Pyrimidine-5-carbonitriles from Methyl *N*-(Aminocarbonyl)- or *N*-(Aminothiocarbonyl)-imidates

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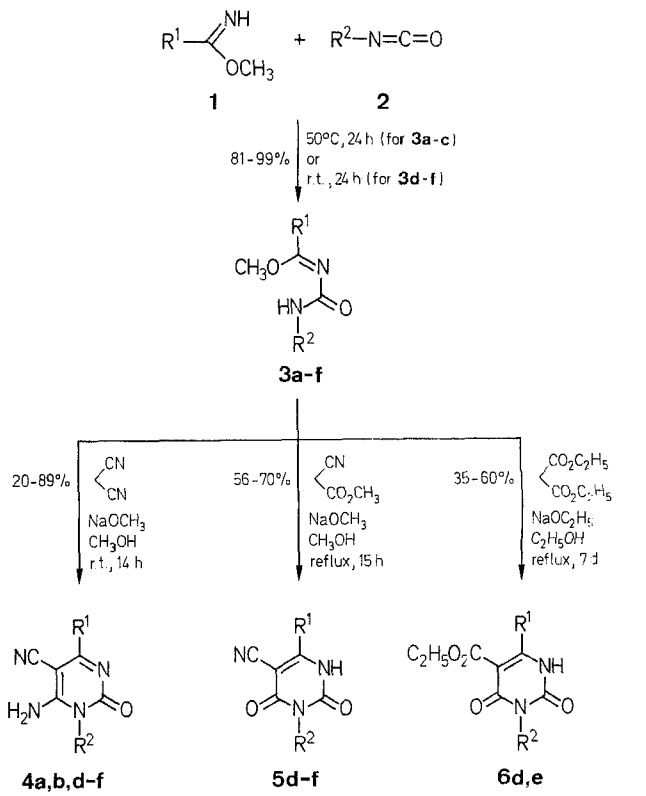
A number of substituted pyrimidine-5-carbonitriles and ethyl pyrimidine-5-carboxylates are prepared by reaction of methyl *N*-(aminocarbonyl)- or *N*-(aminothiocarbonyl)imidates with malononitrile, methyl cyanoacetate, or diethyl malonate.

Carbon-nitrogen double bonds bearing an electron-withdrawing substituent on nitrogen and a leaving group in carbon, such as *N*-substituted imidic esters, can undergo addition of suitable nucleophiles followed by elimination. The intermediates formed in such a way can cyclize intramolecularly to aromatic heterocycles. Thus alkyl *N*-cyanoimidates from pyrimidines[1-3] and alkyl N-acylimidates or *N*-(methoxycarbonyl)imidates afford 1,2,4-triazoles[4] or triazolones and pyrimidine-5-carbonitriles.[5] We now report the reaction of methyl *N*-(ethyl- or phenylaminocarbonyl)imidates **3** or their thiocarbonyl analogues **7** with the sodium salt of malononitrile and related nucleophiles to yield a variety of new pyrimidines. The intermediates in these processes are similar to the ones isolated in the treatment of 3-alkoxy-2-cyanopropenenitriles with ureas.[6,7]

The methyl *N*-(ethyl- or phenylaminocarbonyl)imidates **3** were prepared from methyl imidates **1** and ethyl or phenyl isocyanates **2** by a modification of a reported[8] procedure (Table 1). The reaction of equimolar amounts of the methyl *N*-(aminocarbonyl)imidates **3a–f**, malonitrile and sodium methoxide in dry methanol led to the 6-amino-2-oxopyrimidine-5-carbonitriles **4a, b, d–f** in good yields (Table 2). In an analogous reaction with methyl cyanoacetate, the intermediate initially formed cyclized intramolecularly with participation of the methoxycarbonyl group and not of the carbonitrile group, which agrees with our previous experience with other substrates[3] and can be explained on steric grounds, as we have discussed in detail previously.[3] Thus, the 2,4-dioxo-3-phenyl-pyrimidine-5-



3–6	R^1	R^2	3–6	R^1	R^2
a	C_2H_5	C_6H_5	d	C_6H_5	C_6H_5
b	C_6H_5	C_2H_5	e	4-$CH_3C_6H_4$	C_6H_5
c	4-$CH_3C_6H_4$	C_2H_5	f	4-ClC_6H_4	C_6H_5

Table 1. Methyl *N*-(Aminocarbonyl)imidates **3** Prepared

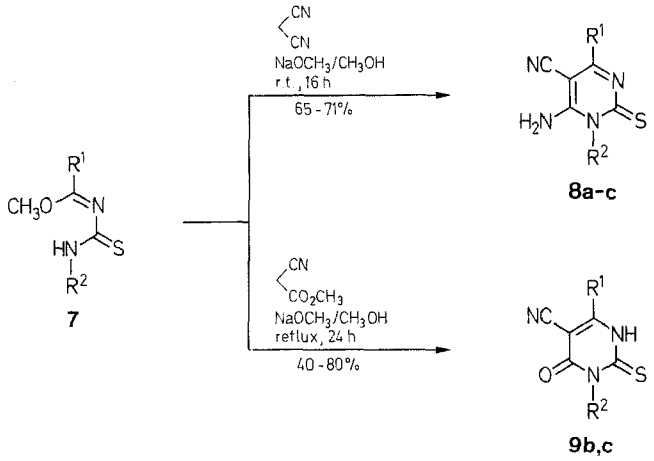
Product	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]	IR (KBr)[d] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)
3a	87	104–107	$C_{11}H_{14}N_2O_2$ (206.3)	3260, 1660, 1640	1.18 (t, 3H, J = 7, CH_3); 2.43 (q, 2H, J = 7, CH_2); 3.72 (s, 3H, CH_3O); 6.9–7.7 (m, 6H, H_{arom} + NH)
3b	90	78–79	$C_{11}H_{14}N_2O_2$ (206.2)	3280, 1660, 1640	1.02 (t, 3H, J = 7, CH_3); 3.15 (q, 2H, J = 7, CH_2); 3.83 (s, 3H, CH_3O); 5.7 (br s, 1H, NH); 7.2–7.9 (m, 5H, H_{arom})
3c	98	69–70	$C_{12}H_{16}N_2O_2$ (220.3)	3420, 1650, 1610	1.07 (t, 3H, J = 7, CH_3); 2.40 (s, 3H, CH_3); 3.20 (q, 2H, J = 7, CH_2); 3.87 (s, 3H, CH_3O); 5.1 (br s, 1H, NH); 7.0–7.9 (m, 4H, H_{arom})
3d	99	116–118	$C_{15}H_{14}N_2O_2$ (254.3)	3380, 1640, 1590	3.90 (s, 3H, CH_3O); 7.0–7.8 (m, 11H, H_{arom} + NH)
3e	97	125–126	$C_{16}H_{16}N_2O_2$ (268.3)	3290, 1665, 1625	2.30 (s, 3H, CH_3); 3.87 (s, 3H, CH_3O); 7.0–7.7 (m, 10H, H_{arom} + NH)
3f	81	124–126	$C_{15}H_{13}ClN_2O_2$ (288.7)	3230, 1660, 1620	3.90 (s, 3H, CH_3O); 7.0–7.9 (m, 10H, H_{arom} + NH)

[a] Yield of isolated pure product.
[b] Uncorrected. Products recrystallized from 2-PrOH.
[c] Satisfactory microanalysis obtained: C ±0.32, H ±0.31, N ±0.32, Cl +0.28.
[d] Recorded on a Perkin-Elmer 257 Infrared spectrophotometer.
[e] Recorded on a Varian T-60A spectrometer.

Table 2. 2-Oxopyrimidine-5-carbonitriles **4**, **5**, **6** Prepared

Product	Yield[a] (%)	mp[b] (°C) (solvent)	Molecular Formula[c]	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS)[e] δ, J (Hz)
4a	20	275–276 (EtOH)	$C_{13}H_{12}N_4O$ (240.3)	3400–3300, 2220, 1670	1.20 (t, 3H, J = 7, CH_3); 2.60 (q, 2H, J = 7, CH_2); 7.2–7.8 (m, 7H, H_{arom} + NH_2[f])
4b	60	237–238 (MeOH)	$C_{13}H_{12}N_4O$ (240.3)	3400–3200, 2220, 1650	2.30 (t, 3H, J = 7, CH_3); 4.07 (q, 2H, J = 7, CH_2); 7.4–7.9 (m, 5H, H_{arom}); 8.3 (br s, 2H, NH_2[f])
4d	79	260–261 (MeOH)	$C_{17}H_{12}N_4O$ (288.3)	3400–3300, 2220, 1655	6.3–8.3 (m, 12H, H_{arom} + NH_2[f])
4e	89	254–256 (MeOH)	$C_{18}H_{14}N_4O$[g] (302.3)	3350–3100, 2210, 1660	2.43 (s, 3H, CH_3); 7.1–7.8 (m, 11H, H_{arom} + NH_2[f])
4f	69	283–284 (EtOH)	$C_{17}H_{11}ClN_4O$ (322.8)	3300, 2220, 1660	7.3–8.1 (m, 11H, H_{arom} + NH_2[f])
5d	56	292–294 (MeOH)	$C_{17}H_{11}N_3O_2$ (289.3)	3500, 2220, 1730, 1650	7.2–7.9 (m, 10H, H_{arom}); 12.7 (s, 1H, NH + OH[f])
5e	70	276–277 (MeOH)	$C_{18}H_{13}N_3O_2$ (303.3)	3500, 2230, 1740, 1670	2.43 (s, 3H, CH_3); 7.2–7.8 (m, 9H, H_{arom}); 12.5 (s, 1H, NH + OH[f])
5f	69	342–344 (MeOH)	$C_{17}H_{10}ClN_3O_2$[h] (323.7)	3500, 2230, 1740, 1650	6.3 (br s, 1H, NH + OH[f]); 7.1–7.9 (m, 9H, H_{arom})
6d	60	230–232 (EtOH)	$C_{19}H_{16}N_2O_4$ (336.4)	3250–2800, 1710, 1650, 1620	1.03 (t, 3H, J = 7, CH_3); 4.13 (q, 2H, J = 7, CH_2); 7.0–7.6 (m, 10H, H_{arom}); 9.66 (s, 1H, NH + OH[f])
6e	35	244–247 (EtOH)	$C_{20}H_{18}N_2O_4$ (350.4)	3200–2800, 1700, 1650, 1620	1.08 (t, 3H, J = 7, CH_3); 2.37 (s, 3H, CH_3); 4.13 (q, 2H, J = 7, CH_2); 6.9–7.6 (m, 9H, H_{arom}); 9.8 (br s, 1H, NH + OH[f])

[a] Yield of isolated pure product.
[b] Uncorrected.
[c] Satisfactory microanalysis obtained: C ±0.38, H ±0.43, N ±0.39, Cl ±0.12.
[d] Recorded on a Perkin-Elmer 257 Infrared spectrophotometer.
[e] Recorded on a Varian T-60A spectrometer. Compounds **6d** and **6e** measured in $CDCl_3$.
[f] Signal exchangeable with trifluoroacetic acid.
[g] **4e**: MS: m/z (%): 302 (M^+, 31), 119 (7), 77 (15).[i]
[h] **5f**: MS: m/z (%): 323 (M^+, 40), 204 (14), 119 (100).[i]
[i] Recorded at 70 eV on a Varian MAT spectrometer.



7–9	R^1	R^2
a	4-$CH_3C_6H_4$	CH_3
b	C_6H_5	C_6H_5
c	4-$CH_3C_6H_4$	C_6H_5

Table 3. 2-Thioxopyrimidine-5-carbonitriles **8**, **9** Prepared

Product	Yield[a] (%)	mp[b] (°C)	Molecular Formula[c]	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS)[e] δ, J (Hz)
8a	65	258–259	$C_{13}H_{12}N_4S$ (256.3)	3400–3140, 2220	2.43 (s, 3H, CH_3); 4.00 (s, 3H, CH_3N); 7.1–7.9 (m, 4H, H_{arom}); 8.4 (br s, 2H, NH_2[f])
8b	71	262–263	$C_{17}H_{12}N_4S$ (304.4)	3360–3120, 2220	7.2–8.3 (m, H_{arom} + NH_2[f])
8c	69	250–252	$C_{18}H_{14}N_4S$ (318.4)	3450–3220, 2215	2.43 (s, 3H, CH_3); 7.2–8.1 (m, 11H, H_{arom} + NH_2[f])
9b	40	320–322	$C_{17}H_{11}N_3OS$ (305.4)	3200–2800, 2240, 1690	7.0–8.1 (m, H_{arom} + NH)
9c	80	308–310	$C_{18}H_{13}N_3OS$ (319.4)	3300–2800, 2240, 1690	2.40 (s, 3H, CH_3); 7.1–7.8 (m, 10H, H_{arom} + NH)

[a] Yield of isolated pure product.
[b] Uncorrected. Products recrystallized from MeOH.
[c] Satisfactory microanalysis obtained: C ±0.37, H ±0.22, N ±0.44; for **9b**, **c**: S +0.26.
[d] Recorded on a Perkin-Elmer 257 Infrared spectrophotometer.
[e] Recorded on a Varian T-60A spectrometer.
[f] Signal exchangeable with trifluoroacetic acid.

carbonitriles **5d–f** were isolated in good yields. Similarly, with diethyl malonate the ethyl 2,4-dioxopyrimidine-5-carboxylates **6d, e** were obtained.

Starting from the methyl *N*-(methyl- or phenylaminothiocarbonyl)imidates[9,10] **7** and malononitrile, the 4-amino-2-thioxopyrimidine-5-carbonitriles **8a–c** were obtained in good yields (Table 3). In an analogous reaction with methyl cyanoacetate, the intramolecular cyclization with the methoxycarbonyl group was again observed leading to the 4-oxo-2-thioxo-pyrimidine-5-carbonitriles **9 b, c**.

Methyl *N*-(Ethyl- or phenylaminocarbonyl)imidates 3; General Procedure:
A mixture of the appropriate imidate **1** (0.1 mol) and ethyl (or phenyl) isocyanate **2** (0.1 mol) is allowed to stand at room temperature **(3d–f)** or at 50 °C **(3a–c)** for 24 h. The solid reaction mixture is then placed under vacuum (10^{-3} Torr) for 3 h at room temperature. The crude product is recrystallized from 2-propanol to yield compounds **3a–f** (Table 1).

6-Amino-1,4-diaryl- or arylalkyl-2-oxo-1,2-dihydropyrimidine-5-carbonitriles 4; General Procedure:
To a solution of Na (0.14 g, 6 mmol) in dry MeOH (15 mL), malononitrile (0.33 g, 5 mmol) and the appropriate imidate **3** (5 mmol) are added. After the reaction mixture is stirred at room temperature for 14 h, it is neutralized with glacial HOAc (0.4 g, 7 mmol) and diluted with water (50 mL). The precipitate is collected by filtration and recrystallized from MeOH (or EtOH for **4a, f**) to yield the pyrimidine-5-carbonitriles **4a, b, d–f** (Table 2).

3,6-Diaryl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles 5; General Procedure:
To a solution of Na (0.28 g, 12 mmol) in dry MeOH (15 mL), methyl cyanoacetate (0.57 g, 5 mmol) and the appropriate imidate **3** (5 mmol) are added. The solution is stirred under reflux for 15 h and allowed to cool to room temperature. The reaction mixture is neutralized with glacial HOAc (0.8 g, 14 mmol) and diluted with water (50 mL). The precipitate is collected by filtration and recrystallized from MeOH to yield the pyrimidine-5-carbonitriles **5d–f** (Table 2).

Ethyl 3,6-Diaryl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylates 6; General Procedure:
Ethyl propanedioate (0.8 g, 5 mmol) and an imidate **3** (5 mmol) are added to a solution of Na (0.28 g, 12 mmol) in dry EtOH (15 mL). The solution is heated under reflux with stirring for 7 d and allowed to cool to room temperature. The reaction mixture is neutralized with conc. H_2SO_4 (to pH 4) and the solvent is evaporated. The residue is diluted with water (50 mL) and extracted with $CHCl_3$ (3 × 20 mL). The organic layer is dried ($MgSO_4$), evaporated and recrystallized from EtOH to afford the ethyl pyrimidine-5-carboxylates **6d, e** (Table 2).

6-Amino-1,4-diaryl- or arylalkyl-2-thioxo-1,2-dihydropyrimidine-5-carbonitriles 8; General Procedure:
To a solution of Na (0.14 g, 6 mmol) in dry MeOH (15 mL) propanedinitrile (0.33 g, 5 mmol) and the appropriate imidate **7** (5 mmol) are added. After stirring the reaction mixture at room temperature for 16 h, glacial HOAc (0.4 g, 7 mmol) and water (50 mL) are added. The precipitate is collected by filtration and recrystallized from MeOH to yield the pyrimidine-5-carbonitriles **8a–c** (Table 3).

3,6-Diaryl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles 9; General Procedure:
To a solution of Na (0.28 g, 12 mmol) in dry MeOH (15 mL), methyl cyanoacetate (0.57 g, 5 mmol) and the appropriate imidate **7** (5 mmol) are added. The solution is stirred under reflux for 24 h and allowed to cool to room temperature. The reaction mixture is neutralized with glacial HOAc (0.8 g, 14 mmol) and diluted with water (50 mL). The precipitate is collected by filtration and recrystallized from MeOH to yield the pyrimidine-5-carbonitriles **9b, c** (Table 3).

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