Activated Nitriles in Heterocyclic Synthesis: A New Procedure for the Synthesis of Pyrimidine Derivatives

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A novel synthesis of pyrimidine derivatives *via* reaction of enamino-nitriles and -esters with trichloroacetonitrile is reported and the synthetic potential of the method is demonstrated.

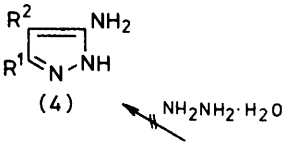
THE biological importance of pyrimidine derivatives has resulted in much interest in their synthesis and chemistry.[1,2] As a part of a programme aimed at exploring the scope and limitation of the enamino-nitriles and -esters in heterocyclic synthesis,[3-5] we have examined the reaction of nitriles with the readily accessible enamino-nitriles and -esters (1a—d) to give polyfunctional pyrimidines.

Taylor and Borror [6] have reported that enamino-nitriles react with nitriles in the presence of a catalyst at high temperatures (190—200 °C) and under pressure to give pyrimidine derivatives in 39—63% yield. Attempts to extend this procedure to effect condensation of (1a—d) with nitriles failed, considerable decomposition and side-reactions taking place; with mild conditions (1a—d) were recovered unchanged. Since Taylor and Borror [6] had reported that the reactivity of the nitrile rather than the basicity of the amino-function is the controlling factor in these condensations, it seemed possible to us that trichloroacetonitrile with its highly activated cyano-group might react with (1a—d) to give pyrimidines under mild conditions. In fact (1a,b) reacted with trichloroacetonitrile in ethanol in the presence of piperidine to yield 1 : 1 adducts, two possible isomeric structures, (2) and (3), for which were considered. Although spectral results were of little help in distinguishing between these structures, the latter was established as being correct on the basis of its chemical behaviour. Thus, with hydrazine hydrate (3a,b) afforded the hydrazinopyrimidines (5a,b); compound (2) would have been expected to form the pyrazole derivatives (4).[2]

The trichloromethyl group in (3a) readily underwent nucleophilic attack to give a variety of substituted derivatives; *e.g.* with sodium hydroxide (3%), it afforded the hydroxypyrimidine (5c) and with ethanolic sodium ethoxide it gave (5d).

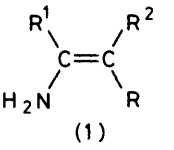
Although, in contrast to (1a,b) the enamino-esters (1c,d) were recovered unchanged when treated with trichloroacetonitrile under the above experimental conditions, the sodium salts of the two compounds when treated with trichloroacetonitrile in ether–benzene gave the pyrimidines (3c,d) in good yield; the latter reacted with hydrazine hydrate to yield the corresponding hydrazinopyrimidines (5e,f).

With its latent functional substituent (3a) was found to be useful for the synthesis of fused pyrimidines.



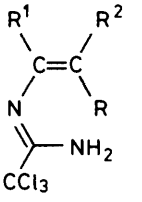
(4)

$NH_2NH_2 \cdot H_2O$



(1)

CCl_3CN



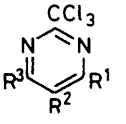
(2)

a; $R^1 = CH_2CN$, $R^2 = R = CN$

b; $R^1 = CCl_3$, $R^2 = R = CN$

c; $R^1 = CH_2CO_2Et$, $R^2 = CN$, $R = CO_2Et$

d; $R^1 = CCl_3$, $R^2 = R = CO_2Et$



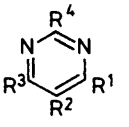
(3)

a; $R^1 = CH_2CN$, $R^2 = CN$, $R^3 = NH_2$

b; $R^1 = CCl_3$, $R^2 = CN$, $R^3 = NH_2$

c; $R^1 = CH_2CO_2Et$, $R_2 = CN$, $R^3 = OH$

d; $R^1 = CCl_3$, $R_2 = CO_2Et$, $R^3 = OH$



(5)

a; $R^1 = CH_2CN$, $R^2 = CN$, $R^3 = NH_2$, $R^4 = NHNH_2$

b; $R^1 = NHNH_2$, $R^2 = CN$, $R^3 = NH_2$, $R^4 = NHNH_2$

c; $R^1 = CH_2CO_2H$, $R^2 = CN$, $R^3 = NH_2$, $R^4 = OH$

d; $R^1 = CH_2CONH_2$, $R^2 = CN$, $R^3 = NH$, $R^4 = OEt$

e; $R^1 = CH_2CONHNH_2$, $R^2 = CN$, $R^3 = OH$, $R^4 = NHNH_2$

f; $R^1 = NHNH_2$, $R^2 = CONHNH_2$, $R^3 = OH$, $R^4 = NHNH_2$

TABLE 1

Compounds (3a—d), (5a—f), and (6)—(10)

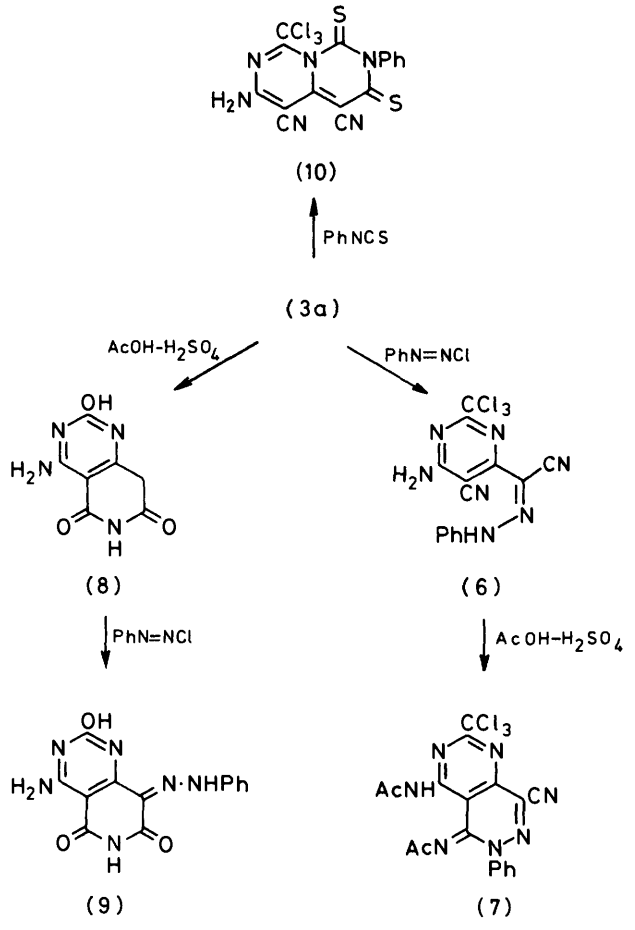
Compound (Colour)	Cryst. solvent	M.p. (°C)	Yield (%)	Mol. formulae (Mol. wt)	Analysis (%) Found (Required) C	H	N	Cl
(3a) (Colourless)	$CHCl_3$	240—242	80	$C_8H_4Cl_2N_5$ (276.53)	35.0 (34.7)	1.6 (1.4)	25.5 (25.3)	38.8 (38.5)
(3b) (Colourless)	EtOH	210	75	$C_7H_2Cl_6N_4$ (355.2)	23.7 (23.6)	0.7 (0.6)	15.8 (15.8)	60.2 (60.0)
(3c) (Colourless)	DMF	222—224	75	$C_{10}H_8Cl_2N_2O_3$ (324.57)	37.0 (37.0)	2.8 (2.5)	13.1 (12.9)	33.1 (32.8)
(3d) (Colourless)	EtOH–H_2O	150—152	65	$C_9H_6Cl_6N_2O_2$ (402.97)	26.5 (26.8)	1.7 (1.5)	6.9 (6.9)	52.6 (52.9)
(5a) (Yellow)	DMF	>300	85	$C_7H_7N_7$ (189.19)	44.7 (44.4)	3.9 (3.7)	52.2 (51.8)	
(5b) (Yellow)	DMF	>300	91	$C_5H_8N_8$ (180.18)	33.0 (33.3)	4.2 (4.4)	62.0 (62.2)	
(5c) (Buff)	DMF–H_2O	>300	55	$C_7H_6N_4O_3$ (194.15)	43.3 (43.3)	3.2 (3.1)	28.5 (28.9)	
(5d) (Colourless)	EtOH	>300	60	$C_9H_{11}N_5O_2$ (221.22)	48.9 (48.9)	4.9 (5.0)	31.5 (31.7)	
(5e) (Brown)	Pr^{i}OH	>300	90	$C_7H_9N_7O_2$ (223.2)	37.4 (37.6)	4.0 (4.0)	43.6 (43.9)	
(5f) (Yellow)	Pr^{i}OH	>300	85	$C_8H_{10}N_8O_2$ (214.1)	28.0 (28.0)	4.4 (4.7)	52.2 (52.3)	
(6) (Yellow)	DMF	208	85	$C_{14}H_8N_7Cl_3$ (380.50)	44.3 (44.2)	2.4 (2.1)	25.5 (25.8)	27.6 (27.9)
(7) (Yellow)	EtOH	>300	65	$C_{16}H_{12}Cl_2N_7O_2$ (464.50)	46.8 (46.5)	2.5 (2.6)	21.4 (21.1)	23.1 (22.9)
(8) (Yellow)	Pr^{i}OH	>300	95	$C_7H_6N_4O_3$ (194.15)	43.0 (43.3)	3.2 (3.1)	28.7 (28.9)	
(9) (Brown)	EtOH–DMF	>300	70	$C_{13}H_{10}N_6O_3$ (298.26)	52.4 (52.4)	3.5 (3.4)	28.0 (28.2)	
(10) (Colourless)	Dioxan	192—194	75	$C_{16}H_7Cl_3N_6S_2$ (453.5)	42.3 (42.3)	1.7 (1.5)	18.3 (18.5)	23.2 (23.5)

TABLE 2

I.r. and ^{1}H n.m.r. data for compounds listed in Table 1

Compound	$\nu_{max.}$/cm^{-1} (selected bands)	^{1}H N.m.r. (δ)
(3a)	3 500, 3 360, and 3 250 (NH_2); 2 220 (CN); 1 640 (C=N)	2.5 (s, 2 H, CH_2) and 7.5 (s, br, 2 H, NH_2)
(3b)	3 390, 3 370, and 3 220 (NH_2); 2 220 (CN); 1 640 (C=N)	
(3c)	3 500, 3 360, and 3 250 (NH); 2 220 (CN); 1 740 (ester CO); 1 670 (ring CO) and 1 620 (C=N)	1.3 (t, 3 H, CH_3), 2.5 (s, 2 H, CH_2), 4.33 (q, 2 H, CH_2), and 7.05 (s, br, 1 H, OH)
(3d)	3 220 and 3 160 (NH); 1 755 (ester CO); 1 690 (ring CO); and 1 620 (C=N)	1.3 (t, 3 H, CH_3), 4.35 (q, 2 H, CH_2), and 7.3 (s, br, 1 H, OH)
(5a)	3 500, 3 360, and 3 250 (NH,NH_2); 2 220 (CN); 1 650—1 580 (δ NH_2 and C=N)	Insoluble in commonly used n.m.r. solvents
(5b)	3 420, 3 400, and 3 200 (NH,NH_2); 2 200 (CN); 1 670—1 580 (δ NH_2 and C=N)	Insoluble in commonly used n.m.r. solvents
(5c)	3 400, 3 360 (NH_2); 2 220 (CN); 1 670 (acid CO) and 1 630 (C=N)	Insoluble in commonly used n.m.r. solvents
(5d)	3 360, 3 200 (NH_2); 2 220 (CN); 1 670 (amide CO); and 1 630 (C=N)	1.3 (t, 3 H, CH_3), 2.5 (s, 2 H, CH_2), 4.3 (q, 2 H, CH_2), and 6.9—9.0 (m, 4 H, $2NH_2$)
(5e)	3 500—3 000 (NH and NH_2); 2 220 (CN); 1 670 (CO amide) 1 650—1 600 (δ NH_2 and C=N)	Insoluble in commonly used n.m.r. solvents
(5f)	3 400—3 000 (NH and NH_2); 1 670 (CO) 1 650—1 600 (δ NH_2 and C=N)	Insoluble in commonly used n.m.r. solvents
(6)	3 360, 3 200, 3 100 (NH and NH_2); 2 225 (CN); and 1 630 (C=N)	7.3 (s, 1 H, NH), 7.5—7.7 (m, 5 H, C_6H_5) and 9.2—10.5 (s, br, 2 H, NH_2)
(7)	3 400—3 200 (NH); 2 220 (CN); 1 690 (acetyl CO); and 1 620 (C=N)	Insoluble in commonly used n.m.r. solvents
(8)	3 400—3 000 (NH and NH_2); 1 730 (CO); and 1630 (C=N)	Insoluble in commonly used n.m.r. solvents
(9)	3 500, 3 200, and 3 000 (NH,NH_2); 1 720, 1 710 (CO); and 1 630 (C=N)	3—4 (br, 4 H, NH, NH_2, OH), 7—7.6 (m, 5 H, C_6H_5), and 12.3 (1 H, NHPh)
(10)	3 490, 3 370, and 3 220 (NH_2); 2 220 (CN); and 1 660 (C=N)	

Thus, it coupled with benzenediazonium chloride to yield the arylhydrazone derivative (6) which cyclised to the pyrimido-pyridazine (7) (See Scheme). It could also be converted into the pyrido-pyrimidine (8), the latter coupling with benzenediazonium chloride to yield the hydrazone derivative (9) (See Scheme). Finally, compound (3a) reacted with phenyl isothiocyanate to give a



good yield of the pyrimido[1,6-*c*]pyrimidine (10). The formation of the latter is assumed to proceed *via* addition of two molecules of phenyl isothiocyanate to (3a) followed by aniline elimination. Similar reactions have been previously reported for 2-cyanomethylthiazole.[7]

EXPERIMENTAL

All melting points are uncorrected. I.r. spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H N.m.r. spectra were obtained in $(CD_3)_2SO$ with a Varian A-60 spectrometer with $SiMe_4$ as internal standard and chemical shifts are expressed as δ values. Microanalytical data were performed by Microanalytical Data Unit at Cairo University.

Compounds (1a—d) were prepared following literature procedures.[8-10]

5-Substituted 4-Amino-5-cyano-2-trichloromethylpyrimidines (3a,b).—A solution of (1a,b) (0.1 mol) in ethanol (100 ml) was treated with trichloroacetonitrile (0.1 mol, 14.35 g) and piperidine (1 ml). The reaction mixture was refluxed for 5 h and then evaporated under reduced pressure. The residue was triturated with ethanol and the resulting product was crystallised.

5,6-Disubstituted 4-Hydroxy-2-trichloromethylpyrimidines (3c,d).—To a suspension of the sodium salt of (1a,c) (0.01 mol) in ether–benzene (20 : 10 ml), trichloroacetonitrile (0.01 mol, 1.4 ml) was added. The reaction mixture was refluxed for 5 h and then evaporated under reduced pressure. The residue was triturated with water, neutralised by addition of concentrated hydrochloric acid, and the resulting product filtered off and crystallised.

4,5,6-Trisubstituted 2-Hydrazinopyrimidines (5a,b,e,f).—A mixture of (3a—d) (0.01 mol) and hydrazine hydrate (0.01 mol, 0.5 ml) was heated at 100 °C (bath temp.) for 5 h. The reaction mixture was triturated with ethanol and the resulting product was filtered off and crystallised.

6-Substituted 4-Amino-5-cyano-2-hydroxypyrimidine (5c).—A solution of 3% sodium hydroxide (100 ml) was treated with (3a) (0.01 mol) and the reaction mixture was refluxed for 2 h; it was then left to cool and acidified with concentrated hydrochloric acid. The product was filtered off and crystallised.

4-Amino-6-carboxamidomethyl-5-cyano-2-ethoxypyrimidine (5d).—A solution of sodium ethoxide [prepared from sodium (0.23 g) and ethanol (50 ml)] was treated with (3a) (0.01 mol) and the reaction mixture was refluxed for 5 h. It was then left to cool, neutralised with concentrated hydrochloric acid, and poured onto water. The product was filtered off and crystallised.

4-Amino-5-cyano-6-[phenylhydrazono(cyano)methyl]-2-trichloromethylpyrimidine (6).—A benzenediazonium chloride solution [prepared from aniline (0.01 mol) and the appropriate quantity of hydrochloric acid and sodium nitrite] was added to a solution of (3a) (0.01 mol, 2.8 g) in DMF (50 ml). The product was filtered off and crystallised.

4-Acetoamido-5-acetylimino-8-cyano-5,6-dihydro-6-phenyl-2-trichloromethylpyrimido[4,5-d]pyridazine (7).—A solution of compound (6) (3.8 g, 0.01 mol) in acetic acid (50 ml) containing sulphuric acid (0.5 ml) was refluxed for 2 h. The reaction mixture was then evaporated under reduced pressure and the remaining product was poured over water and neutralised with ammonium hydroxide. The solid product, so formed, was filtered off and crystallised.

4-Amino-2-hydroxypyrido[4,3-d]pyrimidine-5,7(6H,8H)-dione (8).—A solution of compound (3a) (2.8 g, 0.01 mol) in acetic acid (50 ml) was treated with concentrated sulphuric acid (5 ml). The reaction mixture was refluxed for 2 h after which the product was filtered off and crystallised.

4-Amino-2-hydroxy-8-phenylhydrazonopyrido[4,3-d]-pyrimidine-5,7(6H,8H)-dione.—A solution of benzenediazonium chloride [prepared from aniline (0.92 ml) and appropriate quantities of hydrochloric acid and sodium nitrite] was added to a solution of compound (8) (1.94 g) in pyridine (50 ml). The product was filtered off and crystallised.

6-Amino-4,5-dicyano-2-phenyl-8-trichloromethylpyrimido-[1,6-c]pyrimidine-1,3(2H)-dithione (10).—A solution of compound (3a) (2.8 g) in dioxan (50 ml) was treated with phenyl isothiocyanate (2.8 ml) and the reaction mixture was refluxed for 3 h; it was then left to cool. The product was filtered off and crystallised.

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