mixture was heated under reflux for 2 h and then stirred at room temperature overnight. Addition of iced water (50 mL), followed by extraction with benzene (2 × 50 mL) and drying (Na_2SO_4) and concentration of the benzene extracts yielded an orange solid. Recrystallization from ethanol gave colorless needles: 2.8 g (67%), mp 169–171 °C (Table I).

2,6-Bis[2-(2-thienyl)-6-(*n*-propylthio)-4-pyrimidinyl]pyridine (5, R = 2-C_4H_3S; R^1 = S-*n*-Pr). A mixture of 2-thiophenecarboxamidine hydrochloride (0.69 g, 0.004 mol), NaH (0.4 g, 0.008 mol, 50% oil suspension), and **4** in benzene (25 mL) was treated with DMF (5 mL). The mixture was heated at reflux for 4 h and then stirred at room temperature overnight. Addition of iced water (50 mL) caused separation of a solid which was collected. Further product was isolated by extraction of the filtrate with $CHCl_3$ (3 × 30 mL), drying of the extracts (Na_2SO_4), and concentration. Crystallization from DMF afforded colorless needles: 0.5 g (44%); mp 181–183 °C; ^1H NMR ($CDCl_3$) δ 8.72 (d, 2, py-H_3), 8.20 (s, 2, pyrimid-H_5), 8.14 (dd, 2, thiophene), 8.09 (t, 1, py-H_4), 7.77 (dd, 2, thiophene), 7.22 (dd, 2, thiophene); mass spectrum, *m/e* (relative intensity) 547 (100, M^+·).

Anal. Calcd for $C_{27}H_{25}N_5S_4$: C, 59.20; H, 4.60; N, 12.79. Found: 59.22; H, 4.63; N, 12.77.

5,6-Dihydro-4-(methylthio)-2-(4-pyridinyl)benzo[*h*]quinazoline (7). A mixture of 4-pyridinecarboxamidine hydrochloride (3.46 g, 0.022 mol), NaH (2.1 g, 0.046 mol, 50% oil suspension), and 2-[bis(methylthio)methylene]-1-tetralone (5.0 g, 0.02 mol)[9] in benzene (150 mL) was treated with DMF (5 mL) and the reaction mixture heated at reflux for 1 h and then stirred at room temperature for 48 h. Addition of iced water (200 mL), followed by extraction with CH_2Cl_2 (3 × 50 mL), drying of the combined extracts (Na_2SO_4), and concentration afforded a yellow solid. This crystallized from ethanol as colorless needles: 3.8 g (57%), mp 147–148 °C; ^1H NMR ($CDCl_3$) δ 8.79 (d, 2, py-H_3), 8.42 (d, 2, py-H_2), 8.52–7.36 (m, 4, aromatic), 2.98–2.82 (m, 4, CH_2CH_2), 2.69 (s, 3, SCH_3); mass spectrum, *m/e* (relative intesnity) 305 (100, M^+·).

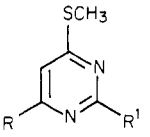
Anal. Calcd for $C_{18}H_{15}N_3S$: C, 70.79; H, 4.95; N, 13.76. Found: C, 70.71; H, 4.99; N, 13.74.

2,6-Bis(6-ethoxy-2-methyl-4-pyrimidinyl)pyridine (5, R = CH_3; R^1 = OEt). The ketene dithioacetal **4** (3.40 g, 0.007 mol) was added to a solution of sodium ethoxide (from 0.64 g Na, 0.028 mol) and acetamidine hydrochloride (1.33 g, 0.014 mol) in ethanol (60 mL). The solution was refluxed overnight, allowed to cool to room temperature, and then diluted with water (40 mL). The precipitate was collected and refluxed in ethanol (60 mL) containing sodium ethoxide (from 0.64 g Na, 0.028 mol) for an ad-

(8) Spectral characterizations were carried out on the following instrumentation: infrared spectra, Perkin-Elmer Model 337 spectrophotometer; ultraviolet spectra, Cary 14 spectrophotometer; NMR spectra, Varian T-60 with Me_4Si as an internal standard; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer, utilizing the direct insertion probe technique with a source temperature of ca. 150 °C. All melting points were determined in capillaries using a Thomas Hoover Capillary Melting Point Apparatus or a Mel-Temp apparatus. Evaporations were carried out under reduced pressure with a Büchi Rotovap apparatus. Microanalyses were by Galbraith Laboratories, Knowville, TN, and Instranal Laboratories, Inc., Rensselaer, N.Y.

(9) Thuillier, A.; Vialle, J. *Bull. Soc. Chim. Fr.* **1959**, 1398.

Table I. Some 2,4-Disubstituted-6-(methylthio)pyrimidines (3)[b]



substituents					
R	R′	mp, °C	yield, %	crystal habit[a]	mol formula
C_6H_5	2-C_4H_3S	127-128	45	prisms, A	$C_{15}H_{12}N_2S_2$
2-C_4H_3O	2-C_4H_3S	91-92	23	needles, A	$C_{13}H_{10}N_2OS_2$
2-C_4H_3S	2-C_4H_3S	90-91	32	prisms, A	$C_{13}H_{10}N_2S_3$
2-C_5H_4N	C_6H_5	104-105	33	needles, A	$C_{16}H_{13}N_3S$
2-C_5H_4N	2-C_4H_3S	140-141	44	needles, A	$C_{14}H_{11}N_3S_2$
2-C_5H_4N	2-C_5H_4N	116-118	10	prisms, B	$C_{15}H_{12}N_4S$
2-C_5H_4N	3-C_5H_4N	140-141	37	prisms, B	$C_{15}H_{12}N_4S$
2-C_5H_4N	4-C_5H_4N	169-171	67	prisms, B	$C_{15}H_{12}N_4S$

[a] All products were colorless crystallizing from A = ethanol; B = petroleum ether, bp 60–80 °C. [b] Satisfactory analytical values (±0.3% for C, H, N) were reported for all compounds in the table. Consistent ^{1}H NMR peaks were reported for all compounds. $M^{+\cdot}$ ions (relative intensity 100%) reported for all compounds.

ditional 16 h. The solution was allowed to cool to room temperature, diluted with water (40 mL), and the precipitate was collected and recrystallized from ethanol from which colorless needles separated: 1.0 g (41%); mp 180–181 °C; λ_{max} (C_6H_{12}) nm (log ϵ) 276 (4.44), 220 (4.48); ^{1}H NMR ($CDCl_3$) δ 8.46 (d, 2, py-H_3, H_5, $J_{3,4}$ = 7.9 Hz), 7.90 (t, 1, py-H_4), 7.66 (s, 2, pyrimid-H_5), 4.47 (q, 4, OCH_2), 2.67 (s, 3, SCH_3), 1.12 (t, 6, OCH_2CH_3); mass spectrum, m/e (relative intensity) 351 (36, $M^{+\cdot}$).

Anal. Calcd for $C_{19}H_{21}N_5O_2$: C, 64.94; H, 6.02; N, 19.93. Found: C, 64.86; H, 5.98; N, 19.94.

2,6-Bis(6-ethoxy-2-phenyl-4-pyrimidinyl)pyridine (5, R = C_6H_5; R^1 = OEt). To a solution of sodium ethoxide (from 0.64 g Na, 0.028 mol) in ethanol (60 mL) was added benzamidine hydrochloride (2.19 g, 0.014 mol) and **4** (3.40 g, 0.007 mol). The solution was refluxed overnight, allowed to cool to room temperature, and then diluted with water (40 mL). The precipitate was collected and refluxed in ethanol (60 mL) containing sodium ethoxide (from 0.64 g, Na, 0.028 mol) for an additional 16 h. The reaction mixture was then cooled to room temperature, and the precipitate was collected. Recrystallization from DMF afforded colorless needles: 0.96 g (29%); mp 255–256 °C; λ_{max} (CH_2Cl_2) nm (log ϵ) 262 (4.58); NMR (CF_3COOH) δ 8.73–7.56 (m, 15, aromatic), 5.03 (q, 4, OCH_2), 1.67 (t, 6, CH_3); mass spectrum, m/e (relative intensity) 475 (55, $M^{+\cdot}$).

Anal. Calcd for $C_{29}H_{25}N_5O_2$: C, 73.24; H, 5.30; N, 14.73. Found: C, 73.06; H, 5.37; N, 14.56.

2,6-Bis(2,3-dihydro-6-ethoxy-2-thioxo-4-pyrimidinyl)-pyridine (5, R = SH; R^1 = OEt). To a stirred solution of sodium ethoxide (prepared from 0.016 q (0.007 mol) of Na) in ethanol (50 mL) was added thiourea (0.53 g, 0.007 mol) and **4** (1.70 g, 0.004 mol). The mixture was heated at reflux for 5 h and then allowed to cool to room temperature. The yellow precipitate which separated was collected and recrystallized from DMF to afford yellow prisms: 0.70 g (52%); mp 230–232 °C; IR (KBr) ν_{NH} 3250, ν_{CS} 1170 cm^{-1}; ^{1}H NMR (CF_3COOH) δ 8.60–7.63 (m, 3, aromatic), 7.46 (s, 2, vinylic), 4.86 (q, 4, OCH_2), 1.59 (t, 6, OCH_2CH_3); mass spectrum, m/e (relative intensity) 387 (93, $M^{+\cdot}$).

Anal. Calcd for $C_{17}H_{17}N_5O_2S_2$: C, 52.71; H, 4.42; N, 18.08. Found: C, 52.31; H, 4.17; N, 17.87.

2,6-Bis(6-ethoxy-2-(methylthio)-4-pyrimidinyl)pyridine (5, R = SCH_3; R^1 = OEt). Compound **5** (R = SH; R^1 = OEt) (0.50 g, 0.001 mol) and NaH (0.11 g of a 57% oil suspension, 0.003 mol) in DMF (30 mL) were stirred together until the solution became clear. MeI (0.60 g, 0.004 mol) was added and the solution stirred for an additional 1 h at room temperature. The crystalline product which separated on cooling was collected and recrystallized from 2-propanol from which it separated as pale yellow needles: 0.40 g (74%); mp 178.5–180 °C; λ_{max} (C_6H_{12}) nm (log ϵ) 302 (4.06), 260 (4.59), 228 (4.51); ^{1}H NMR ($CDCl_3$) δ 8.46 (d, 2, pyridine-H_3, H_5, $J_{3,4}$ = 7.9 Hz), 7.90 (t, 1, pyridine-H_4), 7.53 (s, 2, pyrimidine-H_5), 4.51 (q, 4, OCH_2), 2.66 (s, 6, SCH_3), 1.46 (t, 6, CH_3); mass spectrum, m/e (relative intensity) 415 (100, $M^{+\cdot}$).

Anal. Calcd for $C_{19}H_{21}N_5O_2S$: C, 54.93; H, 5.10; N, 16.86. Found: C, 54.70; H, 5.13; N, 16.84.

Registry No. 1 (R = C_6H_5), 13636-88-9; 1 (R = 2-C_4H_3O), 78078-05-4; 1 (R = 2-C_4H_3S), 41467-29-2; 1 (R = 2-C_5H_4N), 78570-34-0; **2** (R^1 = 2-C_4H_3S), 54610-75-2; **2** (R^1 = C_6H_5), 618-39-3; **2** (R^1 = 2-C_5H_4N), 52313-50-5; **2** (R^1 = 3-C_5H_4N, 23255-20-1; **2** (R^1 = 4-C_5H_4N), 33278-46-5; **3** (R = C_6H_5; R^1 = 2-C_4H_3S), 87568-78-3; **3** (R = 2-C_4H_3O; R^1 = 2-C_4H_3S), 87568-79-4; **3** (R = 2-C_4H_3S; R^1 = 2-C_4H_3S), 82094-04-0; **3** (R = 2-C_5H_4N; R^1 = C_6H_5), 87568-80-7; **3** (R = 2-C_5H_4N; R^1 = 2-C_4H_3S), 87568-81-8; **3** (R = 2-C_5H_4N; R^1 = 2-C_5H_4N), 87568-82-9; **3** (R = 2-C_5H_4N; R^1 = 3-C_5H_4N, 87568-83-0; **3** (R = 2-C_5H_4N; R^1 = 4-C_5H_4N), 87568-84-1; **4**, 87568-85-2; **5** (R = 2-C_4H_3S; R^1 = S-*n*-Pr), 87568-86-3; **5** (R = CH_3; R^1 = OEt), 87568-87-4; **5** (R = C_6H_5; R^1 = OEt, 87568-88-5; **5** (R = SH; R^1 = OEt), 87568-89-6; **5** (R = SCH_3; R^1 = OEt), 87568-90-9; **6**, 57663-21-5; **7**, 87568-91-0; acetamidine hydrochloride, 124-42-5; thiourea, 62-56-6.