BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 46, 299—302 (1973)

Studies on Nitrile Salts. II.[1] A Facile One-step Synthesis of the Pyrimidine Nucleus

Shozo Yanagida, Tetsuo Fujita, Masataka Ohoka, Reiji Kumagai, and Saburo Komori

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Yamadakami, Suita, Osaka

(Received March 18, 1972)

The reaction of *N*-(α-chloroalkenyl)alkylamidine hydrochlorides (**1**) with phosgene was studied. The amidine hydrochlorides (**1a**—**h**) which were prepared from nitriles with more than two α-hydrogens reacted with phosgene at 100—105°C to give good yields of 4,6-dichloro-2,5-disubstituted-pyrimidines (**3a**—**h**). The amidine hydrochlorides (**1j**—**t**), which were obtained from nitriles with only one α-hydrogen, afforded 2-alkylidene-4,6-dichloro-5,5-disubstituted-2,5-dihydropyrimidines (**5j**—**t**) in good yields. The amidine hydrochloride **1i**, however, gave 2-dichloromethylidene-2,5-dihydro-5,5,6-trichloro-4(3*H*)-pyrimidinone (**4i**) under comparable conditions.

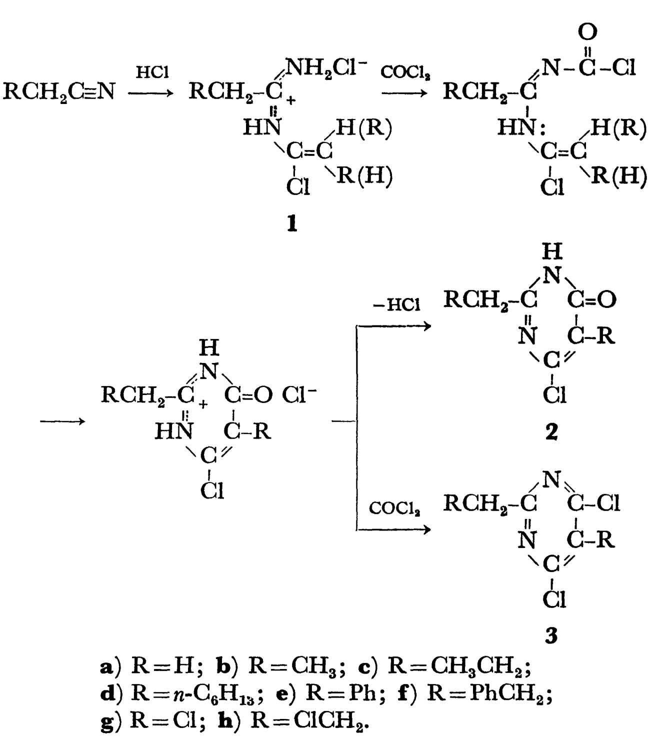
In our previous papers,[2-4] it was shown that the reaction of aliphatic nitriles or amides with phosgene and HCl gave good yields of 6-chloro-2,5-disubstituted-4(3*H*)-pyrimidinones (**2**), with traces of 4,6-dichloro-2,5-disubstituted-pyrimidines (**3**), and that arylacetonitriles gave 1,3-dichloroisoquinoline derivatives with the corresponding pyrimidinones (**2**) and pyrimidines (**3**). Further, we recently showed that most nitriles having α-hydrogen reacted with HCl to give *N*-(α-chloroalkenyl)alkylamidine hydrochlorides (**1**) almost quantitatively.[1]

On the basis of the reaction mechanism proposed for the formation of the pyrimidine derivatives (**2**) and (**3**),[2] the reaction of the amidine hydrochlorides (**1**) with phosgene may be expected to provide a convenient and facile one-step synthesis of the pyrimidine nucleus.

This paper will report the synthesis of pyrimidine derivatives, mainly **3** and **5**, based on this concept.

Results and Discussion

When *N*-(α-chloropropenyl)propioamidine hydrochloride (**1b**) was allowed to react with excess phosgene in chlorobenzene for 260 hr using a sealed glass tube at 60°C, 6-chloro-2-ethyl-5-methyl-4(3*H*)-pyrimidinone (**2b**) was obtained in a 60% yield, as had been expected (Scheme 1). However, the similar treatment of *N*-(α-chlorostyryl)phenylacetamidine hydrochloride (**1e**) with phosgene resulted in the recovery of the starting materials unchanged. Upon continued heating at 100—105°C for a period of 24 hr, 4,6-dichloro-2-benzyl-5-phenylpyrimidine (**3e**) was produced in a 75% yield. It is worth pointing out that 1,3-dichloroisoquinoline, which is the main product in the direct reaction of phenylacetonitrile with phosgene and HCl at 100°C,[4] was not formed. 6-Chloro-2-benzyl-5-phenyl-4(3*H*)-pyrimidinone hydrochloride, a precursor of **2e**,[2] first formed must be converted into **3e** by phosgene because of its strong electrophilicity at high temperatures (Scheme 1.).



a) R=H; **b**) R=CH$_3$; **c**) R=CH$_3$CH$_2$;
d) R=*n*-C$_6$H$_{13}$; **e**) R=Ph; **f**) R=PhCH$_2$;
g) R=Cl; **h**) R=ClCH$_2$.

Scheme 1.

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[1] Part I: S. Yanagida, T. Fujita, M. Ohoka, I. Katagiri, and S. Komori, This Bulletin, **46**, 292 (1973).

[2] S. Yanagida, M. Ohoka, M. Okahara, and S. Komori, *Tetrahedron Lett.*, No. 19, 2351 (1968), *J. Org. Chem.*, **34**, 2972 (1969).

[3] S. Yanagida, H. Hayama, and S. Komori, *ibid.*, **34**, 4180 (1969).

[4] S. Yanagida, M. Ohoka, and S. Komori, *ibid.*, **34**, 4127 (1969).

TABLE 1. PREPARATION AND ANALYSES OF 4,6-DICHLORO-2,5-DISUBSTITUTED-PYRIMIDINES (**3**)

3	R ($R'=H$)	Purification	Yield (%)	Bp (°C/mmHg) [Mp(°C)]	IR (neat) (cm^{-1})	Mass[a] (M^+)	NMR (CCl_4) (τ)	UV(C_6H_{12}) nm(ε_{max})	Elemental analysis[b] C%	H%	N%
3a[c]	H		>70[d]	—	1530[e]	—	—	—	—	—	—
3b	CH_3	Distillation	62	111.0— 111.5/21	1565 1507	190	8.68(t, 3H) 7.59(s, 3H) 7.16(q, 2H)	260(4370)	43.98 (44.01)	4.10 (4.22)	14.57 (14.66)
3c	CH_3CH_2	Distillation	90 (crude)	84.0— 85.0/3	1560 1506	218	9.02(t, 3H)[f] 8.78(t, 3H) 8.12(m, 2H) 7.15(t, 2H) 7.12(q, 2H)	—	50.07 (49.33)	5.42 (5.52)	12.40 (12.79)
3d	n-C_6H_{13}	Distillation	49	149.0— 150.0/0.1	1560 1505	330	—	—	—	—	8.16 (8.46)
3e[c]	Ph	Recrystallized from ethanol	75	[136.0—[g] 138.0]	1550[h] 1495	—	—	234(11600) 265(6620)[i]	—	—	—
3f	$PhCH_2$	Recrystallized from ethanol	80	[69.5— 70.0]	1550 1505	342	6.90(s, 4H)[j] 5.85(s, 2H) 2.88(s, 10H)	260(6150)	66.53 (66.48)	4.64 (4.70)	7.97 (8.16)
3g	Cl	Column chromatography	85	[28.0— 30.0]	1530 1503	230	5.42(s)	232(13410) 268(7630) 275(6540)[i]	25.83 (25.90)	0.84 (0.87)	12.30 (12.08)
3h	$ClCH_2$	Column chromatography and distillation	79	113.0— 116.0/3 [47.0— 48.0]	1562 1510	258	6.66(t, 2H)[f] 6.03(t, 2H) 5.45(s, 2H)	225(7180)	32.31 (32.34)	2.24 (2.33)	10.54 (10.78)

a) 70 eV. b) Values in parentheses are calculated ones. c) Identified by comparison with authentic sample.[2,4] d) By glpc. e) Nujol. f) Measured in $CDCl_3$. g) Lit,[4] 136.0—138.0°C. h) KBr disk. i) Shoulder. j) 6.67(m, 4H), 5.63(s, 2H), 2.60—7.00(complex peaks, 10H) in CF_3COOH.

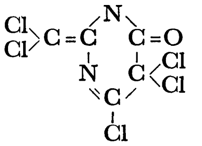
In view of the above facts, the reaction was extended to other amidines **1a**—**h**, employing 100°C as the reaction temperature. The expected dichloropyrimidines **3a**—**h** were obtained in good yields. (Scheme 1). It should be noted that the pyrimidine **3h** was obtained in a satisfactory yield by this reaction. As has been reported previously,[2] the direct reaction of 3-chloropropionitrile with phosgene in the presence of HCl gave a polymeric substance, and neither the pyrimidinone **2h** nor the pyrimidine **3h** was isolated.[5]

These pyrimidines **3** were confirmed on the basis of their physical properties and by elemental analysis, as is summarized in Table 1.

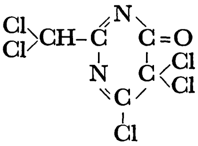
The NMR spectra of the pyrimidine **3f** are of particular interest. As is shown in Table 1, in CCl_4 the signals due to two pairs of methylene protons of the 2-phenethyl group were observed as a singlet, indicating that the phenyl ring of the 2-phenethyl group and the pyrimidine ring in **3f** are magnetically equivalent. A similar spectrum was also obtained in benzene. In CF_3COOH, however, this singlet signal was observed as an A_2B_2 pattern centered at τ 6.67, the signal due to methylene protons of the 5-benzyl group shifted to a lower field, and the signals of both phenyl ring protons, which were observed as a singlet in CCl_4, changed to a complex series of lines. The spectrum complexity is probably due to the protonation at the pyrimidine nitrogen.

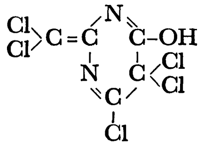
We assumed that the driving forces of this cyclization reaction are the nucleophilicity of the β-carbon of a kind of enamino group [–NH–CCl=CHR] in the amidines **1** (Scheme 1)[6] and the prototropy of the hydrogen on the β-carbon. In view of these assumptions, the amidine hydrochlorides **1i**—**t** prepared from nitriles with only one α-hydrogen were expected to react with phosgene under comparable conditions to give a new type of pyrimidine derivative.

The treatment of the amidine hydrochloride **1i**, where both R and R′ are Cl, with phosgene under the same conditions as above led to a colorless compound, which was analyzed well for $C_5HON_2Cl_5$. The IR spectrum, taken in CCl_4, showed absorption bands at 3070, 2970, 2880 (NH), 1690 (C=O), 1590 (C=N), and 1530 (C=C) cm^{-1}. The series of absorption bands in the NH region were thought to be too low to assign to the NH stretching band. However, the NMR spectrum, measured in CCl_4, showed only a broad signal attributable to the NH proton at τ —2.85. In addition, the IR spectra in the region below 1700 cm^{-1} are quite identical both in the solid state and in solution (CCl_4). On the basis of these spectral analytic results, the compound was formulated as 2-dichloromethylidene-2,5-dihydro-5,5,6-trichloro-4(3*H*)-pyrimidinone (**4i**) rather than the following alternative structures:



4i





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[5] It has been found in our laboratory that 3-chloropropionitrile reacts with phosgene and HCl in chlorobenzene at 100—105°C to give 1,3-dichloropropenyl isocyanate in a moderate yield, which fact will be reported eslewhere in the very near future.

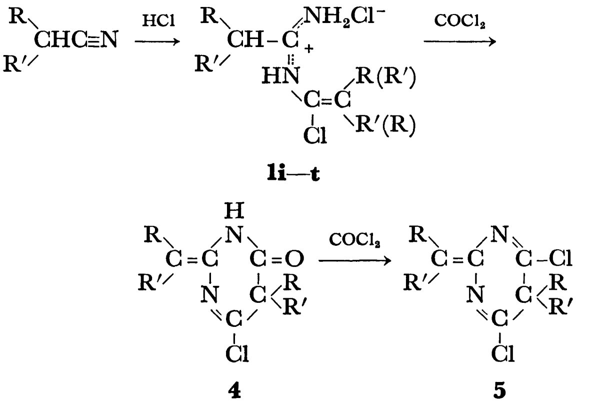
[6] G.H. Alt, "Enamines: Synthesis, Structure, and Reactions," Ch. 4, ed. by A. G. Cook, Marcel Dekker, New York, N. Y. (1969).

TABLE 2. PREPARATION AND ANALYSES OF NEW TYPE PYRIMIDINE DERIVATIVES **4** AND **5**

4 or **5**	R	R′	Purification	Yield (%)	Mp (°C) [Bp(°C/mmHg)]	IR (neat) (cm^{-1})	Mass[a)] (M$^+$)	NMR(CCl_4) (τ)	UV(C_6H_{12}) nm(ε_{max})	Elemental analysis[b)] C%	H%	N%
4i	Cl	Cl	Recrystallized from petroleum ether–ether	97	130.0	1690[c)] 1590 1530	280	−2.85(b)	295(3500) 275(3120)[d)] 242(3990)	21.15 (21.27)	0.31 (0.36)	9.77 (9.92)
5j	CH_3	Cl	Sublimation	73	55.0—57.0	1553[e)] 1518	258	7.48(s, 3H) 7.45(s, 3H)	226(5740) 260(3880)	32.14 (32.34)	2.09 (2.33)	10.81 (10.78)
5k	$ClCH_2$	Cl	Column chromatography	59	46.0—49.0	1552 1515	291[f)]	5.44(s, 2H) 5.20(s, 2H)	232(8490) 258(3880)[d)]	—	—	8.14 (8.52)
5l	n-C_4H_9	Cl	Distillation	93 (crude)	—	1550 1510	342	*ca.* 9.05(m, 6H) *ca.* 8.47(c, 8H) *ca.* 7.23(m, 4H)	—	—	—	8.01 (8.14)
5m	Ph	Cl	Sublimation	93	126.5—127.5	1540[e)] 1500	386[g)]	—	245(10560)	53.12 (53.16)	2.69 (2.62)	7.37 (7.29)
5n	Ph	CH_3	Recrystallized from petroleum ether	74	158.0—159.0	1645[e)] 1605	342	7.97(s, 3H)[h)] 7.49(s, 3H) 2.63(s, 10H)	296(22580)	66.39 (66.48)	4.47 (4.70)	8.32 (8.16)
5o	CH_3CH_2	CH_3CH_2	Column chromatography	56	[107.0—107.5/3]	1650 1610	274	9.13(t, 6H)[h)] 8.95(t, 6H) 8.07(q, 4H) 7.48(q, 4H)	262(17600)	56.93 (56.73)	7.61 (7.32)	9.88 (10.18)

a) 70 eV. b) Values in parentheses are calculated ones. c) Both cases, KBr disk and in CCl_4(11 mg/*ca.* 1 ml). d) Shoulder. e) KBr disk. f) Corresponding to M$^+$—Cl. g) Molecular weight by vapor pressure osmometer (Mechrolab osmometer, Model 301A). h) Measured in $CDCl_3$.

On the other hand, other amidine hydrochlorides **1j**—**t** afforded further chlorinated pyrimidine derivatives formulated by the general formula **5** in good yields (Scheme 2):



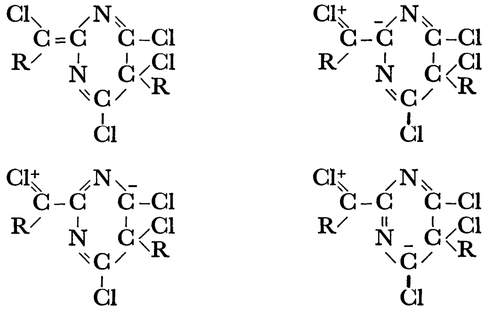
i) R=Cl, R′=Cl; **j**) R=CH_3, R′=Cl;
k) R=$ClCH_2$, R′=Cl; **l**) R=n-C_4H_9, R′=Cl;
m) R=Ph, R′=Cl; **n**) R=Ph, R′=CH_3;
o) R=C_2H_5, R′=C_2H_5; **p**) R=CH_3, R′=CH_3;
q) R=CH_3CH_2, R′=CH_3; **r**) R=n-C_3H_7, R′=CH_3
s) R=n-C_4H_9, R′=CH_3; **t**) R=$ClCH_2$, R′=CH_3.

Scheme 2.

It is apparent that the pyrimidines **5** are formed through the chlorination of the initially-formed pyrimidinones **4** by phosgene, and that the pyrimidinone **4i** must be unreactive to phosgene under the reaction conditions employed.

The structures of **5j**—**o** were confirmed on the basis of their physical properties and by elemental analysis (Table 2). Attempts to isolate analytically-pure pyrimidines **5p**—**t** were unsuccessful. They were characterized by IR and mass spectra (see Experimental section).

It should be noted that, as is shown in Table 2, the IR absorptions attributable to the C=N and C=C stretching vibrations of **5j**—**m** are shifted to frequencies lower by about 100 cm^{-1} compared with those of the other pyrimidines **5o**—**t**. These large shifts may be explained by considering the following structures, based on the mesomeric effect:



The IR spectra of the crude products from the amidines **1p**—**t** showed weak bands around 1750 cm^{-1} and medium bands attributable to the N=C=O stretching vibration around 2260 cm^{-1}, indicating the formation of by-products with a COCl group and/or an N=C=O group.[7)] Accordingly, the crude products from **1p** and **1t** were treated with aniline, unexpectedly giving dimethylmalonoanilide and butylmethylmalonoanilide in 9 and 25% yields, respectively, based on the starting amidines. This fact suggests the formation

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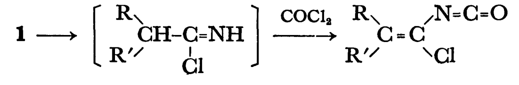
7) As noted in Ref. 6, some nitriles have been found to react with phosgene at high temperature to give α-chloroalkenyl isocyanates. In view of this fact, we assumed the compounds having N=C=O group to be corresponding isocyanates, which are probably produced through imidoyl chlorides formed by the degradation of the amidines **1** as follows;



of disubstituted malonyl chlorides as by-products, we assumed that they were produced through the further reaction of the pyrimidines **5p**—**t** with phosgene.[8] However, no urea derivatives, which were thought to be derived from compounds with an N=C=O group, were isolated.[9]

Further studies of the reactivity of the pyrimidines **5** are now in progress in our laboratory.

Experimental

The melting points were determined on a Yanagimoto micro melting point apparatus and were corrected. The boiling points were uncorrected. The NMR spectra were obtained using a Model JNM–G–60 spectrometer (Japan Electronic Optics Laboratory Co.); the solvent was carbon tetrachloride, except where otherwise noted, with tetramethylsilane as the internal reference. The IR spectra were recorded with a Japan Electroscopic IR–E spectrophotometer, the mass spectra, with a Hitachi mass spectrometer, Model RMU–6E, and the UV spectra, with a Shimadzu double-beam spectrophotometer, UV–200.

Materials. *N*-(α-Chloroalkenyl)alkylamidine hydrochlorides (**1a**—**t**) were prepared according to the method reported previously.[1]

Reaction of the Amidine Hydrochlorides (1) with Phosgene. General Procedure: In a 150 ml glass tube we placed 1.6—3.0 g (*ca.* 20 mmol) of the amidine hydrochloride (**1**) and 20 ml of chlorobenzene. The tube was then immersed in a mixture of ice and water, and 6.2—7.4 g (*ca.* 75 mmol) of phosgene was bubbled into the mixture. The tube was stoppered, cooled in a Dry Ice–acetone mixture, sealed carefully, and heated to 100—105°C in an oil bath for 24 hr. The reaction tube was then chilled in the Dry Ice–acetone mixture and opened carefully. After the removal of the phosgene and chlorobenzene under reduced pressure, the resulting products were purified by recrystallization or distillation, if necessary, after column chromatographic separation, as is shown in Tables 1 and 2. The column chromatography was always done using silica gel, and all the products were eluted with petroleum ether.

In the cases of the pyrimidines **5p**—**t**, repeated distillations after column chromatography did not give the analytically-pure pyrimidines. They were all confirmed in the basis of their IR spectra. The mass spectra also supported the structure of **5**. The crude yields, boiling points, and IR absorption bands attributable to the C=N and C=O streching vibrations are as follows: **5p**: 1655 and 1620 cm^{-1}; **5q**: 58%, *ca.* 85.0—86.0°C/2 mmHg, 1655 and 1615 cm^{-1}; **5r** 52%, 130.0—130.5°C/2 mmHg, 1655 and 1610 cm^{-1}; **5s**: 45%, 1655 and 1610 cm^{-1}; **5t**: 63%, *ca.* 105°C/1 mmHg, 1660 and 1620 cm^{-1}.

Of particular interest is the fact that **5p** is very sensitive to moisture and that the purification of crude **5p** by column chromatography resulted in the unexpected isolation of 5,5-dimethylbarbituric acid (82% yield). An attempt to explain this formation is now under way.

Isolation of Disubstituted Malonoanilides. A typical procedure was as follows: a crude product (0.77 g) obtained from **1p** was mixed with aniline (1.5 g) in 1,2-dichloroethane (10 ml). The mixture was then allowed to stand overnight at room temperature. After the aniline hydrochloride precipitated had been filtered out with suction, the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel; chloroform eluted 0.25 g of dimethylmalonoanilide (9% yield based on the amidine **1p**). It was recrystallized from dichloroethane–ether and analyzed as follows: mp 209.0—210.0°C (lit,[10] 205°C). IR (KBr disk) 3260, 3120, 1645, 1600 cm^{-1}. Mass spectrum (70eV) 282 (M^+). NMR ($CDCl_3$–CF_3COOH) (τ) 8.28 (s, 6H), 2.51—2.86 (m, 10H). Found: C, 72.23; H, 6.25; N, 9.78%. Calcd for $C_{17}H_{18}O_2N_2$: C, 72.32; H, 6.43; N, 9.92%.

Similarly, butylmethylmalonoanilide was isolated in a 25% yield based on the starting amidine **1s**, and was analyzed after recrystallization from ethanol as follows: mp 198.5—199.0°C, IR (KBr disk) 3340, 3240, 1660, 1600 cm^{-1}. Mass spectrum (70 eV) 324 (M^+). NMR (CF_3COOH) (τ) 8.95 (t, 3H), 8.46 (m, 4H), 8.02 (s, 3H), 7.67 (t, 2H), 2.57 (s, 10H), 0.15 (s, 2H). Found: C, 74.20; H, 7.29; N, 8.64%. Calcd for $C_{20}H_{24}O_2N_2$: C, 74.04; H, 7.46; N, 8.64%.

The authors wish to thank Mr. H. Moriguchi for the mass spectrum measurement, Mrs. M. Sakurai for the NMR measurement, and Miss J. Maenaka and Mr. and Mrs. Muneishi for elemental analysis. This work was supported in part by a grant-in-aid from Kokusan Gijutsu Shinkokai. We wish to express our thanks to the founder, the late Mr. Chikara Kurata.

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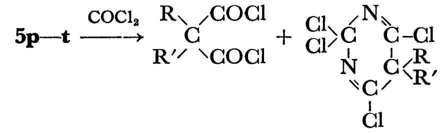
[8] In view of the formation of disubstituted malonyl chlorides, the following reaction can be considered;



However, latter products have not been identified yet.

[9] The following urea derivatives were expected;[4]

However, more polar solvent eluted only black tarry substance.

[10] H. Staudinger, *Helv. Chim. Acta*, **8**, 312 (1922).