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A Convenient Chlorination of Pyrimidines with Thionyl Chloride

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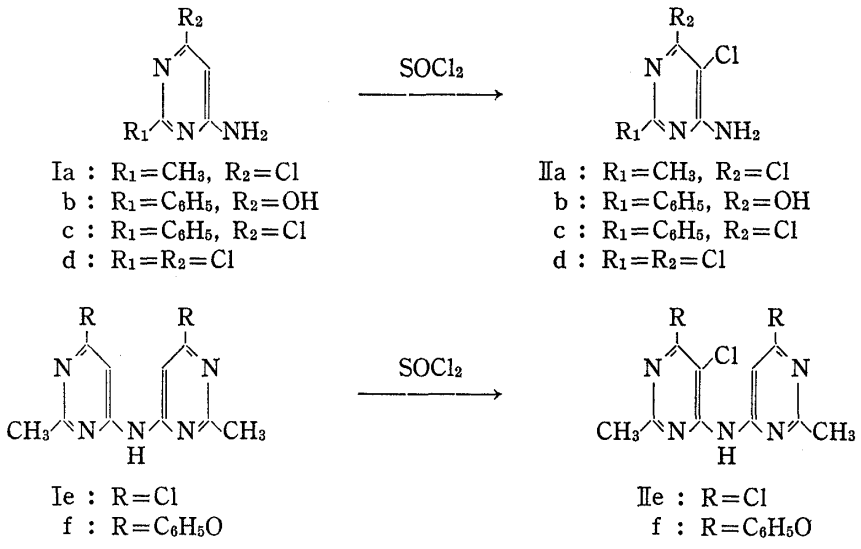
It is well-known that a number of chlorinated pyrimidines have significant antimicrobial, cancerostatic and other biological activities.[2] 5-Chloropyrimidine derivatives would be of interest because of their potential physiological activities and also because of their utility as synthetic intermediates. These 5-chloropyrimidines have customarily been prepared by direct chlorination of a 5-unsubstituted pyrimidine with phosphorus pentachloride,[3a-c] iodine monochloride,[4] sulfuryl chloride,[5] N-chlorosuccinimide,[6] or chlorine.[7a-d] We have found that a wide variety of 6-aminopyrimidines are chlorinated in high yield to 5-chloropyrimidines by treatment with thionyl chloride. Treatment of 1 part of 6-amino-4-chloro-2-methylpyrimidine (Ia)[8] with 10 parts of thionyl chloride at 130° for 3 hr results in the formation of 6-amino-4,5-dichloro-2-methylpyrimidine (IIa) which is isolated by evaporation of the thionyl chloride and addition of water. The structure of IIa was assigned on the basis of the following evidences. Compound IIa shows the presence of chlorine atoms in the Beilstein test. Its infrared spectrum shows primary amino stretching absorption bands at 3120 and 3320 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum in trifluoroacetic



Ia : $R_1=CH_3$, $R_2=Cl$
b : $R_1=C_6H_5$, $R_2=OH$
c : $R_1=C_6H_5$, $R_2=Cl$
d : $R_1=R_2=Cl$

IIa : $R_1=CH_3$, $R_2=Cl$
b : $R_1=C_6H_5$, $R_2=OH$
c : $R_1=C_6H_5$, $R_2=Cl$
d : $R_1=R_2=Cl$

Ie : R=Cl
f : $R=C_6H_5O$

IIe : R=Cl
f : $R=C_6H_5O$

Chart 1

1) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo.*
2) For a recent review on chloropyrimidines in medicinal chemistry, see C.C. Cheng in "Progress in Medicinal Chemistry," Vol. 6, G.P. Ellis and G.B. West, ed., Butterworths, London, 1969, p. 67.
3) *a*) S.J. Childress and R.L. McKee, *J. Am. Chem. Soc.*, **72**, 4271 (1950); *b*) E.C. Taylor and P. Drenchko, *J. Am. Chem. Soc.*, **74**, 1101 (1952); *c*) S.B. Greenbaum, *J. Am. Chem. Soc.*, **76**, 6052 (1954).
4) J. Chesterfield, J.F.W. McOmie and E.R. Sayer, *J. Chem. Soc.*, **1955**, 3478.
5) H. Gershon, R. Braun and A. Scala, *J. Med. Chem.*, **6**, 87 (1963).
6) R.A. West and H.W. Barrett, *J. Am. Chem. Soc.*, **76**, 3146 (1954).
7) *a*) H.W. Barrett, J. Goodman and K. Dittmer, *J. Am. Chem. Soc.*, **70**, 1753 (1948); *b*) H.W. Barrett, U.S. Patent 2585615 (1952) [*C.A.*, **46**, 8148 (1952)]; *c*) T.K. Fukuhara and D.W. Visser, *J. Am. Chem. Soc.*, **77**, 2393 (1955); *d*) D.M. Frisch and D.W. Visser, *J. Am. Chem. Soc.*, **81**, 1756 (1959).
8) Z. Fördi, G.V. Fodor, I. Demjen, H. Szeker and I. Halmos, *Chem. Ber.*, **75**, 755 (1942).

acid shows a sharp and unsplit singlet of methyl proton at 2.80 ppm, and C-5 proton signal could not be observed. The mass spectrometry reveals a parent ion (*m/e* 177), M+2 ion and M+4 ion, which suggests that two chlorine atoms may be contained in the molecule. The assigned structure was confirmed with the information from its elemental analysis. Similarly, other 6-aminopyrimidines under similar conditions yielded the corresponding 6-amino-5-chloropyrimidines, which all gave satisfactory spectral and microanalytical data (see Table I).

When the reaction was applied to 6,6′-dichloro (or diphenoxy)-2,2′-dimethyl-4,4′-iminodipyrimidine (Ie or If),[9] only one chlorine atom was introduced to C-5 position in good yields. The catalytic reduction of IIe over palladium charcoal easily eliminated all of chlorine atoms to give 2,2′-dimethyl-4,4′-iminodipyrimidine.[10]

Table I. Reaction of Pyrimidines with Thionyl Chloride

Starting material	Reaction Time (hr)	Reaction Temp. (°C)	Product	Yield (%)	Recrystn. solvent	mp[a] (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia	3	130	IIa	84	benzene	145	$C_5H_5N_3Cl_2$	33.73	2.83	23.59	33.87	2.90	23.76
b	2	120	b	66	dil. EtOH	289	$C_{10}H_8ON_3Cl$	54.63	3.64	18.96	54.33	3.79	19.08
c	3	130	c	88	EtOH	185—187	$C_{10}H_8N_3Cl_2$	50.02	2.94	17.50	50.29	3.04	17.70
d	4	130	d	75	benzene	161—163[b]	$C_4H_2N_3Cl_3$	24.41	1.02	21.18	24.70	1.23	21.04
Ie	2	95	IIe	90	EtOH	161	$C_{10}H_8N_5Cl_3$	39.43	2.66	23.00	39.62	2.90	23.12
f	2	95	f	73	EtOH	175—176	$C_{22}H_{18}O_2N_5Cl$	62.93	4.32	16.66	62.96	4.48	16.85

a) All melting points are uncorrected.
b) S.J. Childress and R.L. McKee, *J. Am. Chem. Soc.*, **73**, 3862 (1951); mp 170—171.5°

Experimental

General Procedure for Synthesis of 6-Amino-5-chloropyrimidines (IIa—d)——A mixtuer of 0.003 mole of 6-amino-2,4-disubstituted pyrimidine (Ia—d) and 10 parts of thionyl chloride was refluxed as described in Table I. Excess thionyl chloride was removed under reduced pressure, 30 ml of H_2O was added to the residue. Then, separated crystals were collected by filtration. The crystals were extracted with benzene or EtOH, and evaporation of the extract gave the corresponding 6-amino-5-chloropyrimidine.

General Procedure for Synthesis of 6,6′-Disubstituted 5-Chloro-2,2′-dimethyl-4,4′-iminodipyrimidine (IIe, IIf)——A mixture of 0.0037 mole of 6,6′-disubstituted 2,2′-dimethyl-4,4′-iminodipyrimidine and 10 parts of thionyl chloride was refluxed for 2 hr at 95°. Excess thionyl chloride was removed under reduced pressure. The residue was dissolved in 30 ml of MeOH with warming, and neutralized with 5% aqueous NH_3. After standing overnight at room temperature, the precipitated crystals were collected by filtration, and dried to give the corresponding 6,6′-disubstituted 5-chloro-2,2′-dimethyl-4,4′-iminodipyrimidine.

2,2′-Dimethyl-4,4′-iminodipyrimidine——A solution of 0.5 g (0.0016 mole) of IIe and 4 ml of conc. aqueous NH_3 in 30 ml of MeOH was subjected to hydrogenation in the presence of 0.1 g of 10% Pd-C at room temperature and atmospheric pressure. Hydrogenation was stopped when the theoretical volume of hydrogen was consumed. Removal of the catalyst left a pale yellow solution, which was evaporated to dryness. The residue was extracted with acetone with warming and the extract was evaporated to yield 0.32 g (100%) of pale yellow crystals. Recrystallization from benzene gave colorless needles, mp 216—218°. *Anal.* Calcd. for $C_{10}H_{11}N_5$: C, 59.68; H, 5.51; N, 34.81. Found: C, 59.60; H, 5.46; N, 34.90. The NMR spectrum (DMSO-d_6) exhibited six-proton singlet at 2.35 ppm (CH_3), a two-proton doublet at 7.57 ppm (J=6.0 cps) (C_5 H in pyrimidine), a two-proton doublet at 8.67 ppm (J=6.0 cps) (C_6 H in pyrimidine), and a one-proton singlet at 10.48 ppm (NH).

9) S. Nishigaki, K. Senga, K. Ogiwara and F. Yoneda, *Tetrahedron Letters*, **1969**, 539.
10) S. Nishigaki, K. Senga, K. Ogiwara and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **18**, 997 (1970).