A Simple Method for the Preparation of 2-Amino-4-aryl-3-cyanopyridines by the Condensation of Malononitrile with Aromatic Aldehydes and Alkyl Ketones in the Presence of Ammonium Acetate

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We recently reported that 4-oxo-2-thioxotetrahydropyrimidine derivatives can be obtained from the three-component system ethyl cyanoacetate/aldehydes/thiourea in the presence of potassium carbonate[1]. The present communication deals with the direct synthesis of 2-aminopyridine derivatives (**4**) by the condensation of malononitrile (**3**) with aromatic aldehydes (**1**) and alkyl ketones (**2**) in the presence of ammonium acetate. Although the synthesis of 2-aminopyridine derivatives has been largely investigated[2-10] their synthesis form the above starting compounds has not yet been reported. Our synthesis of 2-aminopyridine derivatives (**4**) is easily performed by heating compounds **1**,

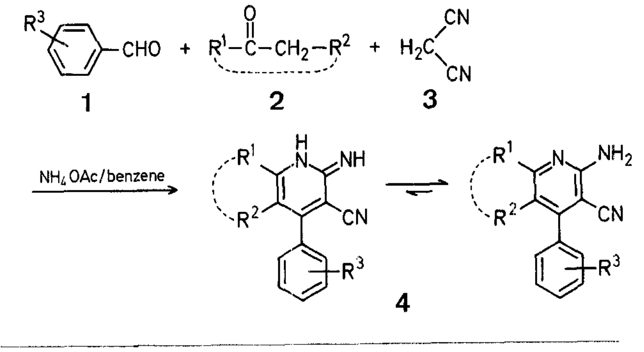

Table 1. Preparation of 2-Amino-4-aryl-3-cyanopyridines (**4**)

4	R^1	R^2	R^3	Yield [%] Method A	Yield [%] Method B	m.p. [°C]	Molecular formula[a] or m.p. reported	
a	CH_3	H	H	60	68	235–236	235–236[10]	
b	i-C_4H_9	H	H	51	55	175–176	$C_{16}H_{17}N_3$	(251.3)
c	C_6H_5	H	H	46	49	186–187	$C_{18}H_{13}N_3$	(271.3)
d	CH_3	H	4-CH_3	59	65	256–257	$C_{14}H_{13}N_3$	(223.3)
e	i-C_4H_9	H	4-CH_3	40	44	176–177	$C_{17}H_{19}N_3$	(265.3)
f	C_6H_5	H	4-CH_3	42	45	177–178	$C_{19}H_{15}N_3$	(285.3)
g	CH_3	H	4-OCH_3	37	44	238–239	$C_{14}H_{13}N_3O$	(239.3)
h	i-C_4H_9	H	4-OCH_3	35	39	171–172	$C_{17}H_{19}N_3O$	(281.3)
i	C_6H_5	H	4-OCH_3	42	46	176–177	$C_{19}H_{15}N_3O$	(301.3)
j	CH_3	CH_3	H	65	68	243–244	$C_{14}H_{13}N_3$	(223.3)
k	CH_3	CH_3	4-CH_3	63	67	259–260	$C_{15}H_{15}N_3$	(237.3)
l	CH_3	CH_3	4-OCH_3	53	57	275–276	$C_{15}H_{15}N_3O$	(253.3)
m	$-(CH_2)_3-$		H	65	69	191–192	$C_{15}H_{13}N_3$	(235.3)
n	$-(CH_2)_4-$		H	66	71	234–235	$C_{16}H_{15}N_3$	(249.3)
o	$-(CH_2)_5-$		H	63	66	225–226	$C_{17}H_{17}N_3$	(263.3)
p	$-(CH_2)_3-$		4-CH_3	61	65	218–219	$C_{16}H_{15}N_3$	(249.3)
q	$-(CH_2)_4-$		4-CH_4	67	74	259–260	$C_{17}H_{17}N_3$	(263.3)
r	$-(CH_2)_5-$		4-CH_3	60	65	232–233	$C_{18}H_{19}N_3$	(277.3)
s	$-(CH_2)_3-$		4-OCH_3	45	48	217–218	$C_{16}H_{15}N_3O$	(265.3)
t	$-(CH_2)_4-$		4-OCH_3	39	46	220–221	$C_{17}H_{17}N_3O$	(279.3)
u	$-(CH_2)_5-$		4-OCH_3	61	68	226–227	$C_{18}H_{19}N_3O$	(293.3)

[a] The microanalyses were in satisfactory agreement with the calculated values:

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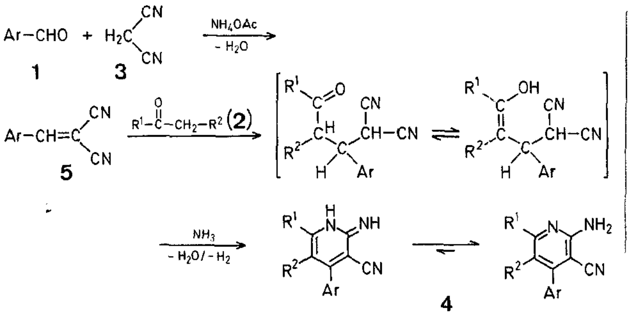
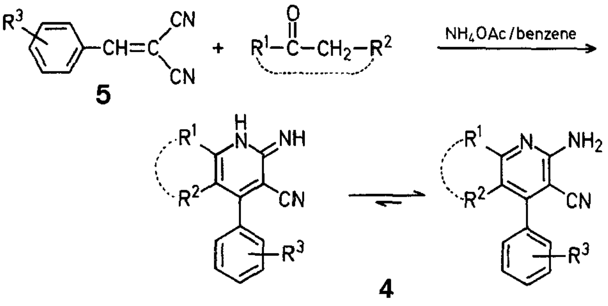
2, and **3** in boiling benzene in the presence of excess ammonium acetate for 4 h (Method A).

The reaction may be assumed to proceed via initial formation of the arylidenemalononitrile **5** which then reacts with the alkyl ketone **2** to give the 2-amino-3-cyanopyridine **4**.



In accord with the above mechanism, compounds **4** may also be obtained from the condensation of arylidenemalononitriles (**5**) with alkyl ketones (**2**) in boiling benzene in the presence of excess ammonium acetate (3 h) (Method B).



The products **4** were identified by microanalytical and spectral data. In the case of product **4a**, the structure was further confirmed by comparison with an authentic sample

Table 2. Spectral Data of Compounds **4**

4	I.R. (nujol)[a] ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6)[b] δ [ppm]
a	3400; 3320; 3160; 2200	2.65 (s, 3H, CH_3); 6.65 (s, 1H, $-CH=$); 6.75–6.90 (br, 2H, NH_2); 7.55 (s, 5H_{arom})
b	3450; 3350; 3200; 2200	1.00–1.20 (d, 6H, 2 CH_3); 1.65–2.30 [m, 1H, $-C\underline{H}(CH_3)_2$]; 2.70–3.00 (d, 2H, $-CH_2-$); 7.06 (s, 1H, $-CH=$); 7.50 (s, 5H_{arom})[c]
c	3450; 3310; 3180; 2220	6.80–7.05 (br, 2H, NH_2); 7.25 (s, 1H, $-CH=$); 7.36–8.30 (m, 10H_{arom})
d	3400; 3310; 3150; 2200	2.50 (s, 3H, CH_3); 2.75 (s, 3H, CH_3); 7.05 (s, 1H, $-CH=$); 7.85–7.90 (q, 4H_{arom})[c]
e	3400; 3300; 3150; 2200	0.85–0.95 (d, 6H, 2 CH_3); 1.65–2.20 [m, 1H, $-C\underline{H}(CH_3)_2$]; 2.35–2.55 (d, 2H, $-CH_2-$); 2.30 (s, 3H, CH_3); 6.55 (s, 1H, $-CH=$); 6.65–6.90 (br, 2H, NH_2); 7.35–7.55 (q, 4H_{arom})
f	3450; 3300; 3160; 2200	2.40 (s, 3H, CH_3); 6.80–7.15 (br, 2H, NH_2); 7.65 (s, 1H, $-CH=$); 7.85–8.80 (m, 9H_{arom})
g	3400; 3300; 3150; 2200	2.32 (s, 3H, CH_3); 3.80 (s, 3H, CH_3); 6.64 (s, 1H, $-CH=$); 6.75–6.90 (br, 2H, NH_2); 7.00–7.70 (q, 4H_{arom})
h	3400; 3300; 3150; 2200	0.85–0.95 (d, 6H, 2 CH_3); 1.40–2.20 [m, 1H, $-C\underline{H}(CH_3)_2$]; 2.46–2.55 (d, 2H, $-CH_2-$); 3.82 (s, 3H, CH_3); 6.25 (s, 1H, $-CH=$); 6.60–6.80 (br, 2H, NH_2); 6.96–7.65 (q, 4H_{arom})
i	3400; 3300; 3150; 2200	3.85 (s, 3H, CH_3); 6.75–6.95 (br, 2H, NH_2); 7.05 (s, 1H, $-CH=$); 7.10–8.25 (m, 9H_{arom})
j	3400; 3300; 3150; 2200	2.15 (s, 3H, CH_3); 2.76 (s, 3H, CH_3); 7.20–7.90 (m, 5H_{arom})[c]
k	3400; 3300; 3150; 2200	1.83 (s, 3H, CH_3); 2.35 (s, 6H, 2 CH_3); 6.30–6.55 (br, 2H, NH_2); 7.05–7.45 (q, 4H_{arom})
l	3400; 3300; 3150; 2200	1.84 (s, 3H, CH_3); 2.33 (s, 3H, CH_3); 3.80 (s, 3H, CH_3); 6.25–6.50 (br, 2H, NH_2); 6.98–7.20 (q, 4H_{arom})
m	3450; 3300; 3150; 2200	1.50–3.00 [m, 6H, $-(CH_2)_3-$]; 6.50–6.90 (br, 2H, NH_2); 7.40–7.70 (m, 5H_{arom})
n	3450; 3300; 3150; 2200	1.55–3.20 [m, 8H, $-(CH_2)_4-$]; 7.20–7.80 (m, 5H_{arom})[c]
o	3400; 3350; 3200; 2200	1.20–3.10 [m, 10H, $-(CH_2)_5-$]; 6.50–6.80 (br, 2H, NH_2); 7.10–7.70 (m, 5H_{arom})
p	3400; 3350; 3200; 2200	1.60–3.10 [m, 9H, $-(CH_2)_3-$, CH_3]; 6.50–6.80 (br, 2H, NH_2); 7.20–7.50 (d, 4H_{arom})
q	3400; 3325; 3200; 2200	1.50–3.30 [m, 11H, $-(CH_2)_4-$, CH_3]; 7.10–7.60 (q, 4H_{arom})[c]
r	3400; 3325; 3195; 2200	1.30–3.40 [m, 13H, $-(CH_2)_5-$, CH_3]; 7.10–7.65 (q, 4H_{arom})[c]
s	3400; 3300; 3150; 2200	1.50–3.15 [m, 6H, $-(CH_2)_3-$]; 3.79 (s, 3H, CH_3); 6.35–6.75 (br, 2H, NH_2); 7.00–7.60 (m, 4H_{arom})
t	3430; 3350; 3250; 2200	1.30–3.20 [m, 8H, $-(CH_2)_4-$]; 3.78 (s, 3H, CH_3); 6.40–6.50 (br, 2H, NH_2); 6.90–7.50 (q, 4H_{arom})
u	3400; 3300; 3170; 2200	1.10–3.00 [m, 10H, $-(CH_2)_5-$]; 3.80 (s, 3H, CH_3); 6.30–6.55 (br, 2H, NH_2); 6.90–7.30 (q, 4H_{arom})

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[a] All I.R. spectra were measured with a Shimadzu I.R.-spectrometer.

[b] All ^{1}H-N.M.R. spectra were measured with a JEOL JNM-MH-60 using TMS as internal standard.

[c] In CF_3COOH.

prepared from methyl styryl ketone and malononitrile in the presence of excess ammonium acetate[10].

Products **4** may exist in two tautomeric forms of which the amino form seems to be favored. In the I.R. spectra, the absorption ~3150–3450 cm^{-1} could be assigned to the NH_2 group of this amino form. In agreement with this observation, the ^1H-N.M.R. spectra show a broad signal in the range $\delta = 6.65-7.10$ ppm corresponding to the NH_2 protons.

2-Amino-4-aryl-3-cyanopyridines (4); General Procedures:

Method A: A mixture of malononitrile (**3**; 0.667 g, 0.01 mol), the aromatic aldehyde (**1**; 0.01 mol), the alkyl ketone (**2**; 0.01 mol), benzene (5 ml), and ammonium acetate (1.16 g, 0.015 mol) is placed in a flask fitted with a reflux condenser and a water separator. The mixture is heated under reflux for 4 h and the solvent is then evaporated using a rotary evaporator. The residue is poured into ethanol (5 ml) and this mixture is allowed to stand for several hours. The resultant precipitate is isolated by suction, washed with water and ethanol, and recrystallized from tetrahydrofuran.

Method B: A mixture of the arylidenemalononitrile (**5**; 0.01 mol), the alkyl ketone (**2**; 0.01 mol), benzene (5 ml), and ammonium acetate (1.16 g, 0.015 mol) is heated under reflux for 3 h. Work-up is as described under Method A.

2-Amino-3-cyano-6-methyl-4-phenylpyridine (4a) from Methyl Styryl Ketone and Malononitrile:

A mixture of malononitrile (**3**; 0.667 g, 0.01 mol), methyl styryl ketone (1.462 g, 0.01 mol), ammonium acetate (1.55 g, ~0.02 mol), and ethanol (5 ml) is refluxed for 4 h and then allowed to cool. The precipitated product is isolated by suction and recrystallized from tetrahydrofuran; yield: 0.5 g (24%); m.p. 235–236 °C (Ref. [10], m.p. 235–236 °C).

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