A Convenient Synthesis of 2-Substituted 4-Amino-5-pyrimidinecarbonitriles

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Synthesis of the novel 2-halogenated 4-amino-5-pyrimidinecarbonitriles **3a,b** starting from ethoxymethylenemalononitrile **1** and cyanamide is described. Nucleophilic substitution of the reactive halogen atom leads to the derivatives **5a-g**, **6** and **7a-h**.

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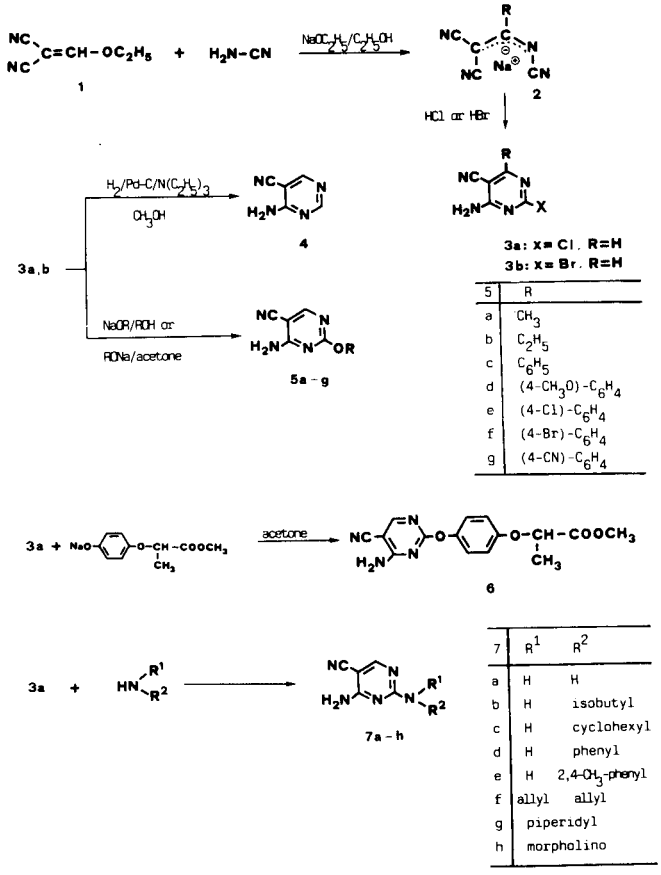
Much attention has been paid to the syntheses of halogenated cyano-substituted heterocyclic compounds by hydrogen halide induced cyclisation of 1,3-dicarbonitriles [1-3]. The reaction of salts of cyanopropenes with hydrogen halides forming substituted pyridines [4-7] and pyrimidines [8] is documented in literature. Kristinsson [9] has reported that alkyl-*N*-cyanoimidates react with malononitrile to give the sodium salts of 3-alkyl-3-cyanamino-2-cyano-propenenitriles **2** (R = alkyl), which can be cyclized with hydrochloric acid to 6-alkyl-4-amino-2-chloro-5-pyrimidine-carbonitriles (**3a**, R = alkyl). Reaction of *N*-cyanoimidate with malononitrile, however, did not give compound **2** (R = H) and further on the wanted 6-unsubstituted pyrimidine derivative **3**.

We now report an alternative route for the synthesis of **3** using ethoxymethylenemalononitrile (**1**) and cyanamide to give the sodium salt **2** (R = H). Cyclization with hydrochloric- and hydrobromic acid, respectively leads to the new 4-amino-2-halo-5-pyrimidinecarbonitriles **3a,b**. Considering the formation of possible isomers [1-3,7,10] depending on the possibilities for the attack of the hydrogen halide to the *N*- or *C*-bonded nitrile group of **2**, structure proof of **3a,b** was achieved by catalytic hydrogenation to the known product **4** [11].

The reactivity of the halogen atom in **3a,b** toward different nucleophiles can be used for a number of substitution reactions, as we did with halogenated pyridines [11]. Especially for the preparation of biologically active pyrimidines [13] and pyrimido[4,5-*d*]pyrimidines [14] this reaction is an improvement compared with the known substitution of the ethylthio group, which affords high temperature or heating under pressure. Treatment of **3a,b** with different sodium alcoholates and phenolates leads to the alkoxy- and aryloxy derivatives **5a-g**. Reaction of **3a** with methyl 4-hydroxy-α-*p*-phenoxy-propionate in acetone gives the pyrimidyloxy-phenoxy-propionic acid derivative **6**, a representative of a well known class of important herbicides [15].

Compounds **3a,b** react with various amines under mild conditions to the corresponding amino derivatives **7a-h**. The products listed in the Table are only some selected examples.



5	R
a	CH_3
b	C_2H_5
c	C_6H_5
d	(4-CH_3O)-C_6H_4
e	(4-Cl)-C_6H_4
f	(4-Br)-C_6H_4
g	(4-CN)-C_6H_4

7	R^1	R^2
a	H	H
b	H	isobutyl
c	H	cyclohexyl
d	H	phenyl
e	H	2,4-CH_3-phenyl
f	allyl	allyl
g	piperidyl	
h	morpholino	

EXPERIMENTAL

3-Cyanamino-2-cyanopropenenitrile Sodium Salt (**2**).

To a solution of sodium (6.9 g, 0.3 mole) in ethanol (200 ml) is added cyanamide (12.6 g, 0.3 mole) over a period of 5 minutes. The suspension is stirred for an additional 5 minutes and ethoxymethylenemalononitrile (36.6 g, 0.3 mole) is added in small portions within about 15 minutes. The resulting slightly yellowish solution is evaporated under reduced pressure, the residue is treated with chloroform (70 ml) and filtered by suction; an analytical sample is recrystallized from methanol, yield, 40.1 g (95%), mp > 260°; ir (potassium bromide): ν 2260, 2240 and 2180 (CN) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 8.08 (1H).

Table 1

2-Substituted 5-Pyrimidinecarbonitriles **3a-b, 5a-g, 7a-h**

Compound	Yield %	Mp °C (Solvent)	Molecular Formula Lit Data °C	Analysis % Calcd./Found C	H	N	IR (cm^{-1}) [a] (potassium bromide)	^{1}H-NMR (δ ppm) [b] (DMSO-d_6)
3a	71	243-244 (methanol)	$C_5H_3ClN_4$ 154.6	38.85 38.72	1.96 1.92	36.24 36.34	3420, 3120 (NH_2), 2260 (CN)	8.30 (s, 2H), 8.53 (s, 1H)
3b	63	> 300 (acetic acid)	$C_5H_3BrN_4$ 199.0	30.18 30.11	1.52 1.48	28.15 28.20	3340, 3040 (NH_2), 2240 (CN)	8.30 (s, 2H), 8.50 (s, 1H)
5a	67	220 (methanol)	221-222 [14]					
5b	65	182-184 (ethanol)	183-184 [16]					
5c	84	200 (ethanol)	$C_{11}H_8N_4O$ 212.2	62.26 62.38	3.80 3.85	26.40 26.65	2230 (CN)	7.20 (m, 5H), 7.83 (s, 2H), 8.48 (s, 1H)
5d	74	191 (ethanol)	$C_{12}H_{10}N_4O_2$ 242.2	59.51 59.69	4.16 4.12	23.13 23.14	2225 (CN)	7.13 (d, 2H), 7.87 (s, 2H), 8.44 (s, 1H)
5e	89	230-232 (ethanol)	$C_{11}H_7ClN_4O$ 246.6	53.58 53.70	2.86 2.85	22.72 22.70	2230 (CN)	7.18 (d, 2H), 7.45 (d, 2H), 7.93 (s, 2H), 8.46 (s, 1H)
5f	95	222 (ethanol)	$C_{11}H_7BrN_4O$ 291.1	45.39 45.55	2.42 2.51	19.25 19.29	2250 (CN)	7.10 (d, 2H), 7.53 (d, 2H), 7.90 (s, 2H), 8.41 (s, 1H)
5g	80	285 (acetic acid)	$C_{12}H_7N_5O$ 237.2	60.76 60.66	2.97 2.96	29.53 29.65	2230 (CN)	7.42 (d, 2H), 7.70 (s broad, 2H), 7.92 (d, 2H), 8.52 (s, 1H)
7a	76	> 310 (acetic acid)	318 [17]					
7b	84	172-174 (methanol/water)	$C_9H_{13}N_5$ 191.2	56.52 56.14	6.85 6.89	36.62 36.42	2230 (CN)	0.75 (s, 3H), 0.88 (s, 3H), 1.79 (m, 1H), 3.07 (dd, 2H), 7.05 (s broad, 2H), 7.40 (d, 1H), 8.15 (s, 1H)
7c	72	181-182 (ethanol)	182-183 [14]					
7d	66	233-234 (ethanol)	234-235 [14]					
7e	68	175 (chloroform)	$C_{13}H_{13}N_5$ 239.5	65.25 65.18	5.48 5.61	29.27 29.41	2230 (CN)	2.16 (s, 3H), 2.28 (s, 3H), 7.13 (m, 5H), 8.92 (s, 1H)
7f	85	97-99 (methanol/water)	$C_{11}H_{13}N_5$ 215.3	61.37 61.11	6.09 6.12	32.54 32.87	2240 (CN)	4.10 (m, 4H), 5.04 (m, 4H), 5.32-6.11 (m, 2H), 7.09 (s, 2H), 8.17 (s, 1H)
7g	81	212 (ethanol)	212-213 [14]					
7h	86	229-231 (ethanol)	$C_9H_{11}N_5O$ 205.2	52.68 52.77	5.40 5.31	34.13 34.30	2240 (CN)	3.61 (s, 8H), 7.20 (s, 2H), 8.21 (s, 1H)

[a] The ir spectra were recorded on a Perkin Elmer 298 spectrophotometer. [b] The nmr spectra were measured on a Varian EM 360A spectrometer.

Anal. Calcd. for C_5HN_4Na (140.1): C, 42.87; H, 0.72; N, 39.99. Found: C, 42.58; H, 0.73; N, 39.67.

4-Amino-2-chloro-5-pyrimidinecarbonitrile (**3a**).

To a stirred solution of concentrated hydrochloric acid (70 ml) of **2** (7.0 g, 50 mmoles) is added in small portions over a period of 30 minutes; the temperature of the solution should not exceed 30°. The resulting mixture is stirred for 20 minutes, diluted with water (200 ml) and again stirred for 10 minutes. The precipitate is isolated by suction and carefully washed with water; analytical data see Table.

4-Amino-2-bromo-5-pyrimidinecarbonitrile (**3b**).

Powdered **2** (4.9 g, 35 mmoles) is stirred at room temperature in hydrobromic acid (50 ml) for 15 minutes. The mixture is diluted with water (100 ml), the precipitate is filtered by suction and washed with water; analytical data see Table.

4-Amino-5-pyrimidinecarbonitrile (**4**).

To a solution of methanol (200 ml) and triethylamine (5 ml) is added **3a** (2.0 g, 13 mmoles) and 5% palladium on charcoal (0.4 g). This solution is

shaken on a low pressure hydrogenator at 30 lb/sq in at room temperature for 3.5 hours. The mixture is filtered, concentrated *in vacuo* and the resulting precipitate isolated. Colourless needles from ethanol, yield, 0.8 g (52%), mp 252-253° (lit [11] 255-256°).

2-Alkoxy-4-amino-5-pyrimidinecarbonitriles **5a,b**.

Compound **3a** (2.0 g, 13 mmoles) and sodiumalcoholate (30 mmoles) are heated under reflux in the corresponding alcohol (50 ml) for 30 minutes. The solution is chilled and the formed precipitate is collected; analytical data see Table.

4-Amino-2-phenoxy-5-pyrimidinecarbonitriles **5c-g**.

General Procedure.

A solution of **3a** or **3b** (10 mmoles) and the sodium salt of the corresponding phenol (20 mmoles) in acetone (100 ml) are refluxed for 10 minutes. After cooling the mixture is diluted with water (50 ml) and the formed precipitate is collected; analytical data see Table.

Methyl 2-[4-(4-Amino-5-cyanopyrimidyl-2-oxy)phenoxy]propionate (**6**).

To a solution of sodium (1.0 g, 45 mmoles) in methanol (40 ml) is slowly added methyl 2-(4-hydroxyphenoxy)propionate (10.0 g, 50 mmoles). After stirring at room temperature the solvent is removed *in vacuo* and the residual sodium salt can be directly used in the next step.

A solution of **3a** (1.5 g, 10 mmoles) and the sodium salt (4.4 g, 20 mmoles) in acetone (50 ml) are refluxed for 45 minutes. The solid obtained after cooling was recrystallized from toluene to yield 2.5 g (80%) of **6**, mp 150°; ir (potassium bromide): ν 2220 (CN), 1740 (C=O) cm^{-1}; nmr (dimethylsulfoxide-d_6): δ 1.55 (d, 3H), 3.70 (s, 3H), 4.95 (q, 1H), 7.05 (m, 4H), 8.50 (s, 1H).

Anal. Calcd. for $C_{15}H_{14}N_4O_4$ (314.3): C, 57.32; H, 4.49; N, 17.83. Found: C, 57.25; H, 4.53; N, 17.84.

2-Amino-substituted 4-Amino-5-pyrimidinecarbonitriles **7a-h**.

General Procedure.

To the stirred corresponding amine (15 ml) is added **3a** (2.5 g, 16 mmoles) at 10-15° in small portions. The mixture is heated in an oil bath at 60° for 20 minutes and after cooling poured onto ice/water (100 ml). The precipitated product is collected by suction; analytical data see Table.

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