Synthetic Studies Using α,β-Unsaturated Nitriles: Facile Synthesis of Pyridine Derivatives

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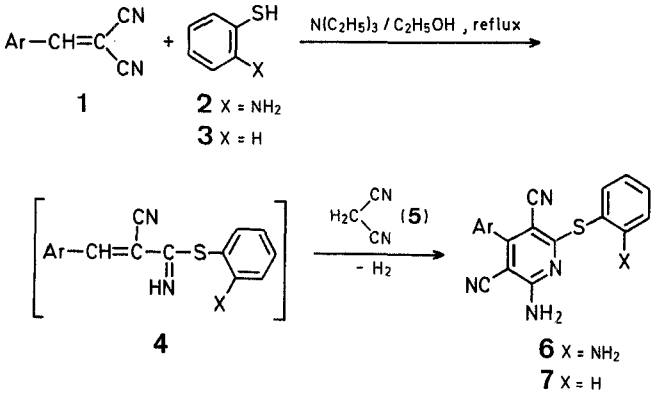
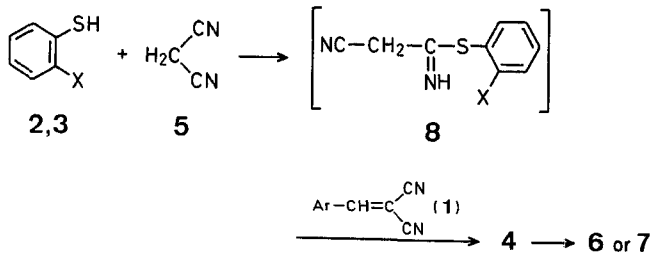
We have previously shown that benzylidenecyanoacetic esters and benzylidenemalononitriles **1** are useful intermediates for the synthesis of heterocyclic compounds[1-6]. In an extension of our studies on pesticidal heterocyclic compounds, the present paper describes a convenient and simple method for the preparation of pyridine derivatives by the condensation of **1** with some thiols.

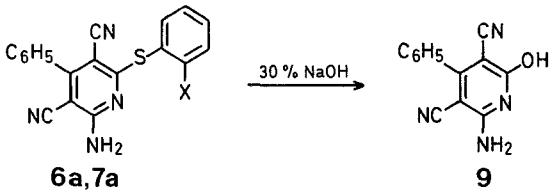
The reaction of **1** with 2-aminobenzenethiol (**2**; X = NH_2) was carried out in ethanol containing triethylamine at reflux temperature giving 2-amino-6-(2-aminophenylthio)-4-aryl-3,5-dicyanopyridine (**6**; X = NH_2) (Method A). The structural elucidation of the product **6** was based on microanalysis and spectral studies. Compound **6** was also prepared from **1, 2** and malononitrile **(5)** in higher yield under the similar conditions (Method B). In contrast with the above Method B, when benzenethiol (**3**; X = H) was used instead of **2**, the reaction of **1** with **3** and **5** led to formation of 2-amino-4-aryl-3,5-dicyano-6-phenylthiopyridine **(7)**. On treatment with 30% aqueous sodium hydroxide, **6a** or **7a** (Ar = C_6H_5) are converted into 2-amino-3,5-dicyano-6-hydroxy-4-phenylpyridine **(9)** which showed an OH group absorption in the I.R. spectrum. This is suggestive of the easy conversion of a sulphide into hydroxy and mercapto derivatives[7].

Route A:



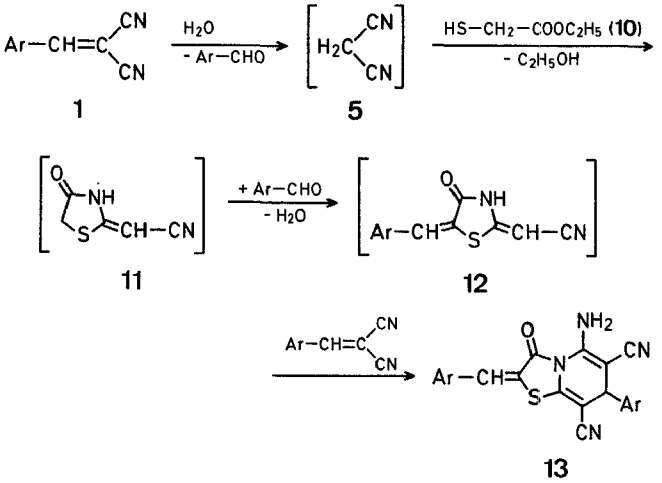
Route B:





Although an investigation of the reaction mechanism was not undertaken, the reaction parthway is considered to proceed via route A or B. Since the compounds **4** or **8** were considered to be intermediates, the reaction was examined at lower temperature in order to obtain **4** or **8**; however, these intermediates could not be isolated.

In an extension of above the reaction, the reaction of **1** with ethyl mercaptoacetate **(10)** was carried out in ethanol containing triethylamine, direct synthesis of 2-amino-4-aryl-3,5-dicyano-6-ethoxycarbonylthiomethylpyridine being expected. However, an unexpected yellow, crystalline product was obtained upon the treatment of **1a** (Ar = C_6H_5) with **10** in ethanol containing triethylamine (Method A). Microanalytical and spectroscopic data confirmed it to be 5-amino-2-benzylidene-6,8-dicyano-3-oxo-7-phenyl-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridine **(13a)**. Reaction of other benzylidenemalononitriles **1** with **10** also gave similar 7*H*-thiazolo[3,2-*a*]pyridine derivatives. On the other hand, when a mixture of **1** and 2-cyanomethylene-4-oxotetrahydrothiazole **(11)**[8], prepared from **5** and **10** in ethanol/acetic acid containing piperidine, was refluxed, the same product **13a** was obtained in 80% yield (Method B). Furthermore, **13a** was also prepared by the condensation of **1** with **10** and benzaldehyde in very high yield (91%) (Method C). The reaction pathway is considered to proceed as shown below.



2-Amino-6-(2-aminophenylthio)-4-aryl-3,5-dicyanopyridines 6; General Procedures:

Method A: A mixture of benzylidenemalononitrile **1** (0.01 mol) and 2-aminobenzenethiol (**2**; 0.63 g, 0.005 mol) in ethanol (10 ml) containing triethylamine (about three drops) is heated under reflux with stirring for 2 h. The colorless crystals which deposit during the reaction are isolated by vacuum filtration, washed with ethanol and water, and air-dried at room temperature. Recrystallization from tetrahydrofuran/ethanol gives the pure product **6**.

Method B: A mixture of benzylidenemalononitrile **1** (0.005 mol), 2-aminobenzenethiol (**2**; 0.63 g, 0.005 mol) and malononitrile (**5**; 0.33 g, 0.005 mol) in ethanol (10 ml) containing triethylamine (about three drops) is heated under reflux with stirring for 2 h. Work-up is as described under Method A.

2-Amino-4-aryl-3,5-dicyano-6-phenylthiopyridines 7; General Procedures:

A mixture of benzylidenemalononitrile **1** (0.005 mol), thiophenol (**4**; 0.55 g, 0.005 mol), and malononitrile (**5**; 0.33 g, 0.005 mol) in ethanol

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Table 1. Preparation and Spectral Data of Compounds **6** (X = NH_2) and **7** (X = H)

Product No.	Ar	Yield [%] by Method A	B	m.p. [°C]	Molecular formula[a]	I.R. (nujol)[b] ν [cm^{-1}]	^{1}H-N.M.R. (DMSO-d_6)[c] δ [ppm]
6a	C_6H_5	19	43	201–202°	$C_{19}H_{13}N_5S$ (343.3)	3390, 3320, 3210, 2200	5.2–5.6 (br, 4H, NH_2); 6.4–7.7 (m, 9 H_{arom})
6b	4-H_3C—C_6H_4	18	41	207–208°	$C_{20}H_{15}N_5S$ (357.5)	3400, 3340, 3225, 2220	2.42 (s, 3H, CH_3); 5.2–5.5 (br, 4H, NH_2); 6.4–7.7 (m, 8 H_{arom})
6c	4-H_3CO—C_6H_4	27	49	235–236°	$C_{20}H_{15}N_5OS$ (373.4)	3450, 3350, 3230, 2225	3.35 (s, 3H, CH_3); 5.1–5.3 (br, 4H, NH_2); 6.4–7.8 (m, 8 H_{arom})
6d	4-Cl—C_6H_4	17	40	223–224°	$C_{19}H_{12}ClN_5S$ (377.5)	3500, 3360, 3230, 2220	5.2–5.5 (br, 4H, NH_2); 6.5–7.8 (m, 8 H_{arom})
7a	C_6H_5		27	223–224°	$C_{19}H_{12}N_4S$ (328.3)	3490, 3360, 3210, 2230	7.4–7.6 (m, 10 H_{arom}); 7.7–7.9 (br, 2H, NH_2)
7b	4-H_3C—C_6H_4		41	215–216°	$C_{20}H_{14}N_4S$ (342.3)	3475, 3330, 3200, 2210	2.40 (s, 3H, CH_3); 7.3–7.6 (m, 9 H_{arom}); 7.7–7.9 (br, 2H, NH_2)
7c	4-H_3CO—C_6H_4		40	254–255°	$C_{20}H_{14}N_4OS$ (358.3)	3450, 3350, 3230, 2220	3.30 (s, 3H, CH_3); 6.9–7.6 (m, 9 H_{arom}); 7.7–7.9 (br, 2H, NH_2)
7d	4-Cl—C_6H_4		36	236–237°	$C_{19}H_{11}ClN_4S$ (362.5)	3490, 3360, 3210, 2230	6.3–6.7 (m, 9 H_{arom}); 6.8–7.0 (br, 2H, NH_2)

[a] All products gave satisfactory microanalysis (C ±0.21, H ±0.08, N ±0.21, S ±0.17).
[b] All I.R. spectra were measured with a Hitachi I.R. 260-30 spectrometer.
[c] All ^{1}H-N.M.R. spectra were measured with a JEOL JNM-MH-60 using TMS as internal standard.

Table 2. Preparation and Spectral Data of Compounds **13**

Product No.	Ar	Yield [%] by Method A	B	C	m.p. [°C]	Molecular formula[a]	I.R. (nujol)[b] ν [cm^{-1}]	^{1}H-N.M.R. (CF_3COOH)[c] δ [ppm]
13a	C_6H_5	63	80	91	244–245°	$C_{22}H_{14}N_4OS$ (382.3)	3380, 3250, 2180, 1720, 1658	4.52 (s, 1H, H-7); 7.42 (s, 5 H_{arom}); 7.58 (s, 5 H_{arom}); 7.99 (s, 1H, =CH—)
13b	4-H_3C—C_6H_4	62	80	84	239–240°	$C_{24}H_{18}N_4OS$ (410.4)	3375, 3270, 2190, 2170, 1720, 1658	2.38 (s, 3H, CH_3); 2.46 (s, 3H, CH_3); 4.49 (s, 1H, H-7); 7.24 (d, 4 H_{arom}); 7.48 (d, 4 H_{arom}); 7.97 (s, 1H, =CH—)
13c	4-H_3CO—C_6H_4	69	80	86	237–238°	$C_{24}H_{18}N_4O_3S$ (442.4)	3350, 3260, 2170, 1705, 1657	4.03 (s, 6H, OCH_3); 4.53 (s, 1H, H-7); 7.14 (d, 2 H_{arom}); 7.15 (d, 2 H_{arom}); 7.48 (d, 2 H_{arom}); 7.64 (d, 2 H_{arom}); 7.94 (s, 1H, =CH—)
13d	4-Cl—C_6H_4	70	75	84	254–255°	$C_{22}H_{12}Cl_2N_4OS$ (451.1)	3380, 3275, 2180, 1728, 1658	4.61 (s, 1H, H-7); 7.3–7.6 (m, 8 H_{arom}); 8.02 (s, 1H, =CH—)

[a] All products gave satisfactory microanalysis (C ±0.17%, H ±0.14%, N ±0.16%, S ±0.10%).
[b] All I.R. spectra were measured with a Hitachi I.R. 260-30 spectrometer.
[c] All ^{1}H-N.M.R. spectra were measured with a JEOL JNM-MH-60 using TMS as internal standard.

(10 ml) containing triethylamine (about three drops) is heated under reflux with stirring for 2 h. Treatment of the solid product which deposits during the reaction is essentially the same as that described above for Method B.

5-Amino-7-aryl-2-benzylidene-6,8-dicyano-3-oxo-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyridines 13; General Procedure:

Method A: To a solution of benzylidenemalononitrile **1** (0.01 mol) and ethyl mercaptoacetate (**10**; 0.55 g, 0.005 mol) in ethanol (10 ml), triethylamine (0.50 g, 0.005 mol) is added drop by drop, then the solution is heated under reflux with stirring for 20 min. A yellow crystalline matter precipitates out during the reaction. After cooling, the resultant crystals are isolated by vacuum filtration, washed with water and ethanol, and recrystallized from dioxan to give the pure product **13**.

Method B: A mixture of benzylidenemalononitrile **1** (0.01 mol) and 2-cyanomethylene-4-oxotetrahydrothiazole[8] (**11**; 0.63 g, 0.005 mol) in ethanol (10 ml) containing triethylamine (0.50 g, 0.005 mol) is heated under reflux with stirring for 15 min. Work-up is as described above for Method A.

Method C: A mixture of 2-cyanomethylene-4-oxotetrahydrothiazole[8] (**11**; 0.63 g, 0.005 mol) and benzaldehyde (0.005 mol) is stirred at room temperature for 10 min, then benzylidenemalononitrile **1** (0.005 mol) is added to the reaction mixture. The mixture is heated under reflux with stirring for 10 min. Work-up is as described above for Method A.

Hydrolysis of 6a or 7a to 9:

To ethanol (5 ml) containing 30% aqueous sodium hydroxide (3 ml) is added **6a** (0.34 g, 0.001 mol) or **7a** (0.33 g, 0.001 mol). The mixture is heated under reflux with stirring for 0.5 h and then cooled to room temperature. The resultant solid product is isolated by vacuum filtration and washed with ethanol. Warm water is added to the solid, which is stirred until complete dissolution. The solution is acidified with 3 molar hydrochloric acid and stirred at room temperature for 1 h. The colorless crystals which deposit during the neutralization are isolated by vacuum filtration, washed with water and ethanol. Recrystallization from tetrahydrofuran gives 2-amino-3,5-dicyano-6-hydroxy-4-phenylpyridine (**9**); yield: 0.15 g (55%) from **6a**; 0.10 g (37%) from **7a**; m.p. 315–320°C (dec.).

$C_{13}H_8N_4O$	calc.	C 66.09	H 3.41	N 23.72
(236.2)	found	65.98	3.32	23.40

I.R. (nujol): ν = 3550; 3450; 3300 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 7.2–7.6 (m, 5 H_{arom}); 7.7–7.8 (br, 2H, NH_2); 11.7–12.4 ppm (br, 1H, OH).

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