67872-74-6; **6b**, 67872-75-7; **7**, 67872-76-8; **9a**, 67872-77-9; **10**, 64847-17-2; **11**, 67872-78-0; **12**, 67872-79-1; **13**, 67872-80-4; **14**, 67872-81-5; **15a**, 67872-82-6; **15b** HCl, 67872-83-7; acrylonitrile, 107-13-1; 3-phenylacrylonitrile, 4360-47-8; diazomethane, 334-88-3; benzoyl chloride; 98-88-4; ethyl diazoacetate, 623-73-4.

References and Notes

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Pyrimido[4,5-*c*]pyridazines. 1. Cyclizations with α-Keto Esters

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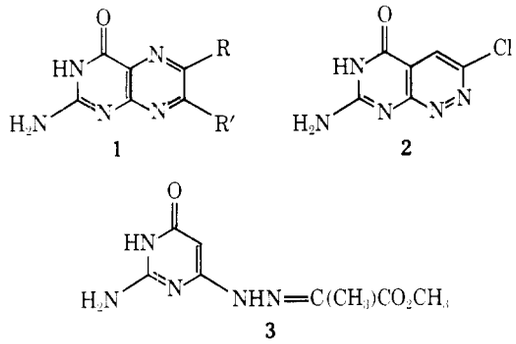
6-(1-Alkylhydrazino)isocytosines cyclize with simple α-keto esters to give pyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-diones. The ease of cyclization for analogous 2-amino-6-(1-alkylhydrazino)pyrimidines varies with the nature of the functional group at position 4. Diethyl ketomalonate cyclizes in an unexpected manner with 6-(1-methylhydrazino)isocytosine to give the 3,5(1*H*,2*H*)-dione **11a**, whereas cyclization with 2,4-diamino-6-(1-methylhydrazino)pyrimidine occurs predictably to give the 4(1*H*)-one **12**.

Our search for analogues of the naturally occurring pterins (**1**)[1] has led to the synthesis of pyrimido[4,5-*c*]pyridazines. Few syntheses of this ring system have been reported,[2] and only one example (**2**) resembles the pterins in the pyrimidine portion of the molecule.[2c]

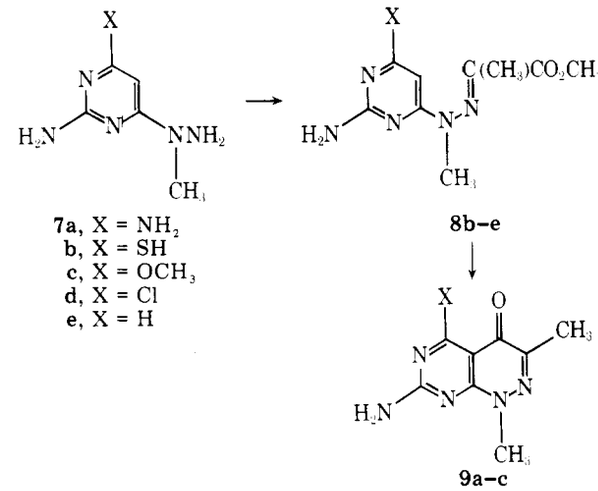
Pfleiderer reported[3] that the hydrazone formed from 1,3-dimethyl-6-hydrazinouracil and methyl pyruvate showed no tendency to cyclize, and we have noted the same behavior with the hydrazone (**3**) formed from methyl pyruvate and 6-hydrazinoisocytosine.[4] In contrast, we have found that 6-(1-*alkyl*hydrazino)isocytosines (**4**) readily form cyclic products (**6**) with a variety of α-keto esters (**5**; Table I). The isomeric pyrimido[4,5-*c*]pyridazine-3,5(1*H*,2*H*)-dione structure was ruled out because of characteristic mass spectral losses of R^2CN from representative molecular ions of these products, while the absence of pyrimidine C-5 protons in the NMR spectra removed the isomeric pyrimido[6,1-*c*]-*as*-triazine structure (and less likely structures which would involve cyclization across the 2-amino group and a ring nitrogen) from consideration.



1 **2**

3

The effect on ring closure of the substituent at position 4 of the pyrimidine ring was examined with a group of 6-(1-methylhydrazino)pyrimidines (**7**) prepared by treatment of the appropriate 6-chloropyrimidines with methylhydrazine. The one exception was the 4-methoxy compound (**7c**), which was prepared by treatment of the 4-chloro compound (**7d**) with methanolic sodium methoxide in a bomb. When these intermediates were allowed to react with methyl pyruvate, substantial differences in behavior were observed. In a qualitative sense, the ease of cyclization paralleled the degree of activation by substituents in electrophilic substitution reactions; cyclization to **9** occurred most readily with the 4-amino substituent (no hydrazone intermediate **8** being isolated), while no conditions could be found for cyclization of the intermediates formed from the 4-chloro or 4-unsubstituted compounds (**8d** and **8e**, respectively).



7a, X = NH_2
b, X = SH
c, X = OCH_3
d, X = Cl
e, X = H

8b–e

9a–c

Hydrazone **8d** did produce pyrimidopyridazine **10** in low yield when heated for 6 days in *n*-propanol, although this same product was produced in better yield by the reaction of hydrazone **8d** with hydrazine **7d**. These results suggest that in the former case the cyclization to **10** may have occurred after a slow solvolysis of **8d** back to **7d**, followed by further reaction with **8d**, thus providing an activating group at pyrimidine position 4 which would then allow the cyclization to proceed.

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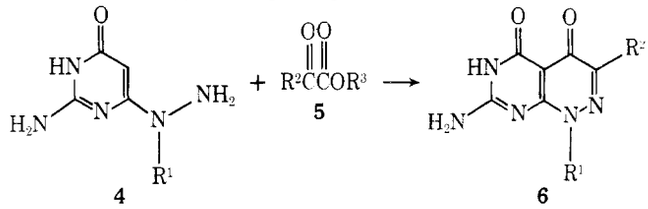
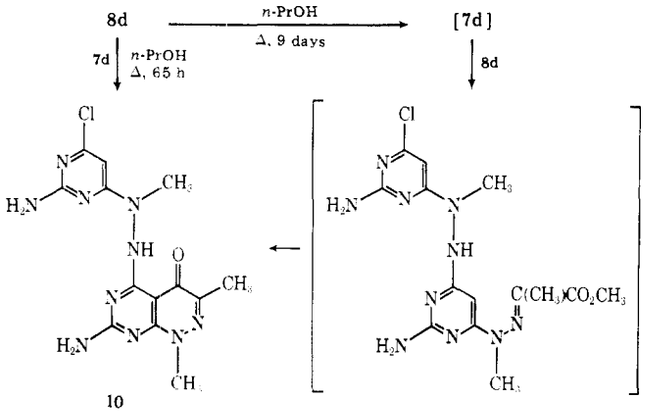
Table I. 7-Aminopyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-diones



4 5 6

	R^1	registry no.	R^2	R^3	5	registry no.	molar ratio 5/4	rxn solvent (reflux time)	yield of 6, %[a]	registry no.
a	CH_3	67873-21-6	CH_3	CH_3	*b*	600-22-6	1.2:1	H_2O (70 min)	51	67873-29-4
b	CH_3		C_2H_5	C_2H_5	*c*	15933-07-0	1.5:1	CH_3OH (72 h)	82	67873-30-7
c	CH_3		n-C_3H_7	C_2H_5	*d*	50461-74-0	1.5:1	H_2O (140 min)	51	67873-31-8
d	CH_3		n-C_6H_{13}	C_2H_5	*e*	67873-26-1	1.5:1	CH_3OH (48 h)	67	67904-79-4
e	CH_3		$CH_2CH(CH_3)_2$	C_2H_5	*f*	26073-09-6	1.5:1	CH_3OH (48 h)	62	67873-32-9
f	CH_3		$CH_2OC(O)CH_3$	C_2H_5	*g*	25007-54-9	1.1:1	CH_3OH (22 h)	40	67873-33-0
g	CH_3		CH_2OH						81[h]	67873-34-1
h	CH_3		$CH_2CO_2C_2H_5$	C_2H_5	*i*	108-56-5	1.7:1	CH_3OH (48 h)	37	67873-35-2
i	CH_3		$C_2H_4CO_2C_2H_5$	C_2H_5	*j*	5965-53-7	1.5:1	H_2O (2 h)	60	67873-36-3
j	CH_3		$CH(CH_3)CO_2C_2H_5$	C_2H_5	*b*	759-65-9	2:1	H_2O (3 h)	58	67873-37-4
k	CH_3		$CH(CH_3)CO_2H$						70[k]	67873-38-5
l	CH_3		$CH(OCH_3)CO_2C_2H_5$	C_2H_5	*l*	67873-27-2	1:5:1	CH_3OH (9 days)	39	67873-39-6
m	CH_3		$CH(OCH_3)CO_2H$						69[l]	67873-40-9
n	CH_3		$CH(CH_2C_6H_5)$-CO_2CH_3	CH_3	*m*	67873-28-3	1.2:1	CH_3OH (69 h)	56	67873-41-0
o	CH_3		C_6H_5	C_2H_5	*b*	1603-79-8	1.5:1	1:1 C_2H_5OH/H_2O (26.5 h)	56	67873-42-1
p	CH_3		$CH_2C_6H_5$	C_2H_5	*n*	6613-41-8	1.1:1	CH_3OH (42 h under N_2)	53[r]	67873-43-2
q	CH_3		$CH_2C_6H_4(NO_2)$ (2)	C_2H_5	*p*	784-98-5	1.5:1	CH_3OH (26 h)	40	67873-44-3
r	CH_3		$CH_2C_6H_3(OCH_3)_2$ (3,4)	C_2H_5	*q*	15504-34-4	1.5:1	CH_3OH (42 h under N_2)	38[r]	67873-45-4
s	CH_3		3-indolyl	CH_3	*s*	18372-22-0	1.5:1	CH_3OH (5 days)	36	67873-46-5
t	CH_3		CH_2-3-indolyl	CH_3	*t*	7417-64-3	1.2:1	6:1 CH_3OH/H_2O (21 h)	11	67873-47-6
u	C_2H_5	67873-22-7	CH_3	CH_3	*b*		1.25:1	H_2O (1 h)	74	67873-48-7
v	CH_2CH_2OH	67873-23-8	CH_3	CH_3	*b*		2:1	H_2O (1.5 h)	61	67873-49-8
w	n-C_4H_9	67873-24-9	CH_3	CH_3	*b*		2:1	H_2O (4 h)	80	67873-50-1
x	$CH_2C_6H_5$	67873-25-0	CH_3	CH_3	*b*		2.5:1	H_2O (23 h)	87	67873-51-2
y	n-C_4H_9		C_6H_5	C_2H_5	*b*		1.5:1	1:1 C_2H_5OH/H_2O (25 h)	78	67873-52-3
z	$CH_2C_6H_5$		C_6H_5	C_2H_5	*b*		1.5:1	1:1 C_2H_5OH/H_2O (26 h)	80	67873-53-4

[a] Yields are based on the (alkylhydrazino)isocytosines used for the cyclizations unless noted otherwise. [b] Aldrich Chemical Co. [c] E. Vogel and H. Schinz, *Helv. Chim. Acta*, **33**, 116 (1950). [d] W. W. Wisaksono and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **80**, 846 (1961). [e] T. Cuvigny, *C. R. Hebd. Seances Acad. Sci.*, **240**, 206 (1955). [f] G. W. Stacy and R. M. McCurdy, *J. Am. Chem. Soc.*, **76**, 1914 (1954). [g] J. Ratusky and F. Sorm, *Chem. Listy*, **51**, 1091 (1957). [h] Isolated as the sodium salt from saponification of **6f**. [i] E. Koike, H. Iida, and A. Kashioka, *Kogyo Kagaku Zasshi*, **57**, 123 (1954). [j] P. C. Dutta, P. K. Dutta, and K. N. S. Sastry, *J. Indian Chem. Soc.*, **31**, 881 (1954). [k] Isolated as the disodium salt from saponification of the corresponding ester. [l] D. S. Breslow, M. S. Bloom, J. C. Shivers, J. T. Adams, M. J. Weiss, R. S. Yost, and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 1232 (1946). [m] New compound prepared from methyl hydrocinnamate and methyl oxalate according to the method reported for the corresponding ethyl esters by W. Wislicenus, *Justus Liebigs Ann. Chem.*, **246**, 315 (1888). This compound could not be distilled under high vacuum since it readily decarbonylated. Microanalysis and NMR of the undistilled product indicated an 85:15 mixture of **5n** with unchanged methyl hydrocinnamate; this mixture was entirely suitable for the subsequent cyclization reaction. [n] H. O. House, J. W. Blaker, and D. A. Madden, *J. Am. Chem. Soc.*, **80**, 6386 (1958). [o] The product was boiled for 15 min with methyl cellosolve to extract a minor impurity. [p] W. Wislicenus and E. Thoma, *Justus Liebigs Ann. Chem.*, **436**, 42 (1924). [q] L. Horner and E. O. Renth, *Justus Liebigs Ann. Chem.*, **703**, 37 (1967). [r] After recrystallization from methyl cellosolve. [s] W. Reeve, R. S. Hudson, and C. W. Woods, *Tetrahedron*, **19**, 1243 (1963). [t] J. A. Bentley, K. R. Farrar, S. Housley, G. F. Smith, and W. C. Taylor, *Biochem. J.*, **64**, 44 (1956).



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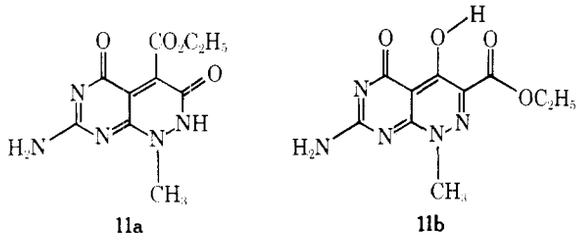
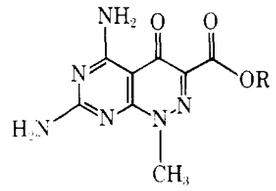
The cyclization behavior of the isocytosine **4a** with diethyl ketomalonate appeared to differ from that of the 2,4-diaminopyrimidine **7a**. In each case the products (**11** and **12**) were considered to be pyrimido[4,5-*c*]pyridazines since they provided the expected molecular ions for monomeric compounds and produced no vinyl C–H NMR signals (in Me_2SO-d_6) in



11a **11b**

11



12a, R = CH_3
b, R = C_2H_5

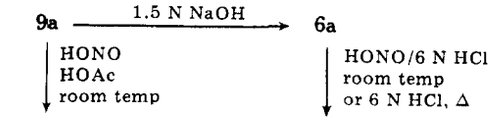
the region between δ 4 and 7 where pyrimidine C-5 protons would normally appear. The ultraviolet spectra suggested, however, that their chromophoric systems were different. The long wavelength maximum for **11** appeared at a substantially higher wavelength than that for the 4,5-diones **6**.

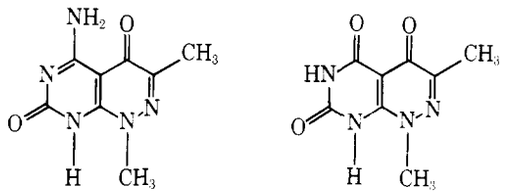
Pyrimidopyridazine **12a** was readily assigned the 4-one structure on the basis of spectral similarities (UV, NMR, and mass spectra) with **9a**. However, the different ultraviolet behavior of **11** could be explained by its being either **11a**, the result of cyclization in a reverse manner, or the expected product after tautomerization to **11b**, in which the enolic hydroxyl group at position 4 is hydrogen bonded to the ester carbonyl attached to position 3.

For an establishment of the structure for **11**, a method was sought for converting both **11** and **12** into a pair of compounds which would be either identical or isomeric. Model experiments were first carried out with the 5,7-diamino compound **9a** (Scheme I) in order to determine whether selective deamination would occur as reported for other fused pyrimidine systems.[5,6] The positions of hydrolytic attack were discerned readily by examination of NMR spectra; the 7-amino protons appear equivalent, whereas those of the 5-amino group are different because of the potential for hydrogen bonding to the 4-oxo group.[7]

Treatment of **9a** with refluxing 1.5 N NaOH for 24 h effected a selective hydrolysis at the 5 position to provide the 4,5-dione **6a**, whereas treatment with nitrous acid in aqueous

Scheme I

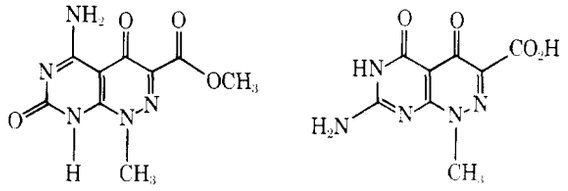




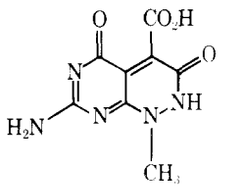
13 **14**

acetic acid at room temperature afforded the isomeric 4,7-dione **13**. Subsequent acid treatment of **6a** with either nitrous acid or hot 6 N HCl produced the 4,5,7-trione **14**.

In an analogous manner, the diamino compound **12a** was treated with nitrous acid to give the 4,7-dione **15** and with aqueous NaOH to give the 3-carboxy-4,5-dione **16** (isolated alternatively as the free acid and the disodium salt). Saponification of compound **11** at room temperature produced the dione acid **17** (isolated as the disodium salt). Microanalytical data indicated that the hygroscopic acid salts **16** and **17** had



15 **16**



17

similar elemental compositions (with minor differences in hydration), but the ultraviolet data indicated clearly that these two compounds were different. Since **12a** provided spectral data characteristic of the 4-ones and since the dione acid produced from it was not the same as that produced from the dione **11**, we can now rule out the tautomeric 4-enol structure **11b** and propose the structure for **11** to be the 3,5-dione **11a** (or a tautomer).

Reasons for this curious and unpredicted reversal in orientation are unclear.

Experimental Section

Melting points were run on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra (Nujol) were recorded on a Perkin-Elmer 267 grating infrared spectrophotometer and quantitative ultraviolet spectra on either Cary 118 or Cary 15 instruments. NMR spectra were determined with Varian T-60 and XL-100 spectrometers with tetramethylsilane as the internal standard; Fourier transform was utilized in cases of poor solubility. Low-resolution mass spectra were obtained with a Varian MAT CH5 DF double-focusing mass spectrometer at 70 eV unless otherwise stated, and probe temperatures were noted; accurate masses were determined by peak matching at 10 000 resolution, 10% valley definition; the MIKES technique (mass analyzed ion kinetic energy spectrometry)[8] was employed for metastable analysis. Accelerating voltage scans keeping the electric and magnetic sectors constant and field desorption data were determined with a Varian MAT 731 spectrometer. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. All C, H, N analyses not reported here were acceptable (±0.4%) and can be found along with other physical data in the supplementary data section.[9] Methylhydrazine was obtained from

Eastman Organic Chemicals. Methyl pyruvate and diethyl ketomalonate were obtained from Aldrich Chemical Co.

6-(1-Alkylhydrazino)pyrimidines. (A) Isocytosines (4). These compounds were prepared from 6-chloroisocytosine[10] and the appropriate hydrazine in refluxing aqueous media. Very pure starting materials should be used since the products are not purified well by ordinary recrystallization procedures. Several are extremely sensitive to the presence of oxygen, particularly when an excess of the starting hydrazine is absent.

6-(1-Methylhydrazino)isocytosine (4a).[11] A stirred mixture of 17.50 g (0.12 mol) of 6-chloroisocytosine[10] and 27.70 g (0.60 mol) of methylhydrazine in 900 mL of water was refluxed for 3 h, and the resulting solution was allowed to stand at room temperature for 6 h before being stored at 0 °C overnight. White crystals were collected by filtration, washed well with 800 mL of water and 200 mL of 95% ethanol, and dried under vacuum at 70 °C: yield 11.01 g (56%); mp 274–280 °C dec; NMR (Me_2SO-d_6) δ 3.12 (s, 3 H), 4.47 (br s, 2 H), 5.00 (s, 1 H), 6.16 (br s, 2 H), 9.68 (br s, 1 H); UV λ_{max} (CH_3OH) 225.5 nm (ϵ 24 000), 274 (17 300). Anal. Calcd for $C_5H_9N_5O \cdot 0.5H_2O$: C, 36.58; H, 6.14; N, 42.66. Found: C, 36.42; H, 6.06; N, 42.61.

Reaction conditions for **4u–x:** (starting hydrazine, molar ratio of the hydrazine to 6-chloroisocytosine, reflux time, yield).

6-(1-Ethylhydrazino)isocytosine (4u):[11] (ethylhydrazine,[12] 2.5:1, 1.5 h, 59%); mp 249–250 °C dec. Anal. ($C_6H_{11}N_5O$).

6-[1-(2-Hydroxyethylhydrazino)]isocytosine (4v): (2-hydroxyethylhydrazine,[13] 5:1, 1.8 h, 54%); mp 232–239 °C dec. Anal. ($C_6H_{11}N_5O_2$).

6-(1-*n*-Butylhydrazino)isocytosine (4w):[11] (*n*-butylhydrazine,[12] 2.2:1, 4 h, 77%); mp 208–215 °C dec. Anal. ($C_8H_{15}N_5O$).

6-(1-Benzylhydrazino)isocytosine (4x): (benzylhydrazine dihydrochloride[13] along with triethylamine, 2:1, +7.5 molar equiv of triethylamine), 9 h, 67%); mp 270–290 °C dec. Anal. ($C_{11}H_{13}N_5O$).

(B) Pyrimidines (7). Conditions: (starting pyrimidine, molar ratio of the pyrimidine to methylhydrazine, reaction medium, reflux time, recrystallization solvent, yield).

2,4-Diamino-6-(1-methylhydrazino)pyrimidine (7a):[11] (6-chloro-2,4-diaminopyrimidine,[13] 1:2.5, CH_3OH, 18 h, 50:1 CH_3OH/methylhydrazine, 42%); mp 214–217 °C dec. Anal. ($C_5H_{10}N_6$).

2-Amino-4-mercapto-6-(1-methylhydrazino)pyrimidine (7b): (2-amino-6-chloro-4-mercaptopyrimidine,[14] 1:2.1, H_2O, 24 h at room temperature, H_2O containing roughly equimolar amounts of methylhydrazine and product, 71%); mp 244–247 °C dec. Anal. ($C_5H_9N_5S$).

2-Amino-4-chloro-6-(1-methylhydrazino)pyrimidine (7d): (2-amino-4,6-dichloropyrimidine,[13] 1:3.6, CH_3OH, 0.5 h, CH_3OH, 63%); mp 196–198 °C. Anal. ($C_5H_8N_5Cl$).

2-Amino-4-methoxy-6-(1-methylhydrazino)pyrimidine (7c). A mixture of 5.00 g (0.0288 mol) of **7d** and sodium methoxide solution, prepared from 0.70 g (0.030 g-atom) of freshly cut sodium and 300 mL of anhydrous methanol, contained in a 500-mL glass-lined steel bomb was heated in an oven (preheated) at 140–156 °C for 10 h. After cooling gradually to room temperature, the yellow solution was concentrated under reduced pressure to a tan solid. Vacuum sublimation of this residue at 150 °C (0.1–0.2 torr) gave 2.43 g of white crystals whose NMR spectrum (Me_2SO) suggested a mixture (approximately 2:1) of the desired (methylhydrazino)pyrimidine and a closely related methylamino-substituted byproduct. A subsequent fractional vacuum sublimation at 115 °C (0.1–0.2 torr) provided 0.85 g of white crystals, mp 150–152 °C. Anal. ($C_6H_{11}N_5O$).

2-Amino-4-(1-methylhydrazino)pyrimidine (7e). To a mixture of 2.14 g (0.0165 mol) of 2-amino-4-chloropyrimidine[15] and 25 mL of methanol at reflux was added 1.90 g (0.0412 mol) of methylhydrazine. The resulting solution was heated at reflux for 2 h before being concentrated under reduced pressure (<50 °C) to an oily residue. Trituration of the residue with 25 mL of benzene produced a white precipitate which was collected and extracted five times with boiling benzene. The benzene solutions (200 mL total) were combined, concentrated to cloudiness, and allowed to cool to room temperature. The separated straw-colored crystals were collected and dried under reduced pressure, yield 0.625 g. The benzene-insoluble solid was recrystallized from ethanol, dissolved in water, and neutralized with 1 N NaOH. Removal of the solvent at reduced pressure, extraction of the white residue with boiling benzene, and subsequent crystallization gave a second crop of the product: combined yield 1.15 g (50%); mp 141–143 °C. Anal. ($C_5H_9N_5$).

Cyclizations to 7-Aminopyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-diones (6). The appropriate α-keto ester was added to a refluxing mixture or a solution prepared from very pure (alkylhydrazino)isocytosine **4** and filtered solvent in the proportion of 1 g in 100 mL (Table I). Significant exceptions to this proportion were the preparations of **6f** (1 g in 30 mL), **6j** (1 g in 65 mL), and **6u** (1 g in 40 mL). Precipitated **6** was collected by filtration of the hot reaction mixture, washed quickly with a small portion of fresh reaction solvent, and then dried at 70 °C in a vacuum oven. A specific example is described below for the preparation of **6a**.

No compound **6** melted or decomposed below 280 °C, and all products of direct cyclization provided solvent-free compounds except for **6x**, which was isolated as the hemihydrate.[9]

7-Amino-1,3-dimethylpyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-dione (6a). Method A. To a stirred, refluxing solution of 8.00 g (0.0487 mol) of 6-(1-methylhydrazino)isocytosine hemihydrate (**4a**) in 1 L of water was added 6.00 g (0.0588 mol) of methyl pyruvate. After 70 min, greenish-yellow solid was collected by filtration of the hot mixture, washed with two portions of water totaling 100 mL, and dried under vacuum at 70 °C: yield 5.11 g (51%); mp >300 °C; NMR[16] (Me_2SO-d_6) δ 2.07 (s, 3 H), 3.71 (s, 3 H), 7.12 (br s, 2 H),[17] 10.75 (br s, 1 H);[17] pK_a 4.1 ± 0.1 and 8.6 ± 0.1; UV λ_{max} (CH_3OH) 255 nm (ϵ 40 000), 299.5 (7600), 310 sh (5600); mass spectrum (185 °C), *m/e* 207 (M, 100%), 179 (3), 166 (M − CH_3CN, 5),[18] 165 (10), 138 (8), 137 (3), 111 (72). The following selected accurate masses were determined: 207.0764 ($C_8H_9N_5O_2$), 179.0825 ($C_7H_9N_5O$), 166.0509 ($C_6H_6N_4O_2$). Anal. Calcd for $C_8H_9N_5O_2$: C, 46.37; H, 4.38; N, 33.80. Found: C, 46.48; H, 4.42; N, 33.91.

Method B. Refluxing a solution of 0.50 g (0.0024 mol) of **9a** in 35 mL of 1.5 N NaOH for 24 h, followed by acidification with 6 N HCl, afforded **6a** in 76% yield.

Hydrolysis of Esters 6.[9] **7-Amino-3-(1-carboxyethyl)-1-methylpyrimido[4,5-*c*]pyridazine-4,5-(1*H*,6*H*)-dione Disodium Salt (6k).** A mixture of 2.97 g (0.0101 mol) of **6j** in 67 mL of 10% (w/w) aqueous NaOH was swirled vigorously (vortex mixer) for 25 min. Although a complete solution was not obtained during the agitation, a solid began to precipitate after 20 min. The mixture was then allowed to stand at room temperature for 1 h before being chilled at 0 °C for 1.5 h. The granular white solid was collected, washed well with three portions of 95% ethanol totaling 75 mL, and dried overnight at room temperature in a vacuum desiccator: yield 2.42 g (70%); mp >300 °C. The dried sample was hygroscopic. Anal. Calcd for $C_{10}H_9N_5Na_2O_4 \cdot 0.5H_2O$: C, 37.74; H, 3.17; N, 22.01; Na, 14.45. Found: C, 37.69; H, 3.21; N, 22.05; Na, 14.44.

Also, the monosodium salt **6g** (isolated as the monohydrate) and the disodium salt **6m** were prepared similarly, mp (in each case) >300 °C.

6-Pyrimidylhydrazones of Methyl Pyruvate. Methyl Pyruvate *N*-(2-Amino-4-mercapto-6-pyrimidyl)-*N*-methylhydrazone (8b).[19] A mixture of 0.337 g (0.0022 mol) of **7b**, 0.300 g (0.0029 mol) of methyl pyruvate, and 25 mL of anhydrous methanol was stirred at reflux, and a complete solution formed. After 19 h the yellow solution was allowed to cool to room temperature during a 3-h period. The yellow needles that separated were collected, washed with cold methanol, and dried under reduced pressure (70 °C): yield 0.430 g (77%); mp > 191 °C dec; NMR (Me_2SO-d_6) δ 2.20 (s, 3 H), 3.38 (s, 3 H), 3.81 (s, 3 H), 6.17 (s, 1 H), 6.85 (br s, 2 H), 11.35 (br s, 1 H); NMR (CF_3COOH) (isomer A) δ 2.49 (s, 3 H), 3.67 (s, 3 H), 4.12 (s, 3 H), 6.65 (s, 1 H); NMR (CF_3COOH) (isomer B) δ 2.61 (s, 3 H), 3.67 (s, 3 H), 4.08 (s, 3 H), 6.56 (s, 1 H); UV λ_{max} (CH_3OH) 240 nm (ϵ 13 300), 290 (12 400), 317 (13 400), 351 (15 100). Anal. Calcd for $C_9H_{13}N_5O_2S$: C, 42.34; H, 5.13; N, 27.43; S, 12.56. Found: C, 42.46; H, 5.19; N, 27.33; S, 12.48.

Reaction conditions for other hydrazones of methyl pyruvate: (starting hydrazinopyrimidine, molar ratio of the pyrimidine to methyl pyruvate, reaction medium, reflux time, yield).

Methyl Pyruvate *N*-(2-Amino-3,4-dihydro-4-oxo-6-pyrimidyl)hydrazone (3): (6-hydrazinoisocytosine,[4] 1:1.2, H_2O, 1.5 h, 70%); mp 282–287 °C dec. Anal. ($C_8H_{11}N_5O_3$).

Methyl Pyruvate *N*-(2-Amino-4-methoxy-6-pyrimidyl)-*N*-methylhydrazone (8c): (7c,[20] 1:1.35, CH_3OH, 3.5 h, 60%); mp 126–127 °C. Anal. ($C_{10}H_{15}N_5O_3$).

Methyl Pyruvate *N*-(2-Amino-4-chloro-6-pyrimidyl)-*N*-methylhydrazone (8d): (7d, 1:1.3, CH_3OH, 1 h, 95%); mp 194–195 °C. Anal. ($C_9H_{12}N_5O_2Cl$).

Methyl Pyruvate *N*-(2-Amino-4-pyrimidyl)-*N*-methylhydrazone (8e): (7e, 1:1.5, CH_3OH, 24 h, 27%), mp 161–163 °C. Anal. ($C_9H_{13}N_5O_2$).

5,7-Diamino-1,3-dimethylpyrimido[4,5-*c*]pyridazin-4(1*H*)-one (9a). To a solution of 500 mg (3.24 mmol) of **7a** in 15 mL of anhydrous methanol at reflux was added 496 mg (4.86 mmol) of methyl pyruvate over a 5-min period. Reflux was continued for 5 h before the separated solid was collected by suction filtration of the hot mixture, washed with methanol, and dried under vacuum (70 °C) to give 508 mg (76%) of analytically pure tan microcrystals: mp >275 °C; NMR (Me_2SO-d_6) δ 2.14 (s, 3 H), 3.74 (s, 3 H), 6.84 (br s, 2 H),[17] 7.72 (br d, 1 H, J = 4 Hz),[17] 8.96 (br d, 1 H, J = 4 Hz);[17] NMR (CF_3COOH) δ 2.47 (s, 3 H),

4.05 (s, 3 H), 8.44 (br s, 1 H); UV λ_{max} (CH_3OH) 222 nm (ϵ 12 800), 247 (31 100), 306 (11 600); mass spectrum (140 °C), *m/e* 206 (M, 78%), 165 (M − CH_3CN, 19), 137 (15), 110 (100), 68 (23), 43 (40). Anal. Calcd for $C_8H_{10}N_6O$: C, 46.59; H, 4.89; N, 40.76. Found: C, 46.66; H, 4.98; N, 40.69.

7-Amino-1,3-dimethyl-5-mercaptopyrimido[4,5-*c*]pyridazin-4(1*H*)-one(9b). A mixture of 730 mg (2.86 mmol) of **8b** and 5 mL of glacial acetic acid was gradually heated to reflux over a 20-min period. Complete solution did not occur, but a thick yellow precipitate formed. During reflux the mixture turned dark brown, and the odor of H_2S could be detected. After 1 h, green solid was collected from the hot mixture, washed with water, and dried under reduced pressure, yield 250 mg. Recrystallization of this crude product from a large volume of methanol afforded 66 mg (10%) of the desired product as small tan crystals, mp >300 °C. Anal. ($C_8H_9N_5OS$).

7-Amino-1,3-dimethyl-5-methoxypyrimido[4,5-*c*]pyridazin-4(1*H*)-one (9c). A mixture of 4.00 g (0.0158 mol) of **8c** and 20 mL of glacial acetic acid was heated at reflux for 2 h and allowed to cool to room temperature before a small amount of sticky, dark substance was removed by filtration (suction). The filtrate was concentrated under reduced pressure (60 °C) to a sticky residue. This residue was taken up in 50 mL of methanol; the small portion that remained undissolved was removed by filtration, and the solvent was again removed under reduced pressure. A solution of the green residue in $CHCl_3$ was added to a column of silica gel (300 g) in benzene. Elution of the column with chloroform and chloroform/ethyl acetate mixtures and finally with pure ethyl acetate, respectively, effected separation of the desired product which came off in ethyl acetate, yield 0.400 g. An analytical sample was obtained by recrystallization from ethyl acetate, mp >275 °C dec. Anal. ($C_9H_{11}N_5O_2$).

7-Amino-5-[2-(2-amino-4-chloro-6-pyrimidyl)-2-methylhydrazino]-1,3-dimethylpyrimido[4,5-*c*]pyridazin-4(1*H*)-one (10). (A) A mixture of 0.20 g (0.0012 mol) of **7d**, 0.30 g (0.0012 mol) of **8d** and 10 mL of *n*-propanol was stirred at reflux, and a complete solution gradually formed before the product began to separate. After 65 h the resulting mixture was filtered while hot. The collected bluish-white powder was washed with *n*-propanol and dried under reduced pressure: yield 0.068 g (16%); mp >300 °C. Anal. Calcd for $C_{13}H_{15}N_{10}OCl$: C, 43.04; H, 4.17; N, 38.61; Cl, 9.77. Found: C, 43.08; H, 4.20; N, 38.45; Cl, 9.82.

(B) Refluxing 0.51 g of **8d** in 10 mL of *n*-propanol for 6 days afforded 0.058 g of **10**.

7-Amino-4-carbethoxy-1-methylpyrimido[4,5-*c*]pyridazine-3,5(1*H*,2*H*)-dione (11a). To a mixture of 6.57 g (0.040 mol) of 6-(1-methylhydrazino)isocytosine hemihydrate (**4a**) and 8.71 g (0.050 mol) of diethyl ketomalonate was added 400 mL of water. The mixture was heated under reflux for 0.5 h while an orange solution formed and then a yellow-orange solid precipitated. This solid, which was collected by filtration of the hot mixture, washed with water, and dried under vacuum (70 °C), weighed 7.96 g. A 1.0-g sample of this solid was recrystallized twice from large volumes of water to give 0.70 g of small orange-yellow crystals: mp >300 °C; IR $\nu_{C=O}$ 1745 cm^{-1}; NMR (CF_3COOH) δ 1.50 (t, 3 H), 4.27 (s, 3 H), 4.70 (q, 2 H), 7.15 (br s, 2 H); mass spectrum (field desorption), *m/e* 265 (M). Anal. Calcd for $C_{10}H_{11}N_5O_4$: C, 45.28; H, 4.18; N, 26.41. Found: C, 45.41; H, 4.28; N, 26.19.

11a was also prepared in glacial acetic acid (87% yield) and absolute ethanol (77% yield).

3-Carbomethoxy-5,7-diamino-1-methylpyrimido-[4,5-*c*]pyridazin-4(1*H*)-one (12a). To a stirred mixture of 0.77 g (0.0050 mol) of **7a** and 50 mL of anhydrous methanol was added 1.16 g (0.0067 mol) of diethyl ketomalonate at room temperature. An orange solution resulted as the mixture was heated to reflux over a 5-min period. The crude (transesterified) product which separated during the subsequent 72-h reflux period was collected by suction filtration of the hot mixture, washed with methanol, and dried under reduced pressure (70 °C) to give 0.80 g of a pale yellow solid, mp 272–274 °C. Recrystallization of 0.70 g of this solid from methanol afforded 0.55 g of pale yellow needles: mp 274–276 °C; IR $\nu_{C=O}$ 1725 cm^{-1}; NMR (Me_2SO-d_6) δ 3.80 (s, 3 H), 3.82 (s, 3 H), 7.07 (br s, 2 H), 7.90 (br d, 1 H, J = 4 Hz), 8.80 (br d, 1 H, J = 4 Hz); UV λ_{max} (CH_3OH) 228 nm (ϵ 15 200), 255.5 (30 300), 261 sh (29 000), 313 (8700); mass spectrum (140 °C), *m/e* 250 (M, 76%), 219 (24), 206 (M − CO_2, 10),[21] 192 (M − CO_2CH_2, 48),[21] 191 (M − CO_2CH_3, 18),[21] 165 (M − $NCCO_2CH_3$, 22).[21] Selected accurate masses were determined: 250.0815 ($C_9H_{10}N_6O_3$), 206.0916 ($C_8H_{10}N_6O$), 165.0656 ($C_6H_7N_5O$). Anal. Calcd for $C_9H_{10}N_6O_3$: C, 43.20; H, 4.03; N, 33.59. Found: C, 43.12; H, 4.05; N, 33.54.

3-Carbethoxy-5,7-diamino-1-methylpyrimido-[4,5-*c*]pyridazin-4(1*H*)-one (12b). Preparation was similar to that of **12a**, except that the reaction medium was absolute ethanol, mp 238.5–239.5 °C. Anal. ($C_{10}H_{12}N_6O_3$).

5-Amino-1,3-dimethylpyrimido[4,5-*c*]pyridazine-4,7(1*H*,8*H*)-dione (13). A mixture of 0.20 g (0.00097 mol) of **9a** in 20 mL of glacial acetic acid was warmed gently (<50 °C) in order to effect solution before a solution of 0.69 g (0.010 mol) of sodium nitrite in 5 mL of water was added dropwise. The clear reaction mixture was allowed to cool to room temperature before an additional 0.69 g of sodium nitrite crystals was added. After standing at room temperature for 70 h, the solution was concentrated under vacuum to a fluffy white solid which was washed three times with a total of 25 mL of water and dried under reduced pressure (70 °C), yield 0.17 g. Recrystallization of 0.11 g of this crude product from glacial acetic acid afforded 0.076 g of a white powder: mp >300 °C; NMR (Me_2SO-d_6) δ 2.13 (s, 3 H), 3.67 (s, 3 H), 8.04 (br, 1 H), 9.64 (br, 1 H), 11.06 (br, 1 H); NMR (CF_3COOH) δ 2.50 (s, 3 H), 4.19 (s, 3 H), 9.00 (br s, 1 H). Anal. Calcd for $C_8H_9N_5O_2$: C, 46.37; H, 4.38; N, 33.80. Found: C, 46.17; H, 4.47; N, 33.92.

1,3-Dimethylpyrimido[4,5-*c*]pyridazine-4,5,7(1*H*,6*H*,8*H*)-trione (14). Method A. To a solution of 0.40 g (0.0019 mol) of **6a** in 6 N hydrochloric acid at room temperature was added dropwise over a 10-min period a solution of 0.40 g (0.0058 mol) of sodium nitrite in 10 mL of water. The yellow solution was stirred at room temperature for 46 h before being adjusted to pH 5.3 with 4 N sodium hydroxide solution. The mixture was then allowed to cool back to room temperature before the precipitated white solid was collected, washed with 15 mL of water, and dried under vacuum (70 °C), yield 0.23 g. This crude product was recrystallized once from water to give 0.19 g of a white solid (22.2% inorganic residue on combustion analysis). Subsequent recrystallization of 0.14 g of this solid from glacial acetic acid gave 0.078 g of fluffy white crystals: mp >300 °C; NMR (CF_3COOH) δ 2.70 (s, 3 H), 4.40 (s, 3 H); NMR (Me_2SO-d_6) δ 2.09 (s, 3 H), 3.76 (s, 3 H), 11.09 (br s, 2 H); mass spectrum (210 °C), *m/e* 208 (M, 100%), 191 (56), 167 (M − CH_3CN, 68). Anal. Calcd for $C_8H_8N_4O_3$: C, 46.16; H, 3.87; N, 26.91. Found: C, 45.93; H, 3.96; N, 26.73.

Method B. Refluxing a solution of 0.40 g (0.0019 mol) of **6a** in 50 mL of 6 N hydrochloric acid for 75 h, followed by adjustment to pH 5 with 4 N NaOH, afforded 0.18 g of **14** as the hemihydrate after recrystallization from glacial acetic acid.

5-Amino-3-carbomethoxy-1-methylpyrimido[4,5-*c*]pyridazine-4,7(1*H*,8*H*)-dione (15). Within 1 min glacial acetic acid (25 mL) and a solution of 1.0 g (0.014 mol) of sodium nitrite in 6 mL of water, respectively, were added to a 50-mL flask contiaining 0.30 g (0.0012 mol) of **12a**. A blue-green solution formed with effervescence, but the color gradually faded to pale yellow. After 18 h the solvent was removed at 40 °C under vacuum. The yellow residue was triturated with 10 mL of water, and the yellowish-white solid was collected and dried under vacuum (70 °C). Recrystallization from glacial acetic acid gave 0.15 g (50%) of yellow crystals: mp >300 °C; NMR (Me_2SO-d_6) δ 3.72 (s, 3 H), 3.81 (s, 3 H), 8.90 (br d, 1 H, J = 4 Hz), 9.52 (br d, 1 H, J = 4 Hz), 11.20 (br s, 1 H); UV λ_{max} (CH_3OH) 257 nm (ϵ 33 600), 314 (8300); mass spectrum (250 °C), *m/e* 251 (M, 76%), 220 (39), 193 (67), 166 (M − $NCCO_2CH_3$, 34), 111 (100). Anal. Calcd for $C_9H_9N_5O_4$: C, 43.03; H, 3.61; N, 27.88. Found: C, 42.86; H, 3.73; N, 27.79.

7-Amino-3-carboxy-1-methylpyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-dione Disodium Salt (16). A mixture of 0.250 g (0.0010 mol) of **12a** and 12.5 mL of 4 N sodium hydroxide solution was stirred at reflux for 2.5 h and then allowed to stand at room temperature for 1 h before the white solid was collected. This solid was recrystallized twice from water/methanol, dried under vacuum (70 °C), and allowed to air-equilibrate to give 0.146 g (45%) of disodium salt as a 2.25 hydrate: mp >300 °C; NMR (CF_3COOH) δ 4.30 (s, 3 H), 7.12 (br s, 2 H); UV λ_{max} (pH 2) 266.5 nm (ϵ 45 700), 314.5 (6300); UV λ_{max} (1 N NaOH) 251 nm (30 400), 305.5 (10 800). Anal. Calcd for $C_8H_5N_5O_4Na_2 \cdot 2.25\ H_2O$: C, 29.87; H, 2.98; N, 21.77; Na, 14.29. Found: C, 29.60; H, 2.60; N, 21.54; Na, 14.08.

The free acid was prepared by dissolving the isolated salt in warm water, followed by adjustment to pH 5 with 6 N HCl, mp >300 °C. Anal. ($C_8H_7N_5O_4$).

7-Amino-4-carboxy-1-methylpyrimido[4,5-*c*]pyridazine-3,5(1*H*,2*H*)-dione Disodium Salt (17). Saponification of 1.00 g (0.00377 mol) of **11a** in 35 mL of 7.2% aqueous solution of sodium hydroxide at room temperature for 4 h and then at 0 °C overnight afforded orange-yellow hygroscopic crystals, yield 0.85 g (after recrystallization from 1:1 methanol/water).

Air equilibration of these crystals gave the trihydrate: mp >300 °C; NMR (CF_3COOH) δ 4.33 (s, 3 H), 7.13 (br s, 2 H); NMR (D_2O) δ 3.97 (s); UV λ_{max} (pH 2) 248 nm (ϵ 22 400), 255 sh (21 100), 380 (4900); UV λ_{max} (1 N NaOH) 253.5 nm (35 800), 276 sh (8000), 409 (5400). Anal.

Calcd for $C_8H_5N_5O_4Na_2 \cdot 3H_2O$: C, 28.66; H, 3.31; N, 20.89. Found: C, 28.67; H, 3.25; N, 20.86.

After drying at 100 °C under high vacuum, the crystals analyzed for a hemihydrate.

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Supplementary Material Available. Full data available include the following: microanalyses on compounds **3, 4u–x, 6, 7, 8c–e, 9b,c, 12b, 14** (by method B), and **16** (free acid); UV data on compounds **3, 4u–x, 6, 7, 8c–e, 9b,c, 10, 12b, 13, 14, and 16** (free acid); NMR data on compounds **3, 4u–x, 6, 7, 8c–e, 9b,c, 10, 12b,** and **16** (free acid); and mass spectral data on **6f, 6h, 6o, 6s, 9b,c 10, 13,** and **16** (free acid) (13 pages). Ordering information is given on any current masthead page.

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(16) Fourier transform.
(17) Exchangeable with D_2O.
(18) A metastable ion for this fragmentation was detected by accelerating voltage scans, keeping the electric and magnetic sectors constant.
(19) When dissolved in 50 mL of methanol at room temperature for 20 days, 100 mg of **8b** provided 30 mg of the analytically pure disulfide as off-white crystals: mp 215–217 °C dec; NMR (Me_2SO-d_6) δ 2.21 (s, 3 H), 3.50 (s, 3 H), 3.69 (s, 3 H), 6.71 (br s, 2 H), 6.77 (s, 1 H); mass spectrum (field desorption), *m/e* 508 (M). Anal. Calcd for $C_{18}H_{24}N_{10}O_4S_2$: C, 42.51; H, 4.76; N, 27.54; S, 12.61. Found: C, 42.41; H, 4.82; N, 27.45; S, 12.58.
(20) It also proved convenient to utilize a 2:1 mixture as described (**7c**) for this synthesis since the hydrazone is easily separated from the reaction mixture by filtration.
(21) A metastable ion for this fragmentation was detected by the MIKES[8] technique.

2-(Trichloroacetyl)pyrroles as Intermediates in the Preparation of 2,4-Disubstituted Pyrroles

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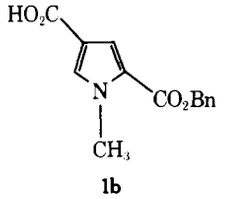
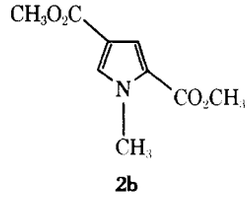
The preparation of several N–H and *N*-methyl-2,4-disubstituted pyrroles is described. Friedel–Crafts formylation using α,α-dichloromethyl methyl ether/$AlCl_3$ and a 2-substituted pyrrole as substrate introduced a 4-formyl group cleanly onto the pyrrole ring in high yield. The question of isomer production in this step was rigorously proven by preparing all isomers in contention and by comparison to known compounds. The use of 2-(trichloroacetyl)-pyrroles as substrates for the Friedel–Crafts formylation allows facile preparation of 4-formyl-2-carboxy-, -2-(alkoxycarbonyl)-, and -2-(aminocarbonyl)pyrroles and provides easy entry to 3-substituted pyrroles by removal of the 2-(trichloroacetyl) group via the carboxylic acid.

In the course of our work on the synthesis of polypyrrole antibiotics, it became necessary to prepare, efficiently and on a large scale, *N*-methylpyrroles suitably substituted at C-2 and C-4. Specifically, we required 2-benzyloxycarbonyl-4-carboxy-*N*-methylpyrrole (**1b**). A recent report[1] of the synthesis of 2,4-bis(methoxycarbonyl)-*N*-methylpyrrole (**2b**) seemed to offer an excellent beginning. However, due to some shortcomings of that procedure, which will be discussed, we have developed an alternate process.

The key to the present method is the Friedel–Crafts formylation of a 2-substituted pyrrole by $AlCl_3/\alpha,\alpha$-dichloromethyl methyl ether. This combination was reported[2] to formylate 2-(methoxycarbonyl)pyrrole (**3a**) at −20 °C selectively in the 4 position. We have extended this process to now



1b



2b

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