Synthesis of Imidazo[1,5-*c*]pyrimidine Derivatives [1]

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Received October 7, 1985

Two complementary procedures, each starting from 6-aminomethyluracil (**2**), have been used to prepare imidazo[1,5-*c*]pyrimidines with a variety of substituents at positions 3, 5, 6, and 7. The starting material, **2**, can be readily prepared from commercially available 6-chloromethyluracil by reaction with anhydrous ammonia. In the first procedure, **2** is acylated and then cyclodehydrated by reaction with phosphorus oxychloride to give a separable mixture of a 3-substituted 5,7-dichloroimidazo[1,5-*c*]pyrimidine and a 3-substituted 7-chloroimidazo[1,5-*c*]pyrimidin-5(6*H*)-one. The relative product distribution is subject to some control by the choice of the acyl substituent on the starting uracil. The resulting dichloro compounds were derivatized by reaction at the 5-position with various nucleophiles, although the 7-chloro substituent is unreactive. An alternative synthetic method proceeds from **2** in six efficient steps (protection as the phthalimide, chlorination, nucleophilic substitution, deprotection, acylation, and cyclodehydration) to 3-substituted-5,7-bis(methylthio)imidazo[1,5-*c*]pyrimidines. These compounds may also be derivatized by nucleophilic substitution at the 5-position.

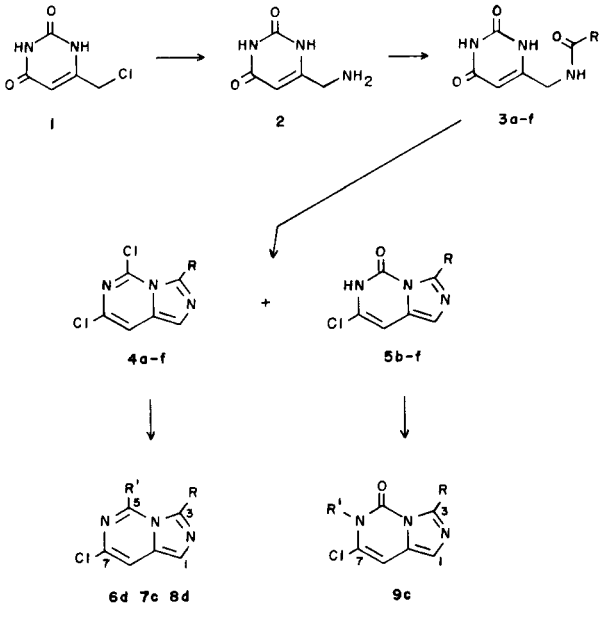
J. Heterocyclic Chem., **23**, 981 (1986).

As part of a medicinal chemistry project in our laboratories, we became interested in the synthesis of the previously unreported imidazo[1,5-*c*]pyrimidine ring system [2]. Cyclodehydration of amides derived from 4-aminomethylpyrimidines seemed to be an attractive potential route to this ring system, but success with such an approach has not been reported [3], although similar cyclodehydrations have been used for many years to prepare imidazo[1,5-*a*]-pyridines from derivatives of 2-aminomethylpyridine [5-10]. We now report two complementary procedures, both involving phosphorus oxychloride cyclodehydration of amides derived from 6-aminomethyluracil (**2**), which lead to several substituted derivatives of the imidazo[1,5-*c*]pyrimidine ring system.

Preparation of **2**, the key starting material for this work, has been reported by Klosa, who describes its preparation in quantitative yield from commercially available 6-chloromethyluracil by reaction with concentrated aqueous ammonia [11]. In our hands, such a reaction resulted in only low yields (5 to 10%) of isolated **2**, along with large amounts of an unidentified polymeric material. However, by reacting the 6-chloromethyluracil with anhydrous ammonia we were able to obtain **2** in 90% yield, with little contamination from by-products.

This amine was acylated to a variety of carboxamides **3** (see Scheme I). Subsequent reaction of, for example, the acetamide **3b** in refluxing phosphorus oxychloride gave a separable mixture of the 5,7-dichloro-3-methylimidazo-[1,5-*c*]pyrimidine (**4b**) and 7-chloro-3-methylimidazo[1,5-*c*]pyrimidin-5(6*H*)-one (**5b**). Attempts to convert **5b** to **4b** using several reagents (phosphorus oxychloride, phenylphosphonic dichloride, and phosphorus pentachloride/-phosphorus oxychloride) were unsuccessful, leaving **5b** untouched. The failure of refluxing phosphorus oxychloride to convert **5b** to **4b** suggested that in order to obtain **4b** from **3b**, the 2-oxo function of the uracil must be chlorinated before the amide function chlorinates and cyclizes. The steric bulk of the acyl substituent might therefore affect the relative proportions of **4** and **5** by affecting the rate of chlorination/cyclization of the amide.

Scheme I [a, b]

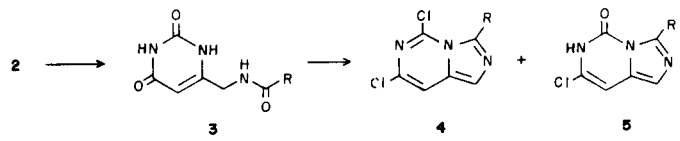


[a] Series a, R = H; b, R = CH_3; c, R = n-Pr; d, R = i-Pr; e, R = Ph; f, R = t-Bu.

[b] Compound 6, R' = N S; 7, R' = OCH_3; 8, R' = $SCH_2CH_2CH_3$; 9, R' = CH_3.

Table I

Preparation and Cyclodehydration of Acylaminomethyluracils



Compound	R	Method	Yield, %	Mp, °C	^{1}H NMR Data (DMSO-d_6)
3a	H	A	85	261-264 dec	8.42 (br t, 1, J = 6 Hz), 8.18 (s, 1), 5.42 (s, 1), 4.07 (d, 2, J = 6 Hz)
3b	Me	A	93	276-281 dec	8.25 (br t, 1, J = 6 Hz), 5.32 (s, 1), 3.95 (d, 2, J = 6 Hz), 1.90 (s, 3)
3c	*n*-Pr	B	54	251 dec	8.17 (br t, 1, J = 6 Hz), 5.30 (s, 1), 3.98 (d, 2, J = 6 Hz), 2.17 (t, 2, J = 6 Hz), 1.55 (m, 1, J = 6 Hz), 0.88 (t, 3, J = 6 Hz)
3d	*i*-Pr	B	69	243-248	8.20 (br t, 1, J = 6 Hz), 5.30 (s, 1), 3.98 (d, 2, J = 6 Hz), 1.08 (d, 6, J = 6 Hz)
3e	Ph	B	68	275-277 dec	8.1-7.3 (m, 6), 5.37 (s, 1), 4.20 (d, 2, J = 6 Hz)
3f	*t*-Bu	B	78	293-296 dec	7.98 (br t, 1, J = 6 Hz), 5.20 (s, 1), 3.97 (d, 2, J = 6 Hz), 1.15 (s, 9)
4a	H	C2 [a]	3	81-82.5	8.28 (s, 1), 7.43 (s, 1), 7.30 (s, 1) [g]
4b	Me	C4, C5 [b]	14	134-135	7.23 (s, 1), 7.12 (s, 1), 3.00 (s, 3) [g]
4c	*n*-Pr	C4, C1 [c, d]	15	74-77	7.70 (s, 1), 7.43 (s, 1), 3.32 (t, 2, J = 8 Hz), 1.82 (m, 2, J = 8 Hz), 1.02 (t, 3, J = 8 Hz)
4d	*i*-Pr	C1 [d]	31	90-93	7.30 (s, 1), 7.15 (s, 1),4.07 (m, 1), 1.45 (d, 6, J = 7 Hz) [g]
4e	Ph	C2 [e]	33	125-126	7.83 (s, 1), 7.62 (s, 1), 7.48 (br s, 5)
4f	*t*-Bu	C2 [d]	39	109-110	7.78 (s, 1), 7.47 (s, 1), 1.35 (s, 9)
5a	H	C2 [a]	0		
5b	Me	C4, C5 [f]	17	239 dec	6.72 (s, 1), 6.57 (s, 1), 2.70 (s, 3)
5c	*n*-Pr	C4, C1, C3 [c]	44	194-196	7.00 (s, 1), 6.63 (s, 1), 3.15 (t, 2, J = 7 Hz), 1.73 (m, 2, J = 7 Hz), 0.93 (t, 3, J = 7 Hz)
5d	*i*-Pr	C1 [a]	20	196-197	11.7 (br s, 1), 7.02 (s, 1), 6.67 (s, 1), 4.00 (m, 1), 1.30 (d, 2, J = 7 Hz)
5e	Ph	C2 [a]	13	214-215	7.8-7.2 (m, 5), 7.17 (s, 1), 6.72 (s, 1)
5f	*t*-Bu	C2 [a]	17	192 dec	7.37 (s, 1), 6.77 (s, 1), 1.55 (s, 9)

[a] Elution with 10% ethyl acetate in dichloromethane. [b] Extraction wth boiling benzene followed by recrystallization from cyclohexane. [c] Extraction with boiling cyclohexane. [d] Elution with 3% ethyl acetate in dichloromethane. [e] Elution with 5% ethyl acetate in dichloromethane. [f] Extraction with boiling benzene followed by ethanol recrystallization of the benzene-insoluble residue. [g] in deuteriochloroform.

The data in Table I indicate that greater steric bulk of the acyl substituent does influence the product distribution by favoring the formation of the dichloro compound **4**.

Compounds **4** and **5** can be further derivatized as suggested in Scheme I. Nucleophilic substitution of **4** is readily effected by sodium methoxide, sodium alkyl mercaptides, and various amines, and some examples of such nucleophilic displacement reactions with **4c** and **4d** are given in the Experimental Section. This substitution takes place presumably at the 5-position, to give compounds **6-8**, since the 7-chloro substituent is not activated by a ring nitrogen. We never observed any disubstitution of **4**, even under forcing conditions. The imidazopyrimidinones **5** can be alkylated on the 6-nitrogen (N-alkylation is indicated by the ir and ^{1}H nmr spectra) to give **9**; the example **9c** (R = methyl) is given in the Experimental.

Although the above sequence is convenient because it is short, the yields make it synthetically attractive only for compounds **4d-f**, **5c**, and their derivatives. The sequence is thus limited in scope by the choice of substituents at the 3-position, and also by the obligatory, yet unreactive,

Scheme II [a,b]

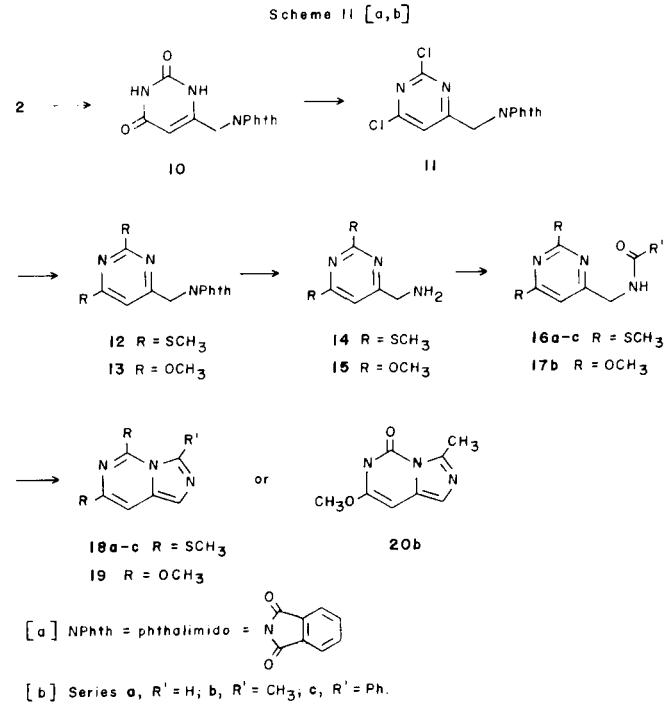
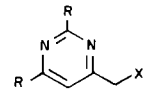


Table II

Intermediate Pyrimidines, 10-17



10-17

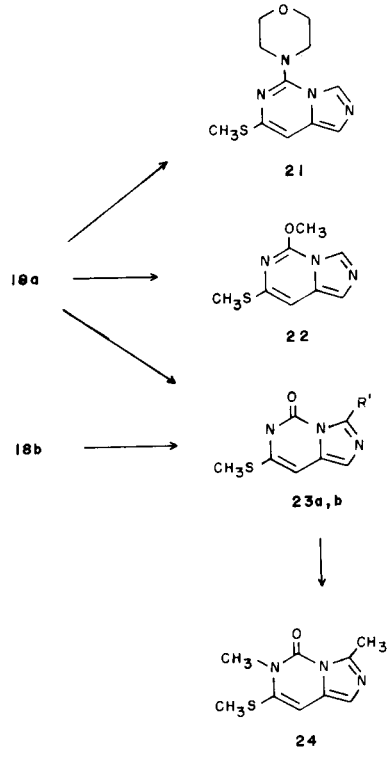
Compound	X	R	Yield, %	Mp, °C	^{1}H NMR Data (deuteriochloroform)
10	NPhth	OH	81	293-296	11.02 (br s, 2), 7.98 (br s, 4), 5.43 (s, 1), 4.53 (s, 2)
11	NPhth	Cl	67	223-225	7.88 (m, 4), 7.22 (s, 1), 4.97 (s, 2) [a]
12	NPhth	SMe	95	154-157	7.82 (m, 4), 6.70 (s, 1), 4.82 (s, 2), 2.52 (s, 3), 2.37 (s, 3)
13	NPhth	OMe	65	150-151	7.83 (m, 4), 6.25 (s, 1), 4.87 (s, 2), 3.97 (s, 3), 3.87 (s, 3)
14	NH_2	SMe	88	83-84	6.87 (s, 1), 3.80 (s, 2), 2.58 (s, 6), 1.65 (br s, 2)
15	NH_2	OMe	62	49-53	6.33 (s, 1), 3.97 (s, 3), 3.93 (s, 3), 3.77 (s, 2), 1.65 (s, 2)
16a	NHCHO	SMe	84	130-131	8.18 (br s, 1), 6.70 (s superimposed on br s), 4.35 (d, 2, J = 6 Hz), 2.52 (s, 6) [a]
16b	NHCOMe	SMe	85	145-146	6.77 (s superimposed on br s), 4.33 (d, 2, J = 6 Hz), 2.57 (s, 6), 2.07 (s, 3)
16c	NHCOPh	SMe	80	127-129	8.0-7.2 (m, 6), 6.80 (s, 1), 4.55 (d, 2, J = 6 Hz), 2.57 (s, 6)
17b	NHCOMe	OMe	66	97-102	6.93 (br s, 1), 6.33 (s, 1), 4.37 (d, 2, J = 6 Hz), 4.00 (s, 3), 3.97 (s, 3), 2.05 (s, 3)

[a] In DMSO-d_6.

7-chloro substituent. A complementary approach to the imidazo[1,5-*c*]pyrimidine ring system is shown in Scheme II. Again, the key starting material is 6-aminomethyluracil (**2**). Protection of the amine function as the phthalimide allows chlorination of the uracil, giving the dichloropyrimidine **11**. Nucleophilic substitution with sodium methyl mercaptide or sodium methoxide followed by deprotection of the amine and acylation leads to the amides **16** and **17**. The bis(methylthio)-substituted amides **16a-c** can be smoothly cyclodehydrated to the imidazo[1,5-*c*]pyrimidines **18a-c** under very mild conditions by briefly heating with one equivalent of phosphorus oxychloride in dioxane. In the case of the dimethoxy-substituted amide **17b**, the cyclization procedure leads cleanly to the imidazopyrimidinone **20b**, presumably by ether cleavage of the 5-methoxy substituent of intermediate **19b**, which was observed by tlc analysis during the course of this reaction, and which could be isolated after short reaction times. The fact that this methyl ether is quite susceptible to cleavage is indicated by this result, and by the facile conversion of **18a,b** to **23a,b** in refluxing sodium methoxide/methanol (*vide infra*).

This overall sequence proceeds in good overall yield (25-28% for the six steps from **2**) for the bis(methylthio)-imidazopyrimidines **18**, purification being necessary only after the final step. Compounds **18a-c** are subject to further derivatization by nucleophilic substitution, presumably at the activated 5-position (see Scheme III). Thus reaction of **18a** with morpholine gives **21**, and reaction

Scheme III [a]

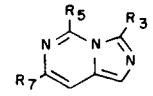


[a] Series a, R' = H; b, R' = CH_3.

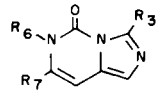
with a catalytic amount of sodium methoxide in refluxing methnol gives **22**. Reaction of **18a** with a full equivalent of

Table III

Imidazo[1,5-c]pyrimidines



6-8, 18, 19, 21, 22



9, 20, 23, 24

Compound	R_3	R_5	R_6		Yield, %	Mp, °C	^{1}H NMR Data (deuteriochloroform)
6d	*i*-Pr	$N(CH_2CH_2)_2S$	–	Cl	91	133-136 [a]	7.23, (s, 1), 6.95 (s, 1), 4.0-3.4 (br m, 5), 3.1-2.7 (br m, 4), 1.37 (d, 6, J = 6 Hz)
7c	*n*-Pr	OMe	–	Cl	81	77-79 [b]	7.05 (s, 1), 6.78 (s, 1), 4.15 (s, 3), 3.17 (t, 2, J = 8 Hz), 1.83 (m, 2, J = 8 Hz), 1.00 (t, 3, J = 8 Hz)
8d	*i*-Pr	*n*-PrS	–	Cl	81	65-69 [c]	7.22 (s, 1), 6.97 (s, 1), 4.13 (m, 1, J = 7 Hz), 3.32 (t, 2, J = 7 Hz), 1.85 (m, 1, J = 7 Hz), 1.43 (d, 6, J = 7 Hz), 1.10 (t, 3, J = 7 Hz)
9c	*n*-Pr	–	Me	Cl	46	88-89 [b]	6.92 (s, 1), 6.43 (s, 1), 3.57 (s, 3), 3.25 (t, 2, J = 8 Hz), 1.82 (m, 2, J = 8 Hz), 1.00 (t, 3, J = 8 Hz)
18a	H	SMe	–	SMe	71	112-114 [d]	7.93 (s, 1), 7.15 (s, 1), 6.80 (s, 1), 2.70 (s, 3), 2.48 (s, 3)
18b	Me	SMe	–	SME	66	124-126 [e]	7.00 (s, 1), 6.70 (s, 1), 3.03 (s, 3), 2.65 (s, 3), 2.52 (s. 3)
18c	Ph	SMe	–	SMe	77	117-118 [b]	7.7-7.2 (br, 5), 6.90 (s, 1), 2.53 (s, 3), 2.47 (s, 3)
19b	Me	OMe	–	OMe	36	119-122	6.88 (s, 1), 5.95 (s, 1), 4.15 (s, 3), 3.83 (s, 3), 2.80 (s, 3)
20b	Me	–	H	OMe	80	228 dec [f]	6.72 (s, 1), 5.70 (s, 1), 3.80 (s, 3), 2.70 (s, 3) [g]
21	H	$N(CH_2CH_2)_2O$	–	SMe	53	132-133	7.97 (s, 1), 7.17 (s, 1), 6.73 (s, 1), 4.1-3.4 (m, 8), 2.50 (s, 3)
22	H	OMe	–	SMe	83	73-74.5	8.12 (s, 1), 7.20 (s, 1), 6.75 (s, 1), 4.22 (s, 3), 2.52 (s, 3)
23a	H	–	H	SMe	71	201-202 dec	11.43 (br s, 1), 8.28 (s, 1), 7.05 (s, 1), 6.45 (s, 1), 2.50 (s, 3) [g]
23b	Me	–	H	SMe	75	221-222	11.08 (br s, 1), 6.87 (s, 1), 6.37 (s, 1), 2.75 (s, 3), 2.48 (s, 3) [a]
24	Me	–	Me	SMe	45	122-123 [b]	6.88 (s, 1), 6.25 (s, 1), 3.62 (s, 3), 2.90 (s, 3), 2.45 (s, 3)

[a] Mp of hydrochloride salt, 202-203°. [b] Recrystallized from cyclohexane. [c] Mp of bisulfate salt, 160-161°. [d] Recrystallized from benzene. [e] Recrystallized from benzene-hexanes. [f] Recrystallized from 2-propanol. [g] in DMSO-d_6.

sodium methoxide in refluxing methanol leads to the imidazopyrimidinone **23a**, presumably by cleavage of the intermediate ether **22** (observed by tlc and isolated; see Experimental) by the sodium methyl mercaptide generated during the course of the displacement reaction. The imidazopyrimidinone **23** may then be alkylated; an example is given in the Experimental Section for alkylation of **23b** to **24** by reaction with sodium hydride and iodomethane.

These two procedures, starting from 6-aminomethyluracil, thus provide access to imidazo[1,5-*c*]pyrimidines with a variety of substituents at positions 3, 5, 6, and 7. Alternative synthetic approaches to imidazo[1,5-*c*]pyrimidines with other substitution patterns, as well as evaluations of pharmacological activity, are underway in our laboratories.

EXPERIMENTAL

Melting points were obtained with a Uni-melt apparatus and are uncorrected. The ir spectra were obtained as Nujol mulls on a Perkin-Elmer Infracord spectrophotometer. The ^{1}H nmr spectra were measured using a Varian T-60 spectrometer and are reported (Tables I-III) in parts per million (δ) downfield from tetramethylsilane. Thin layer chromatography (tlc) analyses were performed, using the indicated eluant systems, with Uniplate™ (Analtech, Inc., Newark, DE) silica gel Gf plates. Preparative high performance liquid chromatography (hplc) separations were performed with a Waters Prep 500 instrument, using PrePak™-500/Silica cartridges. The microanalyses (Table IV) were performed by J. H. Gagnon and co-workers in the Central Research Analytical Group, 3M Co.

6-Aminomethyluracil (**2**).

6-Chloromethyluracil (from Aldrich Chemical Co., 200 g, 1.25 moles) was combined with 400 ml of anhydrous ammonia in a stainless steel high pressure reactor and allowed to stand overnight (18 hours) at room temperature. The reactor was then cooled and opened, and the excess ammonia was allowed to evaporate at room temperature. The solid mass was slurried with ethyl acetate, filtered, and air-dried. The material was then slurried with 1 ℓ of water, filtered, and dried in a vacuum oven at 110° to give 159 g (90%) of a light pink solid, mp 295-297° (lit 296-298° [11]).

This material was generally used without further purification at this stage. The analytically pure hydrochloride salt was obtained as follows: The crude product obtained above (10 g) was treated with 7 ml of concentrated hydrochloric acid in 250 ml of distilled water, the mixture was boiled for a few minutes, and the insolubles were removed by filtration of the hot mixture, amounting to 1.56 g of grey solid when dried. The filtrate was concentrated *in vacuo*, the residue was triturated with a small amount of methanol to give 10.1 g of pale yellow solid; ir: 1750, 1680, 1100 cm^{-1}; ^{1}H nmr (DMSO-d_6): 8.28 (br s, 5), 5.62 (s, 1), 3.67 (s, 2).

Anal. Calcd. for $C_5H_7N_3O_2$·HCl: C, 33.8; H, 4.5; N, 23.7. Found: C, 34.0; H, 4.4; N, 23.9.

6-Acylaminomethyluracils (**3**). Table I. General Procedures.

A mixture of the crude amine **2** (35 mmoles) and the appropriate anhydride (60 ml) was stirred 18 hours at room temperature. The solid

Table IV

Microanalytical Data

Compound	Formula	Analysis, % Calcd./% Found C	H	N
4a	$C_6H_6Cl_2N_3$	38.3/38.4	1.6/1.8	22.4/22.5
4b	$C_7H_5Cl_2N_3$	41.6/41.5	2.5/2.2	20.8/20.9
4c	$C_9H_9Cl_2N_3$	47.0/46.4	3.9/3.7	18.3/18.4
4d	$C_9H_9Cl_2N_3$	47.0/46.4	3.9/4.0	18.3/17.8
4e	$C_{12}H_7Cl_2N_3$	54.6/54.6	2.7/2.3	16.0/16.1
4f	$C_{10}H_{11}Cl_2N_3$	49.2/49.4	4.5/4.6	17.2/17.3
5b	$C_7H_6ClN_3O$	45.8/45.8	3.3/3.1	22.9/22.8
5c	$C_9H_{10}ClN_3O$	51.1/51.1	4.8/4.7	19.9/20.1
5d	$C_9H_{10}ClN_3O$	51.1/51.0	4.8/4.7	19.9/19.8
5e	$C_{12}H_8ClN_3O$	58.7/58.7	3.3/3.3	17.1/17.1
5f	$C_{10}H_{12}ClN_3O$	53.2/52.7	5.4/5.5	18.6/18.7
6d	$C_{13}H_7ClN_4S\cdot HCl$	46.9/46.6	5.4/5.5	16.8/16.9
7c	$C_{10}H_{12}ClN_3O$	53.2/53.1	5.4/5.3	18.6/18.7
8d	$C_{12}H_{16}ClN_3S\cdot H_2SO_4$	39.2/39.1	4.9/4.9	11.4/11.9
9c	$C_{10}H_{12}ClN_3O$	53.2/53.3	5.4/5.4	18.6/18.8
11	$C_{13}H_7Cl_2N_3O_2$	50.7/50.1	2.3/2.0	13.6/13.4
12	$C_{15}H_{13}N_3O_2S_2$	54.4/54.0	4.0/3.8	12.7/12.6
13	$C_{15}H_{13}N_3O_4$	60.2/59.6	4.4/4.1	14.0/13.9
16a	$C_8H_{11}N_3OS_2$	41.9/41.9	4.8/4.8	18.3/18.2
16b	$C_9H_{13}N_3OS_2$	44.4/44.6	5.4/5.4	17.3/17.3
16c	$C_{14}H_{15}N_3OS_2$	55.1/55.0	5.0/5.0	13.8/13.7
17b	$C_9H_{13}N_3O_3$	51.2/51.1	6.2/6.0	19.9/20.0
18a	$C_8H_9N_3S_2$	45.5/45.6	4.3/4.3	19.9/19.9
18b	$C_9H_{11}N_3S_2$	48.0/48.4	4.9/4.7	18.7/19.1
18c	$C_{14}H_{13}N_3S_2$	58.5/58.9	4.6/4.4	14.6/14.7
20b	$C_8H_9N_3O_2$	53.6/53.2	5.1/5.0	23.5/23.7
21	$C_{11}H_{14}N_4OS$	52.8/52.6	5.6/5.6	22.4/22.6
22	$C_8H_9N_3OS$	49.2/49.3	4.7/4.7	21.5/21.5
23a	$C_7H_7N_3OS$	46.4/46.5	3.9/3.9	23.2/23.2
23b	$C_8H_9N_3OS$	49.2/48.9	4.7/4.6	21.5/21.6
24	$C_9H_{11}N_3OS$	51.7/51.7	5.3/5.3	20.1/20.3

was then collected by filtration, washed with methanol, and dried in a vacuum oven at 110° (General Method A). Alternatively, in some cases the crude amine **2** (20 mmoles) and the appropriate anhydride (20 mmoles) were combined in 25 ml of dimethylformamide containing ~0.1 ml of triethylamine, heated at 130-150° for 3 hours, then filtered while hot to remove insolubles. The filtrate was poured into 200 ml of ice-water to precipitate a solid which was isolated by filtration, washed with water, and dried in a vacuum oven at 110° (General Method B). These intermediates were generally used in subsequent reactions without purification.

5,7-Dichloroimidazo[1,5-*c*]pyrimidines **9** and 7-chloroimidazo[1,5-*c*]pyrimidin-5(6*H*)-ones **10**. Table I. General Method C.

A general procedure is exemplified by the cyclization of the isobutyramide **3d**. Thus 3.00 g (14.2 mmoles) of **3d** in 50 ml of phosphorus oxychloride was heated at 75° for 4 hours, then at reflux for 16 hours. The dark solution was concentrated *in vacuo* and the residue carefully poured into about 200 ml of ice-water. The mixture was brought carefully to *p*H 7 by the addition, with cooling, of concentrated ammonium hydroxide, then extracted with 4 100-ml portions of chloroform. The combined extracts were washed with 3 100-ml portions of water, dried (magnesium sulfate), and concentrated *in vacuo* to 2.00 g of brown solid. This material was purified by hplc, eluting first with 3% ethyl acetate in dichloromethane, then changing to a 10% mixture of solvents. Thus were obtained 1.00 g (31%) of **4d** and 0.60 g (20%) of **5d**.

The other bicyclic compounds **4** and **5** were obtained by General Method C, using the appropriate starting amides **3**. The products were separated and purified by a variety of methods as indicated in Table I, including hplc (Method C1), flash chromatography [12] (Method C2), extraction of **5** from **4** with dilute aqueous sodium hydroxide (Method C3), preferential solubility of **4** in nonpolar solvents (Method C4), and recrystallization (Method C5).

Nucleophilic Substitutions of **4**.

We have carried out a number of nucleophilic displacements of the 5-chloro substituent of **4**. The following examples are representative; the products are listed in Tables III and IV.

7-Chloro-3-(2-propyl)-5-(4-thiomorpholino)imidazo[1,5-*c*]pyrimidine (**6d**).

Thiomorpholine (from Aldrich Chemical Co., 1.90 g, 18.4 mmoles) and **4d** (2.00 g, 8.70 mmoles) were combined in 30 ml of dioxane and stirred 6 hours at room temperature. The mixture was poured into 100 ml of chloroform, washed with 3 50-ml portions of water, dried (magnesium sulfate), and concentrated *in vacuo* to 2.35 g (91%) of an oil which solidified on standing. The hydrochloride salt was prepared from anhydrous hydrogen chloride in dioxane.

7-Chloro-5-methoxy-3-(1-propyl)imidazo[1,5-*c*]pyrimidine (**7c**).

A solution of sodium methoxide was prepared by dissolving sodium metal (0.11 g, 4.8 mg-atoms) in 40 ml of methanol under nitrogen. The dichloro compound **4c** (1.00 g, 4.35 mmoles) was added and the mixture was stirred 1 hour at room temperature, then concentrated *in vacuo*. The residue was taken up in 50 ml of water and extracted with 4 25-ml portions of chloroform. The combined extracts were washed with 25 ml of 5% sodium hydroxide, then 25 ml of water, followed by 25 ml of brine, dried (magnesium sulfate), and concentrated *in vacuo* to 0.80 g (81%) of an oil which solidified on standing; ir 1630 cm^{-1}.

7-Chloro-3-(2-propyl)-5-(1-propylthio)imidazo[1,5-*c*]pyrimidine (**8d**).

The mineral oil was removed from sodium hydride (0.50 g of 60% oil dispersion, 12.5 mmoles) by rinsing it with several portions of hexanes under a nitrogen atmosphere. The solid sodium hydride was then suspended in 50 ml of dry tetrahydrofuran and the mixture was cooled in an ice bath. Propanethiol (1.7 ml, 19 mmoles) was added gradually over 3 minutes and the mixture was stirred at 0° for 15 minutes. The dichloro compound **4d** (1.00 g, 4.35 mmoles) was added and the mixture was stirred 18 hours at room temperature, then poured into 50 ml of water and extracted with 4 50-ml portions of chloroform. The combined extracts were washed with 3 100-ml portions of water, dried (magnesium sulfate), and concentrated *in vacuo* to an oil which solidified on standing. The bisulfate salt was prepared in ethanol-ether using 0.50 g (5.1 mmoles) of concentrated sulfuric acid to give 1.30 g (81%) of a white solid.

Alkylation of **5**.7-Chloro-3-(1-propyl)-6-methylimidazo[1,5-*c*]pyrimidin-5(6*H*)-one (**9c**).

To the pyrimidinone **5c** (2.00 g, 9.45 mmoles), in 50 ml of dimethylformamide under a nitrogen atmosphere, was added a 60% oil dispersion of sodium hydride (0.45 g, 11 mmoles). After 30 minutes, iodomethane (2.00 g, 14.1 mmoles) was added and the mixture was stirred for 18 hours at 50°. The dark mixture was poured into 150 ml of ice-water and extracted with 4 50-ml portions of chloroform. The combined extracts were washed with 2 75-ml portions of saturated aqueous sodium bicarbonate, then with 6 100-ml portions of water, dried (magnesium sulfate), and concentrated *in vacuo* to a brown solid which was purified by flash chromatography [12] (10% ethyl acetate in dichloromethane) to give 0.98 g (46%) of off-white solid (Table III); ir: 1720, 1630 cm^{-1}.

Intermediate Pyrimidines **10-17**. Table II.

The intermediates described below were generally used in subsequent reactions without purification. Microanalytical data were obtained for most compounds, as listed in Table IV. Microanalyses were not obtained for compounds **10**, **14**, and **15**; we were unable to satisfactorily purify **10**, and the low-melting aminomethyl compounds **14** and **15** were generally prepared and immediately acylated in an essentialy "one-pot" fashion.

6-Phthalimidomethyluracil (**10**).

Phthalic anhydride (83.0 g, 0.561 mole) and the 6-aminomethyluracil (**2**, 75.0 g, 0.532 mole), were combined in 500 ml of dry dimethylformamide, 1 ml of triethylamine was added, and the mixture was heated for 3 hours at 120°, then poured into 2 ℓ of ice-water. The solid was collected by filtration, washed with water, and dried *in vacuo* to give 119.5 (81%) of yellow solid; ir: 3150, 1720, 1670 cm^{-1}.

2,4-Dichloro-6-phthalimidomethylpyrimidine (**11**).

The protected uracil **10** was refluxed 17 hours in 200 ml of phosphorus oxychloride. The mixture was concentrated *in vacuo* and the thick, dark residue was treated dropwise, with cooling, with 150 ml of methanol. The methanol slurry was added carefully to 600 ml of ice-cold saturated aqueous sodium bicarbonate. The resulting solid was isolated by filtration, washed with water, then a small amount of methanol, and dried *in vacuo*. The solid was taken up in 700 ml of boiling chloroform, filtered while hot to remove dark insolubles, and the filtrate was concentrated *in vacuo* to 11.25 g (67%) of off-white solid; ir: 1705, 950 cm^{-1}.

2,4-Bis(methylthio)-6-phthalimidomethylpyrimidine (**12**).

A solution of sodium methoxide was prepared by dissolution of sodium metal (4.00 g, 0.17 g-atom) in 250 ml of methanol under a nitrogen atmosphere. The mixture was cooled in an ice bath and methanethiol (14 ml, 0.25 mole) was added. The mixture was stirred for 30 minutes at 0°, then the dichloropyrimidine **11** (20.0 g, 0.0649 mole) was added, and the mixture was allowed to come to room temperature and stirred 17 hours. The solid was collected by filtration, washed with water, then methanol, and dried to give 20.3 g (95%) of white solid; ir: 1705, 948 cm^{-1}.

2,4-Dimethoxy-6-phthalimidomethylpyrimidine (**13**).

A solution of sodium methoxide was prepared by dissolution of sodium metal (3.70 g, 0.16 g-atom) in 250 ml of methanol under a nitrogen atmosphere. The dichloropyrimidine **11** (20.0 g, 0.0649 mole) was added, and the mixture was refluxed 4 hours, then concentrated *in vacuo*. The residue was triturated with water, isolated by filtration, and dried to give 12.7 g (65%) of white solid; ir: 1705, 953 cm^{-1}.

6-Aminomethyl-2,4-bis(methylthio)pyrimidine (**14**).

The phthalimide **12** (20.1 g, 60.8 mmoles) was combined with hydrazine hydrate (3.30 g, 66.0 mmoles) in 250 ml of 50% ethanol/dioxane and refluxed for 3 days. The mixture was concentrated *in vacuo*, and the residue was taken up in 300 ml of water containing 8 ml of concentrated hydrochloric acid. This mixture was stirred at 70-80° for 30 minutes, then cooled to 10° and the solid was removed by filtration. The filtrate was cooled and basified with 10% aqueous sodium hydroxide and immediately extracted with 5 75-ml portions of chloroform. The combined extracts were washed with 2 150-ml portions of water, dried (magnesium sulfate), and concentrated *in vacuo* to 10.7 g (88%) of yellow solid.

6-Aminomethyl-2,4-dimethoxypyrimidine (**15**).

The phthalimide **13** (4.03 g, 13.5 mmoles) was combined with hydrazine hydrate (0.70 g, 14 mmoles) in 75 ml of ethanol and refluxed 42 hours. The mixture was concentrated *in vacuo* and the residue was taken up in 100 ml of water containing 3 ml of concentrated hydrochloric acid. This mixture was stirred at 70-80° for 20 minutes, then cooled to 10° and the solid was removed by filtration. The filtrate was cooled and basified with 10% aqueous sodium hydroxide and immediately extracted with 4 50-ml portions of chloroform. The combined extracts were washed with 2 50-ml portions of water, dried (magnesium sulfate), and concentrated *in vacuo* to an oil which solidified upon cooling to 1.42 g (62%) of yellow solid.

2,4-bis(methylthio)-6-formylaminomethylpyrimidine (**16a**).

The amine **14** (1.00 g, 4.98 mmoles) was taken up in 10 ml of 95% formic acid, refluxed 4 hours, and concentrated *in vacuo*. The residue was diluted with 50 ml of water, neutralized with sodium bicarbonate, and extracted with 3 50-ml portions of chloroform. The combined extracts were washed with 2 50-ml portions of water, 2 50-ml portions of 3% aqueous hydrochloric acid, 2 more 50-ml portions of water, then dried (magnesium sulfate) and concentrated *in vacuo* to 0.96 g (84%) of off-white solid; ir: 3250, 1650 cm^{-1}.

6-Acetylaminomethyl-2,4-bis(methylthio)pyrimidine (**16b**)

The phthalimide **12** (20.0 g, 60.4 mmoles), was deprotected to the amine **14** as described above, using 3.30 g (66.0 mmoles) of hydrazine hydrate. The product was immediately suspended in 75 ml of acetic anhydride and stirred overnight at room temperature. The resulting solid was isolated by filtration, washed with a small amount of methanol, and dried *in vacuo* to give 11.03 g (75% from **12**) of white solid; ir: 3250, 1650 cm^{-1}.

6-Benzoylaminomethyl-2,4-bis(methylthio)pyrimidine (**16c**).

The amine **14** (6.90 g, 34.3 mmoles) was combined with 3.60 g (35.6 mmoles) of triethylamine in 50 ml of chloroform and cooled in an ice bath under a nitrogen atmosphere while benzoyl chloride (5.00 g, 35.6 mmoles) was added dropwise over 3 minutes. The mixture was allowed to come to room temperature and stirred overnight. The solution was diluted to 200 ml with chloroform and washed with 2 50-ml portions of dilute aqueous sodium carbonate followed by 3 50-ml portions of water, dried (magnesium sulfate), and concentrated *in vacuo* to an oil which crystallized upon trituration with ether. Filtration gave 8.35 g (80%) of white solid; ir: 3280, 1640 cm^{-1}.

6-Acetylaminomethyl-2,4-dimethoxypyrimidine (**17d**).

The amine **15** (1.40 g, 8.28 mmoles) was suspended in 5 ml of acetic anhydride and stirred overnight at room temperature under a nitrogen atmosphere. The mixture was blown dry under a stream of nitrogen and the residue was triturated with ether and filtered to give 1.15 g (66%) of a white solid; ir: 3250, 1655 cm^{-1}.

5,7-Bis(methylthio)imidazo[1,5-*c*]pyrimidines (**18**). Table III.

The method is exemplified by the preparation of **18b**. The acetamide **16b** (11.0 g, 45.3 mmoles) was dissolved in 100 ml of dry dioxane and phosphorus oxychloride (7.50 g, 48.9 mmoles) was added dropwise over 5 minutes under nitrogen. The mixture was refluxed 1 hour, then poured into 200 ml of ice-water and neutralized by the careful addition of sodium bicarbonate to precipitate a yellow solid which was isolated by filtration, washed with water, and dried to give 10.0 g of yellow solid. Recrystallization from benzene-hexanes gave 6.73 g (66%) of analytically pure material. Compounds **18a** and **18c** were made in similar fashion from **16a** and **16c**, using reflux times of 30 minutes and 2 hours, and benzene and cyclohexane as recrystallization solvents, respectively.

5,7-Dimethoxy-3-methylimidazo[1,5-*c*]pyrimidine (**19b**) and 7-methoxy-3-methylimidazo[1,5-*c*]pyrimidin-5(6*H*)-one (**20b**).

The amide **17b** (1.00 g, 4.74 mmoles) in 20 ml of dry dioxane was treated with phosphorus oxychloride (0.90 g, 5.87 mmoles) and refluxed 30 minutes under nitrogen. Tlc analysis (elution with 50% ethyl acetate/benzene) indicated the presence of 2 compounds (Rf 0.11 and 0.19). The mixture was poured into 100 ml of ice-water, neutralized with solid sodium bicarbonate, and extracted with 4 25-ml portions of chloroform. The combined extracts were washed with 2 50-ml portions of water, 50 ml of brine, dried (magnesium sulfate), and concentrated *in vacuo*. The solid residue was triturated with hexanes and an insoluble material was isolated by filtration and dried, amounting to 0.34 g; tlc analysis indicated this was a mixture of the compounds as indicated above. The hexane filtrate was concentrated *in vacuo* to provide 0.33 g (36%) of yellow solid. The nmr data for this material (Table III) is consistent for the dimethoxy compound **19b**.

When the above phosphorous oxychloride cyclization reaction of **17b** (3.20 g, 15.2 mmoles) was conducted with a 2-hour reflux period, rather than 30 minutes, tlc analysis (50% ethyl acetate/benzene) indicated only one product was present (Rf 0.11). Workup as above provided 2.19 g (80%) of solid **20b** (Table III); ir: 1740, 1660 cm^{-1}.

7-Methylthio-5-(4-morpholino)imidazo[1,5-*c*]pyrimidine (**21**).

Compound **18a** (2.10 g, 9.95 mmoles) was refluxed 40 hours in 15 ml of morpholine. The dark mixture was then poured into 100 ml of water and extracted with 4 75-ml portions of chloroform. The combined extracts were washed with 6 150-ml portions of water, dried (magnesium sulfate), and concentrated *in vacuo* to an oil which crystallized upon trituration with ether to give 2.09 g (84%) of tan solid. This material was purified by flash chromatography [12], eluting with 50% ethyl acetate in dichloromethane to give 1.33 g (53%) of white solid (Table III); ir: 1605 cm^{-1}.

5-Methoxy-7-methylthioimidazo[1,5-*c*]pyrimidine (**22**).

Compound **18a** (2.00 g. 9.48 mmoles) was suspended in 50 ml of methanol and ~3 mg of sodium hydride (60% oil dispersion) was added. The mixture was refluxed under a nitrogen atmosphere for 50 hours, then concentrated *in vacuo*. The residue was dissolved in 150 ml of chloroform, and this solution was washed with 2 50-ml portions of 5% aqueous sodium hydroxide followed by 3 50-ml portions of water, dried (magnesium sulfate), and concentrated *in vacuo* to 1.53 g (83%) of light tan solid (Table III); ir: 1640 cm^{-1}.

7-Methylthioimidazo[1,5-*c*]pyrimidin-5(6*H*)-one (**23a**).

Compound **18a** (1.00 g, 4.74 mmoles) was dissolved in 25 ml of methanol and a 25% solution of sodium methoxide in methanol (1.2 g, 5.5 mmoles) was added. The mixture was refluxed under nitrogen; samples were periodically removed and analyzed by tlc (10% ethyl acetate in dichloromethane), along with samples of **18a** and **22**. This analysis indicated that the starting material (Rf 0.27) disappeared within 1 hour, while a spot identical to that of **22** (Rf 0.21) was evident within 15 minutes. A third spot (Rf 0.05) also appeared within 15 minutes, and gradually increased in intensity as refluxing continued. After 28 hours, the mixture was concentrated *in vacuo*, the residue was dissolved in 25 ml of water and extracted with 4 25-ml portions of ether. The aqueous phase was saved for use as described below, and the combined ether extracts were washed with 2 30-ml portions of 5% aqueous sodium hydroxide followed by 2 30-ml portions of water, dried (magnesium sulfate), and concentrated *in vacuo* to 0.07 g (~7%) of an oil which solidified upon cooling; nmr (deuteriochloroform): and tlc (10% ethyl acetate in dichloromethane) data were identical to that of **22** above. The initial aqueous phase (see above) was carefully neutralized with concentrated hydrochloric acid to precipitate a solid which was isolated by filtration, washed with water, and dried to provide 0.61 g (71%) of **23a** as a yellow solid (Table III); ir: 3200, 1730 cm^{-1}.

3-Methyl-7-methylthioimidazo[1,5-*c*]pyrimidin-5(6*H*)-one (**23b**).

This compound was prepared from **18b** (3.00 g, 13.3 mmoles) by the method described above for **23a**, to provide 1.94 g (75%) of white solid (Table III); ir: 1725 cm^{-1}.

3,6-Dimethyl-7-methylthioimidazo[1,5-*c*]pyrimidin-5(6*H*)-one (**24**).

To compound **23b** (1.60 g, 8.21 mmoles) in 50 ml of dry dimethylformamide, was added sodium hydride (0.40 g of a 60% oil dispersion, 10 mmoles), and the mixture was stirred 15 minutes under nitrogen. Iodomethane (0.90 ml, 14 mmoles) was then added, and the mixture was stirred 1 hour at room temperature, then overnight at 45°. The mixture was poured into 100 ml of ice-water and extracted with 4 50-ml portions of chloroform. The combined extracts were washed with 6 100-ml portions of water, dried (magnesium sulfate), and concentrated *in vacuo* to a tan solid which was triturated with hexanes and isolated by filtration as 0.77 g (45%) of tan solid (Table III); ir: 1705 cm^{-1}.

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