Reaction of Nitriles under Acidic Conditions. Part I. A General Method of Synthesis of Condensed Pyrimidines

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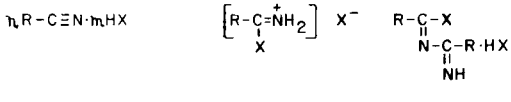
Received April 17, 1980

Nitriles are known to give rise to salts of different compositions with halogen acids. Many of the reactions undergone by nitriles under the influence of halogen acids are, in many cases, assumed to proceed *via* the intermediate formation of highly reactive imidoyl derivatives. The intermediates produced, *in situ*, by the reaction of nitriles with hydrogen chloride should, in principle, be capable of reacting with compounds containing appropriately placed nucleophilic and electrophilic centers leading to the formation of a heterocycle incorporating the C=N of the nitrile. Thus, the reaction of aliphatic, aromatic and heterocyclic nitriles with a variety of *ortho* aminocarbonyl derivatives such as nitriles, amides, esters and ketones of benzene, thiophen, furan, pyrrole, benzothiophene and pyridothiophene have been found to yield the corresponding condensed pyrimidines in fair to good yields. This constitutes a facile and versatile one-pot synthesis of condensed pyrimidines.

J. Heterocyclic Chem., **17**, 1497 (1980).

Nitriles, when reacted with halogen acids are known to give rise to salts of different compositions **1-3** (2-7). Highly reactive imidoyl halides or nitrilium halides have been suggested as the initial intermediate in a variety of reactions undergone by nitriles in the presence of halogen acids (8-10).

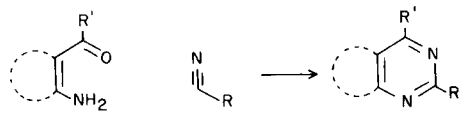


1 **2** **3**

Herein, we report a facile one-pot synthesis of condensed pyrimidines by reaction of *ortho* aminocarbonyl compounds such as esters, amides, nitriles and ketones with nitriles in the presence of hydrogen chloride. The reaction consists of reacting the two components in the presence of dry hydrogen chloride gas with or without a solvent followed by the usual work up to isolate the pyrimidine formed in the reaction.

A variety of aliphatic, aromatic and heterocyclic nitriles **4** have been reacted with *ortho* aminocarbonyl derivatives of benzene, thiophene, furan, pyrrole, benzothiophene and pyridothiophene. The choice of carbonyl variants such as ketone **5**, ester **6**, amide **7** or a nitrile **8** leads to the formation of the corresponding 4-substituted condensed pyrimidines **9**, **10** and **11** (Scheme I).

SCHEME I



5 **4** **9**

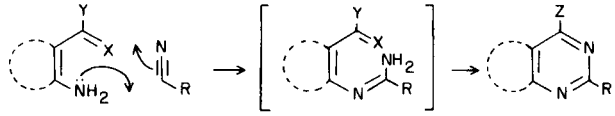
6, Y=OC_2H_5
7, Y=NHR

10

8 **11**

This pyrimidine cyclization of *ortho* aminocarbonyl compounds **12** with nitriles under acidic conditions, presumably, proceeds *via* the amidine intermediate **13**, which undergoes intramolecular cyclization by nucleophilic attack on the carbonyl function to yield the pyrimidine **14** (11) (Scheme II). The protonation of the carbonyl compound also seems to facilitate the cyclization.

SCHEME II



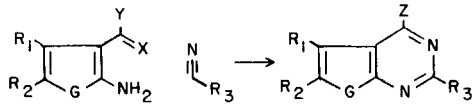
12 **13** **14**

In the cyclization of *ortho* aminoamide **15** to pyrimidine (Scheme III), the cyclization of the intermediate amidine **16** takes place by the elimination of the amine from the carbamoyl function (path a) and not by the loss of ammonia from the amidine function (path b) as is indicated by the formation of 3-*N*-unsubstituted pyrimidine **27** and not the 3-*N*-substituted pyrimidine **17**.

0022-152X/80/071497-04$02.25

Table I

Thieno[2,3-*d*]pyrimidines, Furano[2,3-*d*]pyrimidine and Pyrrolo[2,3-*d*]pyrimidine

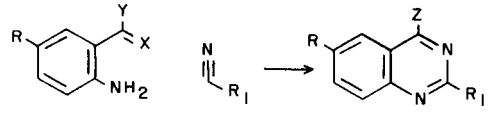


Compound No.	R_1	R_2	R_3	G	Y C=X	Z	M.p. °C	% Yield	Recrystallization Solvent (a)	Molecular Formula	Molecular Weight	M⁺	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
20	CH_3	$CO_2C_2H_5$	CH_3	S	$CO_2C_2H_5$	OH	294-296 (b)	80	D	$C_{11}H_{12}N_2O_3S$	252	252	52.38	52.45	4.80	5.03
21		H	$CH_2CO_2C_2H_5$	S	$CO_2C_2H_5$	OH	183-185	88	E	$C_{17}H_{16}N_2O_4S$	344	344	59.30	59.20	4.68	4.99
22		H		S	$CO_2C_2H_5$	OH	237-241	75	E-C	$C_{20}H_{16}N_2O_2S$	348	348	68.96	68.94	4.63	4.93
23	$-(CH_2)_4-$		CH_2CH_2Cl	S	$CO_2C_2H_5$	OH	>360	50	E-C	$C_{12}H_{13}ClN_2OS$	268.5	268	53.63	53.13	4.84	5.00
24	$-(CH_2)_4-$			S	$CO_2C_2H_5$	OH	315-317	50	E-C	$C_{18}H_{16}N_2OS$	308	308	70.13	70.22	5.23	5.61
25	$-(CH_2)_4-$			S	$CO_2C_2H_5$	OH	315-316	65	D	$C_{16}H_{13}ClN_2OS$	316.5	316	60.67	60.98	4.14	4.50
26	$-(CH_2)_4-$			S	$CONH_2$	OH	300-302 (c)	71	D	$C_{16}H_{14}N_2OS$	282	282	68.10	68.01	4.97	5.31
27	$-(CH_2)_4-$		CH_3	S	$CONHCH_3$	OH	300-302 (d)	80	D	$C_{11}H_{12}N_2OS$	220	220	59.99	60.15	5.49	5.56
28	H	C_2H_5		S	$CO_2C_2H_5$	OH	228-230	70	D-E	$C_{13}H_{11}N_3OS$	257	257	60.70	60.40	4.28	4.57
29	$-(CH_2)_4-$		CH_3	S	C≡N	NH_2	224-225	50	B	$C_{11}H_{13}N_3S$	219	219	60.29	60.30	5.93	6.25
30	$-(CH_2)_4-$			S	C≡N	NH_2	195-197	47	B	$C_{16}H_{15}N_3S$	281		68.32	67.96	5.33	5.49
31	$-(CH_2)_4-$		CH_3	S	COC_6H_5	C_6H_5	118-120	53	E	$C_{17}H_{16}N_2S$	280	280	72.85	73.02	5.71	6.07
32	$-(CH_2)_4-$		CH_2-$CO_2C_2H_5$	S	COC_6H_5	C_6H_5	82-84	57	E	$C_{20}H_{20}N_2O_2S$	352	352	68.19	68.08	5.68	5.81
33			CH_3	O	C≡N	NH_2	253-255	68	B	$C_{19}H_{15}N_3O$	301	301	75.74	75.80	4.98	5.01
34			CH_3		C≡N	NH_2	287-289	60	D	$C_{25}H_{20}N_4$	376		79.79	79.56	5.32	5.53

(a) D = Dimethylformamide, E = Ethanol, C = Chloroform, B = Benzene. (b) Lit. (14) m.p. 257°. (c) Lit. (14) m.p. 287°, Lit. (15) m.p. 301°. (d) Lit. (14) m.p. 270-271°. Lit (15) m.p. 303°.

Table II

Quinazolines



Compound No.	R	Y C=X	R_1	Z	M.p. °C	% Yield	Recrystallization Solvent (a)	Molecular Formula	Molecular Weight	M⁺	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
35	H	$CO_2C_2H_5$	$CH_2CO_2C_2H_5$	OH	165-166 (b)	68	E	$C_{12}H_{12}N_2O_3$	232		62.06	62.09	5.21	5.34
36	Cl	C-C_6H_5 ‖ NOH	CH_3	C_6H_5	106-108 (c)	75 (e)	B-H	$C_{15}H_{11}ClN_2$	254.5	254	70.73	70.57	4.32	4.57
37	Cl	COC_6H_5	CH_2Cl	C_6H_5	126-128 (d)	70	B-H	$C_{15}H_{10}Cl_2N_2$	289		62.28	62.31	3.46	3.65

(a) E = Ethanol, B = Benzene, H = Hexane. (b) Lit. (18) m.p. 163°. (c) Lit. (17) m.p., 105-106°. (d) Lit. (17) m.p., 126-127°. (e) Obtained in 70% yield from 2-amino-5-chlorobenzophenone.

SCHEME III

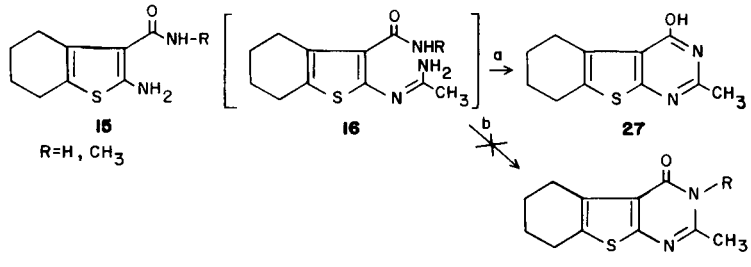


Table III

Benzothieno[3,2-*d*]pyrimidines and Pyridothieno[3,2-*d*]pyrimidines

Compound No.	R_1	R_2	R_3	G	A	Y C=X	Z	M.p. °C	% Yield	Recrystallization Solvent (a)	Molecular Formula	Molecular Weight	M⁺	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
38	OCH_3	H	CH_3	S	CH	$CO_2C_2H_5$	OH	320-325	53 (b)	E-C	$C_{12}H_{10}N_2O_2S$	246	246	58.53	58.28	4.09	4.27
39	OCH_3	H	$CH_2CO_2C_2H_5$	S	CH	$CO_2C_2H_5$	OH	303-305	58 (b)	E-C	$C_{15}H_{14}N_2O_4S$	318		56.60	56.42	4.43	4.56
40	CH_3	CH_3	CH_3	S	N	$CO_2C_2H_5$	OH	>360	58 (b)	D	$C_{12}H_{11}N_3OS$	245	245	58.77	58.30	4.49	4.48

(a) C = Chloroform, D = Dimethylformamide, E = Ethanol. (b) the reaction mixture heated on a steam bath for 7-8 hours after passing hydrogen chloride.

It is interesting to note that the reaction of 2-amino-5-chlorobenzophenone oxime **18**, with acetonitrile gave the quinazoline **36** and not the *N*-oxide **19**.

18 36 19

With acrylonitrile, 2-(2′-chloroethyl)pyrimidine **23** was obtained, while reaction with cinnamonitrile under similar conditions yielded 2-styryl pyrimidine **24**.

23 24

All the condensed pyrimidines synthesised were characterised by their correct elemental analysis and spectral data as listed in Tables I-III.

This facile one-pot reaction is versatile and offers an attractive alternative to the existing methods of synthesis of condensed pyrimidines.

EXPERIMENTAL

All melting points are uncorrected. Ultraviolet absorption spectra were determined in 95% ethanol using Beckman Model 25 spectrophotometer. Infrared spectra were taken in nujol mulls using Perkin-Elmer 337 Grating spectrophotometer. Nmr spectra were run on a Varian A60 spectrophotometer. Mass spectra were recorded on Varian-Atlas CH-7 mass spectrophotometer at 70 eV ionising beam and using direct insertion probe.

General Procedure.

A stream of dry hydrogen chloride gas was passed through a mixture of the *ortho*-aminocarbonyl compound (0.02 mole) and nitrile (0.022 mole) in dioxane (20 ml.) for about 5 hours. The solvent was removed under reduced pressure and the residue triturated with ice water and basified with 10% ammonium hydroxide solution. The precipitate obtained was filtered, dried and crystallized from a suitable solvent.

In some cases, the removal of the solvent is not essential. Dilution of the reaction mixture with ice water and basification affords the pyrimidines in good yields. With aromatic nitriles the yields are improved by refluxing the reaction mixture for a few hours after passing hydrogen chloride gas. In the case of reaction with acetonitrile, excess of it was used as the solvent.

2-(2′-Chloroethyl)-4-hydroxy-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (**23**).

A stream of dry hydrogen chloride gas was passed through a mixture of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo[*b*]thiophene (12) (4.5 g., 0.02 mole) and acrylonitrile (2.10 g., 0.04 mole) in dioxane (20 ml.) for 5 hours. The reaction mixture was poured into ice water and basified with 10% ammonium hydroxide solution. The precipitate obtained was filtered, dried and crystallized from an ethanol-chloroform mixture, m.p. > 360°, yield 2.7 g. (50%); ir (potassium bromide): cm^{-1}, 3400, 1665, 1590; ms: m/e 270, 268 (M^+), 266, 233, 232, 178, 162, 135, 116.

2-Styryl-4-hydroxy-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (**24**).

A stream of dry hydrogen chloride gas was passed through a mixture of 2-amino-3-cabethoxy-4,5,6,7-tetrahydrobenzo[*b*]thiophene (12) (4.5 g., 0.02 mole) and cinnamonitrile (2.84 g., 0.022 mole) in dioxane (20 ml.) for 5 hours. The reaction mixture was poured into ice water and basified with 10% ammonium hydroxide solution. The solid obtained was filtered, dried and crystallized from an ethanol-chloroform mixture, m.p. 315-317°, yield 3.1 g. (50%); ir (potassium bromide): cm^{-1}, 2940, 1650; ms: m/e 308 (M^+), 293, 280, 203, 179.

2-Methyl-4-hydroxy-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (**27**) (14,15).

A stream of dry hydrogen chloride gas was passed through a mixture of 2-amino-3-(*N*-methylcarboxamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene (13) (2.1 g., 0.01 mole) and acetonitrile (10 ml.) for about 4-5 hours. The reaction mixture was poured into ice water and basified with 10% ammonium hydroxide solution. The solid obtained was filtered, dried and crystallized from DMF, m.p., 300-302°, yield 1.70 g. (80%); uv (ethanol): λ max 277 (4.64); ir (nujol): cm^{-1}, 1670, 1610, 1470, 1390; ms: m/e 220 (M^+), 205, 192, 164, 123, 91, 83. This compoud was found to be identical with the compound obtained from the reaction of 2-amino-3-carbethoxy-4,5,6,7-tetrahydrobenzo[*b*]thiophene (12) or 2-amino-3-carboxamido-4,5,6,7-tetrahydrobenzo[*b*]thiophene (12) with acetonitrile under similar conditions (16).

2-Methyl-4-phenyl-6-chloroquinazoline (**36**) (17).

A stream of dry hydrogen chloride gas was passed through a mixture of 2-amino-5-chlorobenzophenone α-oxime (17) (2.46 g., 0.01 mole) and acetonitrile (10 ml.) for about 5 hours. The reaction mixture was poured into ice-water and basified with 10% ammonium hydroxide solution. The precipitate obtained was filtered, dried and crystallized from a benzene-hexane mixture, m.p. 106-108°, yield 2.0 g. (75%); ir (nujol): cm^{-1}, 1540, 1480, 1450, 1380; ms: m/e 256, 254 (M^+), 253, 219, 177. This compound was identical with the compound obtained from 2-amino-5-chlorobenzophenone with acetonitrile under similar conditions.

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(19) We wish to thank Dr. S. Selvavinayakam, CIBA-GEIGY Research Centre, Goregaon, Bombay, India for microanalysis and spectra. We thank Shroffs Industrial Chemicals Pvt. Ltd., Vapi and Cadila Laboratories, Ahmedabad for material help. We are grateful to Dr. (Miss) B. M. Trivedi for providing facilities to carry out this work. Financial assistance by William H. Rorer Inc., Fort Washington, U.G.C., New Delhi, India (to S.A.) and C.S.I.R., India (to V.S.B) is gratefully acknowledged.