Synthesis of 2-Amino-5-pyrimidinecarbonitrile Derivatives

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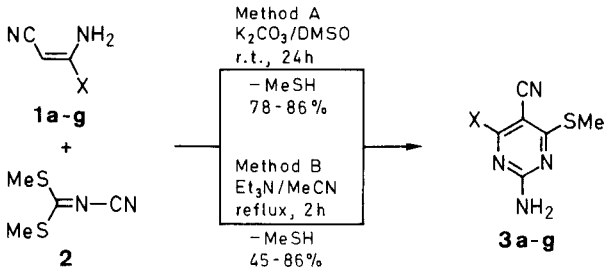
2-Amino-4-dialkylamino- or -4-ethoxy-6-methylthio-5-pyrimidinecarbonitriles **3** are obtained through a base-induced reaction between 3-amino-3-(dialkylamino)propenenitriles **1** and *N*-[bis(methylthio)methylene]cyanamide **(2)**.

Pyrimidine derivatives are very important biologically compounds. Many drugs contain the pyrimidine ring such as hypnotic drugs, antimalarial, antibacterial and others. Moreover, they are also interesting as starting materials for conversion into other heterocyclic compounds, especially into fused pyrimidine derivatives. Since direct introduction of specific substituents in the pyrimidine nucleus is sometimes difficult a number of indirect synthetic methods have been developed.[1] Among these the most commonly used in preparing pyrimidine derivatives is the condensation reaction of ketene dithioacetals bearing electron-withdrawing groups and amidine derivatives in presence of an appropriate base.[2,3] The present study reports a convenient method for the synthesis of functionalized pyrimidines **3** by reaction of 3-amino-3-(dialkylamino)propenenitriles **1** with *N*-[bis(methylthio)methylene]cyanamide **(2)**.

N-[Bis(methylthio)methylene]cyanamide is an electrophilic reagent which allows introduction of the C=N–C=N unit in the heterocyclic nucleus and the cyanoacetamidines are particularly reactive and easily accessible nucleophiles.[4] Excellent yield of 2-amino-4-dialkylamino-6-methylthio-5-pyrimidinecarbonitriles **3** are obtained by two methods: in the first (Method A) the enaminonitriles **1** are reacted with compound **2** at room temperature the presence of potassium carbonate in dimethyl sulfoxide (DMSO), while in the second



1, 3	X	1, 3	X
a	OEt	**e**	morpholino
b	pyrrolidino	**f**	4-methylpiperazino
c	piperidino	**g**	4-ethoxycarbonyl-piperazino
d	4-ethoxycarbonyl-piperidino		

(Method B) the enaminonitriles **1** and compound **2** in a 1:1.5 molar ratio are heated under reflux in acetonitrile in the presence of an excess of triethylamine for a few hours.

The structures of the compounds agree with the elemental analysis and spectral data reported in the Table. As the starting materials are readily available and as high yields are obtained, this preparative method for the synthesis of pyrimidine derivatives is undoubtedly a very important synthetic method.

3-Amino-3-ethoxypropenenitrile **(1a)** was prepared according to literature procedure.[5] *N*-[Bis(methylthio)methylene]cyanamide **(2)** was purchased from Janssen Chimica.

Table. Pyrimidine Derivatives **3** Prepared[a]

Product	Yield (%) Method A	Yield (%) Method B	mp (°C)[b] (solvent)	Molecular[c] Formula	IR (Nujol)[d] ν (cm^{-1})	^{1}H-NMR (solvent/TMS)[e] δ
3a	85	45	174 (MeCN)	$C_8H_{10}N_4OS$ (210.2)	3520, 3400, 2210, 1610	(DMSO-d_6): 1.25 (t, 3H, CH_3), 2.48 (s, 3H, CH_3), 4.35 (q, 2H, CH_2), 7.60 (s, 2H, NH_2)
3b	80	83	214 (EtOH)	$C_{10}H_{13}N_5S$ (235.2)	3500, 3340, 2195, 1615	($CDCl_3$): 1.85 (m, 4H, $2CH_2$), 2.45 (s, 3H, CH_3), 3.68 (m, 4H, CH_2NCH_2), 5.00 (brs, 2H, NH_2)
3c	86	66	139 (EtOH)	$C_{11}H_{15}N_5S$ (249.3)	3480, 3340, 2195, 1610	($CDCl_3$): 1.65 (m, 6H, $3CH_2$), 2.43 (s, 3H, CH_3), 3.70 (m, 4H, CH_2NCH_2), 5.12 (brs, 2H, NH_2)
3d	85	88	133 (MeCN)	$C_{14}H_{19}N_5O_2S$ (321.3)	3470, 3350, 2190, 1720, 1620	(DMSO-d_6): 1.12 (t, 3H, CH_3), 1.80, 2.89, 3.08, 4.39 (4m, $9H_{piperidinyl}$), 2.42 (s, 3H, CH_3), 4.03 (q, 2H, CH_2), 7.08 (s, 2H, NH_2)
3e	85	80	182 (MeCN)	$C_{10}H_{13}N_5OS$ (251.2)	3460, 3320, 2200, 1630	($CDCl_3$): 2.45 (s, 3H, CH_3), 3.75 (m, $8H_{morpholinyl}$), 5.06 (brs, 2H, NH_2)
3f	79	78	174 (MeCN)	$C_{11}H_{16}N_6S$ (264.3)	3490, 3280, 2200, 1635	(DMSO-d_6): 2.13 (s, 3H, NCH_3), 2.30, 3.70 (2m, $8H_{piperazinyl}$), 2.43 (s, 3H, SCH_3), 7.10 (s, 2H, NH_2)
3g	78	74	209 (EtOH)	$C_{13}H_{18}N_6O_2S$ (322.3)	3450, 3340, 2200, 1695	(DMSO-d_6): 1.14 (t, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.45, 3.70 (2m, $8H_{piperazinyl}$), 4.02 (q, 2H, CH_2), 7.12 (s, 2H, NH_2)

[a] All compounds are new.
[b] Uncorrected, measured with a Köfler hot stage.
[c] Satisfactory microanalyses obtained: C, H, N ± 0.35
[d] Recorded on Perkin-Elmer 3250 Infrared Spectrophotometer.
[e] Recorded on Varian FT 80 Spectrometer.

3-Amino-3-(dialkylamino)propenenitriles 1b–g; General Procedure:
A solution of 3-amino-3-ethoxypropenenitrile (**1a**; 1.1 g, 10 mmol) and amine (10 mmol) in absolute EtOH (10 mL) is stirred for 24 h at 25 °C. The formed precipitate is filtered off and washed with dry Et_2O to give the enaminonitriles **1**.

3-Amino-3-(4-ethoxycarbonylpiperidino)propenenitrile (**1d**): yield 1.51 g (68%); mp 62 °C (Et_2O/CH_2Cl_2).

$C_{11}H_{17}N_3O_2$	calc.	C 59.17	H 7.68	N 18.82
(223.3)	found	59.08	7.61	18.80

IR (Nujol): ν = 3420, 3340, 3240, 2190, 1675, 1645, 1565 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.12 (t, 3H, CH_3), 1.58, 2.57, 3.55 (3 m, 9 $H_{piperidinyl}$), 3.02 (s, 1H, =CH), 4.02 (q, 2H, CH_2), 5.75 (s, 2H, NH_2).

3-Amino-3-(4-methylpiperazino)propenenitrile (**1f**):

yield: 1.19 g (72%); mp 117–118 °C (benzene).

$C_8H_{14}N_4$	calc.	C 57.80	H 8.49	N 33.71
(166.2)	found	57.71	8.43	33.65

IR (Nujol): ν = 3370, 3180, 2800, 2190, 1650, 1555 cm^{-1}.

^{1}H-NMR (DMSO-d_6/TMS): δ = 2.12 (s, 3H, CH_3), 2.18, 3.18 (2 m, 8 $H_{piperazinyl}$), 3.00 (s, 1H, =CH), 5.78 (s, 2H, NH_2).

3-Amino-3-(4-ethoxycarbonylpiperazino)propenenitrile (**1g**): yield: 1.83 g (82%); mp 122–123 °C (benzene).

$C_{10}H_{16}N_4O_2$	calc.	C 53.55	H 7.19	N 24.99
(224.2)	found	53.50	7.15	24.91

IR (Nujol): ν = 3420, 3350, 3250, 2185, 1685, 1655, 1500 cm^{-1}.

^{1}H-NMR (DMSO-d_6/TMS): δ = 1.14 (t, 3H, CH_3), 3.03 (s, 1H, =CH), 3.05, 3.25 (2 m, 8 $H_{piperazinyl}$), 4.00 (q, 2H, CH_2), 5.86 (s, 2H, NH_2).

2-Amino-4-dialkylamino- or -4-ethoxy-6-methylthio-5-pyrimidinecarbonitriles 3; General Procedure:

Method A: 40% Aq K_2CO_3 (1.75 mL) is added to a stirred solution of enaminonitriles **1** (5 mmol) and compound **2** (5 mmol) in DMSO (15 mL). The mixture is stirred at 25 °C (r.t.) for 24 h then diluted with ice-water. The precipitate is collected by filtration, washed, dried and crystallized to give the pyrimidines **3** in 78–86% yields.

Method B: Et_3N (10 mL) is added to a mixture of enaminonitriles **1** (5 mmol) and compound **2** (7.5 mmol) in MeCN (5 mL). The solution is heated at reflux for 2 h. The hot solution is then concentrated to dryness and the residue collected and crystallized to give the pyrimidines **3** in 45–86% yield. The methanethiol produced is destroyed by passage into one wash bottle containing aq NaOCl (13% active Cl_2).

Received: 1 August 1990; revised 6 February 1991

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