AN EXPEDITIOUS SYNTHESIS OF 2-DIALKYLAMINO-4-CHLOROPYRIMIDINES FROM SILYLATED PRIMARY ENAMINES AND PHOSGENIMINIUM SALTS

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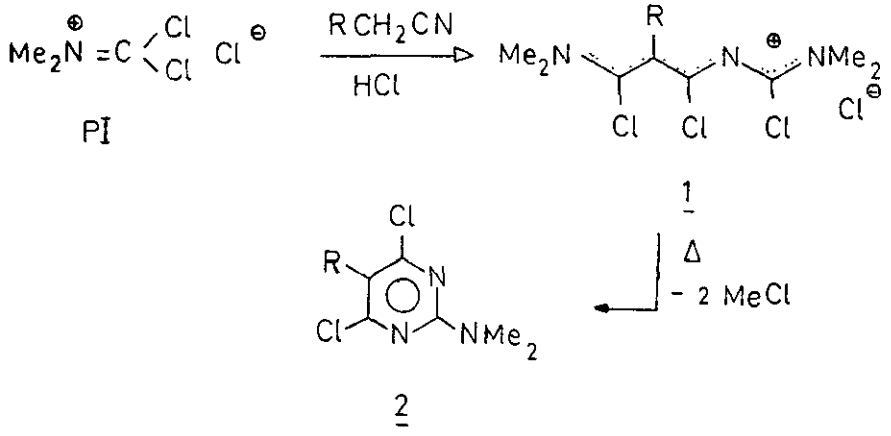
Abstract - Trimethylsilyl-protected primary enamines **4** condense with two equivalents of phosgeniminium chloride (PI) to form 2-aza-1,5-dichloropentamethine cyanines **5**. These versatile intermediates cyclize upon heating to 2-(dialkylamino)-5-alkyl-6-aryl-4-chloropyrimidines **6** via a loss of the corresponding alkyl chloride. The reactions are completely regiospecific and represent a new useful entry to pyrimidine nuclei.

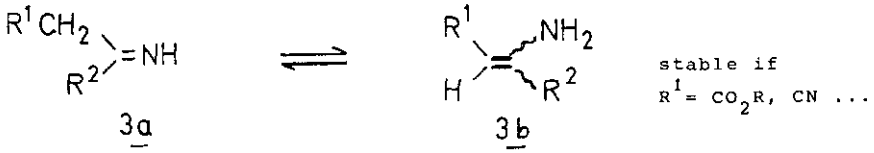
Phosgeniminium salts (PI) are valuable synthons in heterocyclic chemistry because of their three mobile chlorine atoms[1-4]. This is even more true for various trimethine and pentamethine cyanines and for their aza-analogues which are readily obtained from PI salts, usually in a single step process.

Thus, for example, monosubstituted acetonitriles or eventually the corresponding primary amides condense smoothly with PI in the presence of hydrochloric acid to give 1,3,5-trichloro-2-azapentamethine cyanines **1**[5] carrying a substituent - even a

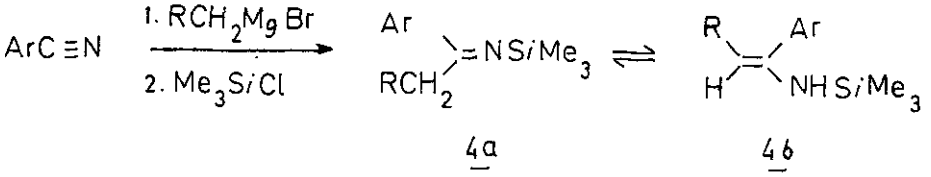


fluorine atom[6] - in the 4-position. We noticed that upon thermolysis (120-180°C) one dimethylamino group acts as the internal nucleophile thereby leading to the ring-closed products **2** via a loss of two molecules of methyl (or alkyl) chloride[5]. This finding is of foremost importance because such a synthetic principle has not been used in the past and also because of the multifaceted biological activities of pyrimidine nuclei[7,8]. In the above case only one group R can be varied, the 4- and 6-positions being occupied by chlorine atoms.

Inasmuch as a large series of polysubstituted pyrimidines was required in order to perform their biological screening, we investigated the reaction between PI salts and primary enamines **3b**. It is well-known that **3b** as well as their imine tautomers **3a** are unstable unless some special features are present. This may be for instance an electron-withdrawing group in the β-position.



Fortunately, both forms **3a,b** can be stabilized by silylating the nitrogen atom[9]. The tautomeric mixtures of **4a,b** are conveniently obtained in a single-flask reaction from nitriles and Grignard reagents followed by silylation of imine salts formed in situ. Products **4** can be distilled and it is unimportant which isomer, either **4a** or **4b**, predominates in the equilibrium mixture for the following condensation with PI salts.

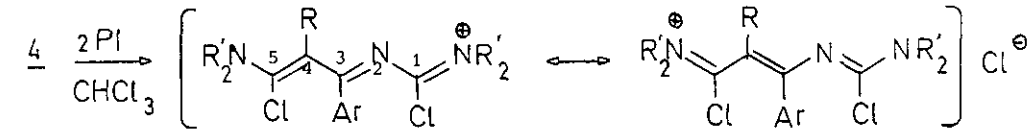


This method works well with non-enolizable nitrile such as substituted benzonitriles or heteroaromatic nitriles e.g. 2-cyanothiophene (Table 1).

Table 1. Yields and Boiling Points of **4**

entry	1	2	3	4	5	6	7	8	9
RCH_2	CH_3	Ph	CH_3	CH_3	CH_3	CH_3	$CH_3(CH_2)_2$	$CH_3(CH_2)_6$	CH_3
Ar	Ph	Ph	pPh-CF_3	pPh-F	pPh-OMe	mPh-Br	Ph	Ph	1-thienyl
Bp(°C)	47-48°	110°	51-52°	39°	81°	91°	76°	95°	56-58°
P.(Torr)	10^{-3}	0.1	0.01	0.01	0.03	0.2	0.03	0.3	0.03
Yield %	82	40	62	53	53	81	53.5	29	80
Ref							(10)		

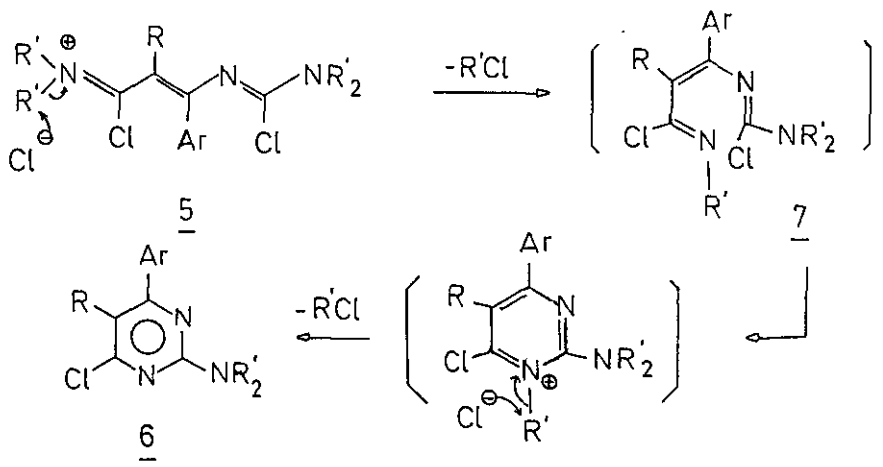
Tautomeric compounds **4** condense smoothly with two equivalents of the appropriate PI salt at 20°C in chloroform solution, the only by-products being trimethylsilyl chloride and hydrochloric acid. The cyanines **5** are dried in vacuo and are thermolyzed in a *Kugelrohr apparatus at 120°C/0.01 mmHg*. The distilled pyrimidines **6** are recrystallized from ethanol after removal of some tarry materials by filtration through silicagel.



5 **5'**

5 and **5'** are the two extreme canonical structures but it would be wrong to assume that **5** is completely charge-delocalized, because of the dissymetry induced by the more electronegative nitrogen. In all cases hitherto studied the cyclisation was regiospecific, namely the nitrogen at C-5 loses two *alkyl chloride groups* and substitutes the chlorine at C-1.

Some insight concerning the electronic structure of **5** can be gathered from the ^{13}C nmr spectrum of **5a**, (R=Me) because the chemical shifts are good probes of the charge density at the corresponding carbon atoms. These shifts observed at 50 MHz in $CDCl_3$ are : C-1 : 154.9 ppm (Sm); C-3 : 139.8 (Sm); C-4 : 111.6 (Sq); C-5 : 172.9 (Sm). These data show that the C-5 carries apparently most of the positive charge as it is the case in the limiting structure **5'**. The iminium nitrogen then undergoes a dealkylation via a SN_2 attack by the chloride counter ion. This leads to an imidoyl chloride **7** which cyclises and the dealkylation is repeated whereby stable pyrimidines **6** arise.



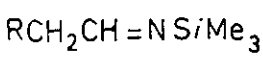
Although the mechanism shown above is temptative, the reaction has a broad scope and its synthetic interest is obvious (Table 2).

Table 2. Cyanines **5** and Pyrimidines **6**

Entry	R	Ar	R'_2	Yield of **5** %	Yield of **6** %
a	Me	C_6H_5	Me	90	90
b	C_6H_5	C_6H_5	Me	90	95
c	Me	p-C_6H_4-CF_3	Me	50	90
d	Me	p-C_6H_4-F	Me	95	90
e	Me	p-C_6H_4-OMe	Me	95	69
f	Me	m-C_6H_4-Br	Me	80	71
g	$CH_3(CH_2)_2$	C_6H_5	Me	70	47
h	$CH_3(CH_2)_6$	C_6H_5	Me	62	87
i	Me	2-thienyl	Me	90	20
j	Me	C_6H_5	$-(CH_2)_4-$	a	85
k	Me	C_6H_5	$-(CH_2)_5-$	a	62
l	Me	C_6H_5	$-(CH_2)_2O(CH_2)_2-$	a	18
m	Me	C_6H_5	$-(CH_2)_6-$	a	66

a) liquid, not isolated

The synthesis of pyrimidines where the aryl group is replaced by a hydrogen atom would require the use of N-silylaldimines 8. Such compounds, in principle, are known but not readily available[11]. Also, a few communications mention the existence of a few N,N-bis(trimethylsilyl)enamine 9[12,13,14]



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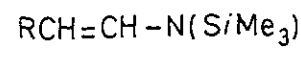

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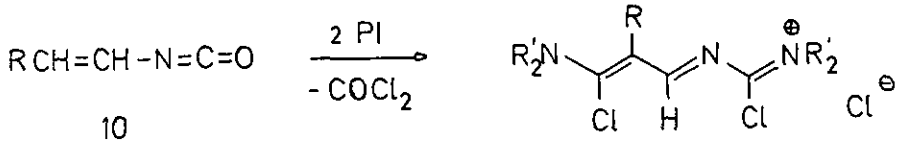
Interestingly, we have found earlier that vinylisocyanates 10[15] are still sufficiently electron-rich to be able to condense with two equivalents of PI. Phosgene is lost whereby the corresponding 5 are formed[16].



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While the details of this investigation will be published elsewhere, we want to stress that the intramolecular N,N-dealkylation of aza-pentamethinium salts constitutes a valuable new approach to polysubstituted 4-chloropyrimidines. Moreover their mobile chlorine permits nucleophilic substitutions and also new annulation reactions[17].

ACKNOWLEDGMENT

We thank Dr Cl. Lambert for valuable discussions as well as Rhône-Poulenc Industries (France) and SPPS (Belgium) for financial support.

EXPERIMENTAL

All melting points were taken using a Dr. Tottoli apparatus. Ir and mass spectra were measured on a Perkin Elmer 1710 and a Varian Mat 44SEI apparatus, respectively. ^{1}H And ^{13}C-nmr spectra were recorded on a Varian EM 360 A or Varian XL200 spectrometer. The following abbreviations are used : s : singlet, d : doublet, t : triplet, q : quartet, m : multiplet.

General procedure for the preparation of N-trimethysilylketimines.

A solution of arylnitrile (0.9 eq.) in dry ether is added dropwise to a solution of alkyl- or arylmagnesium bromide in ether (prepared from 1.1 eq. of alkyl- or aryl

bromide and 1.02 eq. of magnesium) at a rate to maintain moderate refluxing. The resulting mixture is then refluxed for 1 to 2 h. Trimethylsilyl chloride (1 eq.) is then slowly added at 20°C. The mixture is stirred overnight, the solid formed is filtered off and washed with dry ether. Ether is evaporated and the residue is distilled in vacuo using a short Vigreux column.

General procedure for preparation of 4-chloropyrimidines :

A solution of N-trimethylsilylketimine **4** (2.0g, 9.7 mmol) in dry chloroform (10 ml) is added dropwise at room temperature to a stirred suspension of PI chloride (19.4 mmol) in dry chloroform (10 ml). The resulting mixture is then refluxed for about 1 hour in order to achieve complete dissolution of PI and cessation of HCl evolution. The solvent is removed in vacuo and the residue is washed 3-4 times with dry ether (10 ml) and azacyanines **5** are dried in vacuo at room temperature.

5 are thermolysed in a horizontal distillation apparatus (Kugelrohr) at 120-140°C/0.04 mbar. The distilled **6** are further purified by filtration through short silica gel columns using ethyl acetate:petroleum (1:9) as eluents, and then they are eventually recrystallized from ethanol.

4-Chloro-2-dimethylamino-5-methyl-6-phenylpyrimidine. **6a**

Yield : 81%; mp 81-82°C; ir ($CHCl_3$) ν 3019, 1588, 1574, 1544, 1516, 1492, 1442, 705, 645 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 2.20 s (3H), 3.17 s (6H), 7.40-7.55 m (5H); Anal. calcd for $C_{13}H_{14}ClN_3$: C, 63.03%; H, 5.69; N, 16.96. Found: C, 63.02%; H, 5.69; N, 17.01. M^+, 247 m/z.

4-Chloro-2-dimethylamino-5,6-diphenylpyrimidine. **6b**

Yield : 85.5%; mp 92-93°C; ir ($CHCl_3$) ν 3020, 1586, 1573, 1505, 1485, 1443, 702, 644 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 3.23 s (6H), 7.08-7.34 m (10H); Anal. calcd for $C_{18}H_{16}ClN_3$: C, 69.79%; H, 5.21; N, 13.56. Found: C, 69.80%; H, 5.26; N, 13.61. M^+, 309 m/z.

4-Chloro-2-dimethylamino-5-methyl-6-[4'-(trifluoromethyl)phenyl]pyrimidine. **6c**

Yield : 45%; mp 65-66°C; ir ($CHCl_3$) ν 1588, 1574, 1525, 1505, 1448, 1325, 699, 668 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 2.19 s (3H), 3.18 s (6H), 7.62-7.73 m (4H); M^+, 315 m/z.

4-Chloro-2-dimethylamino-6-[4'-fluorophenyl]-5-methylpyrimidine. **6d**

Yield : 85.5%; mp 102°C; ir ($CHCl_3$) ν 3020, 1600, 1580, 1500, 1449, 1413 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 2.20 s (3H), 3.17 s (6H), 7.07-7.57 m (4H); M^+ 265 m/z.

4-Chloro-2-dimethylamino-6-[4'-methoxyphenyl]-5-methylpyrimidine. **6e**

Yield : 65.5%; mp 97-98°C; ir ($CHCl_3$) ν 3017, 1611, 1587, 1570, 1544, 1500, 1413,

673, 666 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 2.24 s (3H), 3.17 s (6H), 3.84 s (3H), 6.94 d (2H), 7.52 d (2H); Anal. calcd for $C_{14}H_{16}ClN_3O$: C, 60.54%; H, 5.81; N, 15.13. Found: C, 60.55%; H, 6.72; N, 15.20. M^+, 277 m/z.

6-[3'-Bromophenyl]-4-chloro-2-dimethylamino-5-methylpyrimidine. **6f**

Yield : 56.8%; mp 106-107°C; ir ($CHCl_3$) ν 3019, 1585, 1562, 1514, 1474, 697 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 2.20 s (3H), 3.18 s (6H), 7.30-7.68 m (4H); Anal. calcd for $C_{13}H_{13}BrClN_3$: C, 47.80%; H, 4.01; N, 12.87. Found: C, 47.77%; H, 3.96; N, 12.89. M^+, 325 m/z.

4-Chloro-2-dimethylamino-6-phenyl-5-propylpyrimidine. **6g**

Yield : 33%; mp 54-55°C; ir ($CHCl_3$) ν 3060, 1585, 1573, 1533, 1510, 1489, 1464, 1444, 701, 644 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 0.80 t (J=7.5 Hz, 3H), 1.49 m (J=7.5-8 Hz, 2H), 2.53 m (J=7.5-8 Hz, 2H), 3.14 s (6H), 7.35-7.48 m (5H).

4-Chloro-2-dimethylamino-5-heptyl-6-phenylpyrimidine. **6h**

Yield : 53.9%; mp 31°C; ir ($CHCl_3$) ν 3020, 1573, 1537, 1511, 1489, 1412, 702, 644 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 0.84 t (J=6.5 Hz, 3H), 1.17 s (6H), 1.24 m (2H), 1.46 m (2H), 2.50-2.58 m (2H), 3.16 s (6H), 7.38-7.46 m (5H); M^+, 331 m/z.

4-Chloro-2-dimethylamino-5-methyl-6-[2'-thienyl]pyrimidine. **6i**

Yield : 18%; mp 81-82°C; ir ($CHCl_3$) ν 3077, 1581, 1546, 1507, 1450, 1434, 1411, 1380, 1334, 714 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 2.38 s (3H), 3.12 s (6H), 7.05 dd (J=5.1/3.8 Hz, 1H), 7.40 dd (J=5.1/1.1 Hz, 1H), 7.48 dd (J=3.8/1.0 Hz, 1H); Anal. calcd for $C_{11}H_{12}ClN_3S$: C, 52.07%; H, 4.76; N, 16.56. Found: C, 52.20%; H, 5.67; N, 16.79. M^+, 253 m/z.

4-Chloro-5-methyl-6-phenyl-2-pyrrolidinopyrimidine. **6j**

Yield : 85%; mp 94-95°C; ir ($CHCl_3$), ν 3064, 1586, 1572, 1528, 1511, 1489, 1461, 704, 669 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 1.94 m (4H), 2.19 s (3H), 3.57 s (4H), 7.37-7.55 m (5H); Anal. calcd for $C_{15}H_{16}ClN_3$: C, 65.81%; H, 5.89; N, 15.35. Found: C, 65.81%; H, 5.93; N, 15.46. M^+, 273 m/z.

4-Chloro-5-methyl-6-phenyl-2-piperidinopyrimidine. **6k**

Yield : 62%; mp 88-89°C; ir ($CHCl_3$), ν 3020, 1586, 1572, 1517, 1492, 1465, 1448, 705, 647 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 1.61 m (6H), 2.19 s (3H), 3.76 s (4H), 7.39-7.53 m (5H); M^+, 287 m/z.

4-Chloro-5-methyl-2-morpholino-6-phenylpyrimidine. **6l**

Yield : 18%; ir ($CHCl_3$), ν 3011, 1585, 1572, 1519, 1493, 1449, 1334, 705, 651 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 2.22 s (3H), 3.76 m (8H), 7.41-7.55 m (5H); Anal. calcd for $C_{15}H_{16}ClN_3O$: C, 62.17%; H, 5.56; N, 14.50; Cl, 12.23. Found: C, 62.31%; H,

4.15; N, 14.55; Cl, 12.17. M^+, 289 m/z.

4-Chloro-2-perhydroazepinyl-5-methyl-6-phenylpyrimidine. **6m**

Yield : 66%; ir ($CHCl_3$), ν 3064, 1586, 1571, 1521, 1491, 1469, 1437, 705, 646 cm^{-1}; ^1H nmr (200 MHz/$CDCl_3$), δ 1.55 m (4H), 1.77 m (4H), 2.21 s (3H), 3.75 m (4H), 7.41-7.57 m (5H); M^+, 301 m/z.

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