The Synthesis of Triazines from *N*-Cyanoamidines[1]

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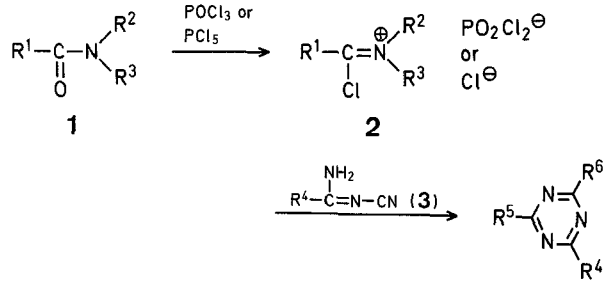
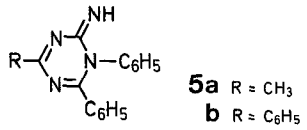
N-Cyanoamidines, potentially useful synthons for heterocyclic ring formation, have received scant attention, despite their ready availability from imidates or amidines[2,3]. Their conversion to 1,3,5-triazines by condensation with amides, imidates, amidines, and nitriles under a variety of conditions was described by Huffman and Schaefer[2], but yields were disappointing (15–50%). More recently, Ried and Kothe[4] reported low yields of iminodihydrotriazines in the reaction of *N*-cyanoamidines with *N*-substituted chloroformamidines and imidoyl chlorides, and in one case isolated a 1,3,5-triazine. We now report our studies on the reaction of *N*-cyanoamidines with chloromethyleniminium salts, which have led to the development of a versatile and convenient synthesis of 1,3,5-triazines.

Thus, reaction of the chloromethyleniminium salt (**2a**; *N,N*-dimethylbenzamide/phosphoryl chloride complex) with *N*-cyanobenzamidine (**3**) in acetonitrile at room temperature gives 2-chloro-4,6-diphenyl-1,3,5-triazine (**4a**) in 70% yield. Extension of the reaction (Scheme **A**) to other chloromethyleneiminium salts **2**, conveniently prepared *in situ* from *N*-substituted amides **1** and phosphoryl chloride or phosphorus pentachloride, gives the appropriately substituted 1,3,5-triazine **4** in good yield. Other *N*-cyanoamidines react analogously, and examples of triazines so prepared are given in the Table.



Scheme A

In addition to chlorotriazines, small quantities of aminotriazines are sometimes formed, and these become major products when *N*-arylamides are used as starting material (see Table). The aminotriazines may be formed in a secondary reaction between initially formed chlorotriazines and amines liberated during the cyclisation. Indeed, **4e** and **4f** are formed from **4c** and **4a**, respectively, on reaction with aniline in acetonitrile (reflux, 30 min), thus unequivocally establishing their structure. These anilinotriazines are identical (m.p., mixture m.p. ^{1}H-N.M.R., I.R., and mass spectrum) to the products of the reaction of *N*-phenylbenzimidoyl chloride with *N*-cyanoacetamidine and *N*-cyanobenzamidine, respectively, as described by Ried and Kothe[4]. The iminodihydrotriazine structures (**5a, b**) proposed by these authors therefore appear to be in error.



5a R = CH_3
b R = C_6H_5

The choice of conditions for the triazine synthesis is governed principally by the reactivity of the amide precursor of the chloromethyleniminium salt: reactive amides such as

Table. 1,3,5-Triazines **4**

Chloromethyleniminium Salt No.	R^1	R^2	R^3	$X^\ominus$	*N*-Cyanoamidine[1] No.	R^4	1,3,5-Triazine[a,b] No.	R^4	R^5	R^6	Reaction conditions (solvent/time/temperature)	Yield [%]	m.p. [°C]	Molecular formula or Lit. m.p. [°C]
2a	C_6H_5	CH_3	CH_3	$PO_2Cl_2^\ominus$	**3a**	C_6H_5	**4a**	C_6H_5	C_6H_5	Cl	CH_3CN/30 min/reflux	70	139°	138–139°[7]
2b	H	CH_3	CH_3	$PO_2Cl_2^\ominus$	**3a**	C_6H_5	**4b**	C_6H_5	H	Cl	CH_3CN/15 min/25 °C	56	86–87°	$C_9H_6ClN_3$ (191.6)
2c	CH_3	CH_3	CH_3	$PO_2Cl_2^\ominus$	**3a**	C_6H_5	**4c**	C_6H_5	CH_3	Cl	C_6H_6/18 h/25 °C	81	75°	75.5–76.5°[8]
2d	CH_3	H	C_6H_5	$PO_2Cl_2^\ominus$	**3a**	C_6H_5	**4d**	C_6H_5	CH_3	$N(CH_3)_2$		5	63°	$C_{12}H_{14}N_4$ (214.3)
							4c	C_6H_5	CH_3	Cl	CH_3CN/1 h/reflux	4	75°	—
2e	C_6H_5	H	C_6H_5	$Cl^\ominus$	**3a**	C_6H_5	**4e**	C_6H_5	CH_3	NHC_6H_5		84	133°	$C_{16}H_{14}N_4$ (262.3)
							4a	C_6H_5	C_6H_5	Cl	CH_3CN/1 h/reflux	48	139°	—
2f	indol-3-yl	CH_3	CH_3	$PO_2Cl_2^\ominus$	**3a**	C_6H_5	**4f**	C_6H_5	C_6H_5	NHC_6H_5		25	155°	155°[7]
2g	Cl	CH_3	CH_3	Cl	**3a**	C_6H_5	**4g**	C_6H_5	indol-3-yl	Cl	CH_3CN/144 h/25 °C	47	195°	$C_{17}H_{11}ClN_4$ (306.8)
2h	H_3CS	CH_3	CH_3	Cl	**3a**	C_6H_5	**4h**	C_6H_5	$(H_3C)_2N$	Cl	$POCl_3$/15 min/reflux	85	105°	$C_{11}H_{11}ClN_4$ (234.7)
2a	C_6H_5	CH_3	CH_3	$PO_2Cl_2^\ominus$	**3b**	CH_3	**4i**	C_6H_5	H_3CS	Cl	$POCl_3$/30 min/reflux	56	89°	$C_{10}H_8ClN_3S$ (237.7)
							4c	CH_3	C_6H_5	Cl	CH_3CN/30 min/reflux	49	75°	—
2a	C_6H_5	CH_3	CH_3	$PO_2Cl_2^\ominus$	**3c**	$ClCH_2$	**4d**	CH_3	C_6H_5	$N(CH_3)_2$		5	63°	—
							4j	$ClCH_2$	C_6H_5	Cl	CH_3CN/1 h/reflux	88	86–87°	$C_{10}H_7Cl_2N_3$ (240.1)

[a] The microanalyses for the new compounds were in satisfactory agreement with the calculated values (maximum deviations: C ±0.42, H ±0.27, N ±0.32).

[b] Mass spectra, recorded on an A.E.I. MS-9 instrument, all showed molecular ion peaks for ^{35}Cl.

0039-7881/80/1032-0841 $ 03.00

dimethylformamide and dimethylacetamide can be reacted with phosphoryl chloride in acetonitrile or other inert solvent at room temperature whereas unreactive amides such as benzanilide require use of phosphorus pentachloride as the acid chloride component. In many cases phosphoryl chloride can be used in excess as solvent for the reaction.

Triazines are formed also in the reaction of *N*-cyanoamidines with dichloromethyleniminium salts (e.g. **2g**)[5] and alkylthiochloromethyleniminium salts (e.g. **2h**)[6] (see Table). These two classes of reagent are generated from *S,N,N*-trialkyl dithiocarbamates by reaction with chlorine and phosgene respectively, and the latter can be generated *in situ* as are the alkyl- and arylchloromethyleniminium salts. This reaction therefore represents a facile route to diversely substituted 1,3,5-triazines, many of which are not otherwise readily accessible.

2-Chloro-4,6-diphenyl-1,3,5-triazine (4a):
N,N-Dimethylbenzamide (1.49 g, 10 mmol) is heated with phosphoryl chloride (1 ml) on a steam bath at 100 °C for 5 min. The resulting complex is dissolved in acetonitrile (10 ml) and a solution of *N*-cyanobenzamidine (1.45 g, 10 mmol) in acetonitrile (20 ml) is added. After several minutes the triazine begins to separate; after 30 min, water (100 ml) is added to complete the precipitation and the product is collected, washed with water, and recrystallized from ethanol/water; yield: 1.8 g (70%); m.p. 139 °C (Lit.[7], 138–139 °C).

2-Anilino-4-methyl-6-phenyl-1,3,5-triazine (4e):
N-Cyanobenzamidine (1.45 g, 10 mmol), acetanilide (1.35 g, 10 mmol), and phosphoryl chloride (1 ml) are refluxed in acetonitrile (20 ml) for 1 h. The hydrochloride of **4d** precipitates as a pale yellow crystalline solid, m.p. 198–204 °C, and is collected after the mixture has been allowed to stand at room temperature over night; yield: 2.5 g (84%).

The free triazine is obtained as colorless flat needles, m.p. 133 °C and is identical (m.p., mixture m.p., ^{1}H-N.M.R., I.R., and mass spectrum) with samples prepared by reaction of **4c** with aniline in acetonitrile (reflux, 30 min) and from the reaction of *N*-phenylbenzimidoyl chloride and *N*-cyanoacetamide according to Ried and Kothe[4]. The benzene-soluble fraction from the reaction mixture is washed with dilute ammonia, dried with magnesium sulfate, and chromatographed on silica gel (Merck 70–30 mesh ASTM) eluting with benzene. The first fractions from the column contain **4c** (0.075 g, 3.7%); m.p. 75 °C (Lit.[8], 75.5–76.5 °C).

2-Chloro-4-phenyl-6-methylthio-1,3,5-triazine (4i):
S,N,N-Trimethyl dithiocarbamate[6] (1.35 g, 10 mmol) is dissolved in toluene (10 ml) containing phosgene (20%, w/v) and the solution kept at room temperature protected from moisture for 1 h. The solvent and excess phosgene are evaporated in vacuo and to the residue is added phosphoryl chloride (10 ml) and *N*-cyanobenzamidine (1.45 g). The mixture is refluxed for 30 min and poured into water (100 ml). The product is extracted into benzene (2 × 25 ml) and purified by chromatography on silica gel eluting with benzene; the first fractions contain the methylthiotriazine (**4i**); yield: 1.3 g (56%); m.p. 89 °C.

Received: April 28, 1980

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