SYNTHESIS OF SOME 4-BROMOPYRIMIDINES AND CONDENSED 4-BROMOPYRIMIDINES BY ONE-POT REACTION

Mahesh. T. Chhabria* and Chamanlal J. Shishoo

Department of Pharmaceutical Chemistry, L. M. College of Pharmacy, Navrangpura, Ahmedabad - 380 009, Gujarat, India

Abstract - Simple one-pot reaction has been developed for the synthesis of 4-bromopyrimidines and condensed 4-bromopyrimidines. Under the catalytical influence of dry hydrogen bromide, *N*-(cyanovinyl)amidines cyclised to 4-bromopyrimidines, and 2-aminonitrile compounds with halogenoacetonitriles gave condensed 4-bromopyrimidines, in good yields.

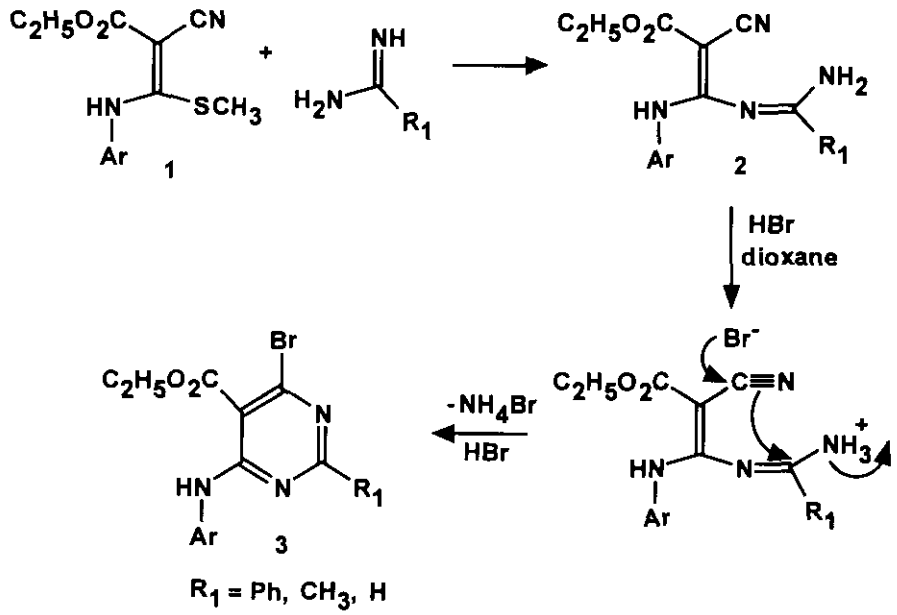
4-(Substituted amino)pyrimidines and condensed 4-(substituted amino)pyrimidines are known to have a variety of biological activity.[1-3] 4-Bromopyrimidines and condensed 4-bromopyrimidines are important precursors in the synthesis of 4-(substituted amino)pyrimidines and condensed pyrimidines. 4-Halo substituent in pyrimidines is prone to undergo displacement by amines.

A few reports are available on the synthesis of 4-bromopyrimidine and condensed 4-bromopyrimidines. Available methods involve bromination of the corresponding hydroxypyrimidine using reagents like phosphorous pentabromide, phosphorous tribromide, phosphorous oxybromide or combination of these reagents.[4] Application of these reagents, however, involves multistep reactions. Herein, we are reporting a simple, one-pot reaction for the synthesis of 4-bromopyrimidines and condensed 4-bromopyrimidines.

We have reported isolation of *N*-cyanovinylamidines **(2)**, otherwise difficultly isolable intermediates in the synthesis of pyrimidines, from the reaction of α-cyanoketene *S,N*-acetals **(1)**, with different amidines namely formamidine, acetamidine, and benzamidine, under

controlled reaction conditions.[5,6] This intermediate undergoes cyclisation in presence of dry hydrogen bromide to give 4-bromopyrimidines **(3), (Scheme 1).**

Scheme 1



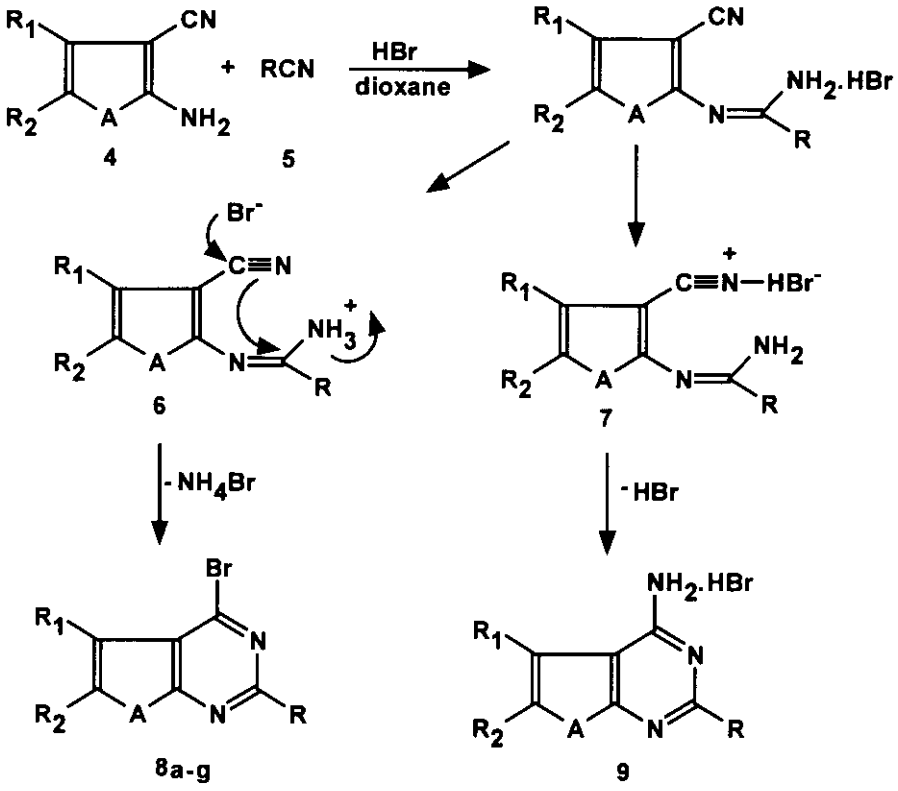
The enhanced reactivity of nitriles towards nucleophiles in the presence of acids, particularly hydrogen halides, is known.[7-10] However, utilisation of the enhanced reactivity of nitriles in the presence of acid for the synthesis of condensed pyrimidines through the reaction with 2-aminocarbonyl compounds, has hitherto, remained unexplored. Synthesis of various condensed pyrimidines from 2-aminocarbonyl compounds with various nitriles in presence of dry hydrogen chloride gas has been reported from our laboratory.[11]

We have observed here the unusual direct formation of condensed 4-bromopyrimidine **(8)** instead of the normally expected condensed 4-aminopyrimidines **(9)** in the condensation of 2-aminonitriles **(4)** with chloroacetonitriles **(5)**. The exclusive formation of 4-bromopyrimidines **(8)** over that of 4-aminopyrimidine **(9)** may be due to preferential cyclisation of amidine intermediate in which electrophilicity of amidine carbon is increased and nucleophilicity of amidine nitrogen is decreased due to electron withdrawing effect of chlorine atom in the nitrile. **(Scheme 2)**

Table 1 : Physical and Spectral characteristics of 4-bromo-6-(substituted amino)-2-(substituted)pyrimidines

Sr. No.	R_1	R_2	Mol. Formula	m. p. (°C)	Yield (%)	^1H NMR ($CDCl_3$) δ, J (Hz)	MS (m/z)	Elemental analysis Required % C	% H	Found % C	% H
3a	C_6H_5	H	$C_{13}H_{12}N_3O_2Br$	71 – 72	54	1.45 (t, 3H $OCH_2\underline{CH_3}$, J = 7), 4.50 (q, 2H, OCH_2CH_3, J = 10), 7.42 (m, 4H *arom*), 8.33 (s, 1H*Pyrim*), 9.71 (s, 1H, NH-Ar)	322 (M+) 324 (M+2)	48.46	3.76	48.80	3.75
3b	*p*-CH_3-C_6H_4	H	$C_{14}H_{14}N_3O_2Br$	72 – 73	48	1.42 (t, 3H $OCH_2\underline{CH_3}$, J = 7),2.36 (s, 3H, $\underline{CH_3}$arom), 4.42 (q, 2H, OCH_2CH_3, J = 10), 7.22 (m, 4H arom), 8.35 (s, 1HPyrim), 9.65 (s, 1H, NH-Ar)	336 (M+) 338 (M+2)	50.01	4.20	50.40	4.20
3c	*o*-CH_3O-C_6H_4	H	$C_{14}H_{14}N_3O_3Br$	75 – 77	61	1.50 (t, 3H $OCH_2\underline{CH_3}$, J = 7), 3.90 (s, 3H, OCH_3arom), 4.50 (q, 2H, $OCH_2\underline{CH_3}$, J = 10), 7.00 (m, 4H arom), 8.35 (s, 1HPyrim), 9.82 (s, 1H, NH-Ar)	352 (M+) 354 (M+2)	47.74	4.01	47.73	3.96
3d	*p*-chloro-C_6H_4	H	$C_{13}H_{11}N_3O_2BrCl$	94 – 96	60	1.52 (t, 3H $OCH_2\underline{CH_3}$, J = 7), 4.45 (q, 2H, OCH_2CH_3, J = 10), 7.38 (m, 4H arom), 8.30 (s, 1HPyrim), 9.73 (s, 1H, NH-Ar)	356 (M+) 358 (M+2)	43.78	3.11	44.11	3.07
3e	*p*-bromo-C_6H_4	H	$C_{13}H_{11}N_3O_2\ Br_2$	98 – 100	56	1.54 (t, 3H $OCH_2\underline{CH_3}$, J = 7), 4.44 (q, 2H, OCH_2CH_3, J = 10), 7.45 (m, 4H arom), 8.30 (s, 1Hpyrim), 9.65 (s, 1H, NH-Ar)	401 (M+) 403 (M+2)	38.93	2.77	39.20	2.71
3f	C_6H_5	CH_3	$C_{14}H_{14}N_3O_2Br$	68 – 69	50	1.50 (t, 3H $OCH_2\underline{CH_3}$, J = 7), 3.80 (s, $\underline{CH_3}$Pyrim), 4.45 (q, 2H, OCH_2CH_3, J = 10), 7.25 (m, 4H arom), 9.68 (s, 1H, NH-Ar)	336 (M+) 338 (M+2)	50.01	4.20	50.06	4.18
3g	*p*-CH_3-C_6H_4	CH_3	$C_{15}H_{16}N_3O_2Br$	70 - 71	56	1.45 (t, 3H $OCH_2\underline{CH_3}$, J = 7), 2.35 (s, $\underline{CH_3}$arom), 3.52 (s, $\underline{CH_3}$Pyrim), 4.42 (q, 2H, OCH_2CH_3, J = 10), 7.28 (m, 4Harom), 9.72 (s, 1H, NH-Ar)	350 (M+) 352 (M+2)	51.44	4.61	51.38	4.50
3h	*o*-CH_3O-C_6H_4	CH_3	$C_{15}H_{16}N_3O_3Br$	72 - 74	52	1.46 (t, 3H $OCH_2\underline{CH_3}$, J = 7), 3.50 (s, 3H, $\underline{CH_3}$arom), 3.80 (s, 3H, $\underline{CH_3}$pyrim), 4.44 (q, 2H, OCH_2CH_3, J = 10), 7.33 (m, 4Harom), 9.68 (s, 1H, NH-Ar)	366 (M+) 368 (M+2)	49.19	4.40	49.57	4.59
3i	C_6H_5	C_6H_5	$C_{19}H_{16}N_3O_2Br$	125 - 126	58	1.50 (t, 3H $OCH_2\underline{CH_3}$, J = 7), 4.46 (q, 2H, OCH_2CH_3, J = 10), 7.46 (m, 10H arom), 9.85 (s, 1H, NH-Ar)	398 (M+) 400 (M+2)	57.30	4.05	56.98	3.80
3j	*p*-CH_3-C_6H_4	C_6H_5	$C_{20}H_{18}N_3O_2Br$	127 - 128	62	1.38 (t, 3H $OCH_2\underline{CH_3}$, J = 7), 2.30 (s, 3H, $\underline{CH_3}$arom), 4.37 (q, 2H, OCH_2CH_3, J = 10), 7.46 (m, 10Harom), 9.85 (s, 1H, NH-Ar)	412 (M+) 414 (M+2)	58.26	4.40	58.65	4.39
3k	*o*-CH_3O-C_6H_4	C_6H_5	$C_{20}H_{18}N_3O_3Br$	110 - 111	60	1.47 (t, 3H $OCH_2\underline{CH_3}$, J = 7), 3.90 (s, 3H, OCH_3arom), 4.47 (q, 2H, OCH_2CH_3, J = 10), 7.20 (m, 10Harom), 9.9 (s, 1H, NH-Ar)	428 (M+) 430 (M+2)	56.08	4.24	56.21	4.18
3l	*p*-chloro-C_6H_4	C_6H_5	$C_{19}H_{15}N_3O_2BrCl$	129 - 131	61	1.48 (t, 3H $OCH_2\underline{CH_3}$, J = 7), 4.42 (q, 2H, OCH_2CH_3, J = 10), 7.40 (m, 4Harom), 9.92 (s, 1H, NH-Ar)	433 (M+) 435(M+2)	52.73	3.49	52.43	3.48

Scheme 2



R_1, R_2 = H, Ph, CH_3, $-(CH_2)_4-$

R = CH_2Cl or $CHCl_2$

A = -CH=CH-, -O-, -S-

Above both the reactions involve simple stirring of reactants in presence of dry hydrogen bromide gas[12] in dioxane for 2 h. Work-up of the reaction mixture after 1 h gave the final product in good yield.

In conclusion, simple one-pot method has been developed for the synthesis of 4-bromopyrimidines and condensed 4-bromopyrimidines, The method offers an attractive alternative for the synthesis of 6-(substituted amino)-4-bromopyrimidine which are otherwise difficultly accessible. Moreover, the synthesis of 4-bromopyrimidines by this reaction is less time consuming.

Table 2 : Physical and Spectral characteristics of condensed 4-bromopyrimidines

Sr. No.	R_1	R_2	A	R	Mol. Formula	mp (°C)	Yield (%)	^{1}H NMR ($CDCl_3$) δ, J (Hz)	MS (m/z)	Elemental analysis Required % C	% H	Found % C	% H
8a	H	H	-CH=CH-	CH_2Cl	$C_9H_6N_2BrCl$	95 - 97	54	4.65 (s, 2H, $C\underline{H}_2Cl$), 7.85 (m, $4H_{arom}$)	258 (M+) 260(M+2)	41.97	2.35	42.32	2.54
8b	CH_3	CH_3	S	CH_2Cl	$C_9H_8N_2BrClS$	156 - 158	30	4.72 (s, 2H, $C\underline{H}_2Cl$), 7.45 (m, $10H_{arom}$)	400(M+) 402(M+2)	57.09	3.03	57.45	3.40
8c	C_6H_5	C_6H_5	O	CH_2Cl	$C_{19}H_{12}N_2OBrCl$	118 - 119	58	6.80 (s, 1H, $C\underline{H}Cl_2$), 7.45 (m, $10H_{arom}$)	434(M+) 436(M+2)	52.76	2.55	52.83	2.56
8d	C_6H_5	C_6H_5	O	$CHCl_2$	$C_{19}H_{11}N_2OBrCl_2$	160 - 161	34	2.55 (s, 6H, ^{5}C-$C\underline{H}_3$ and ^{6}C-$C\underline{H}_3$), 4.62 (s, 2H, $C\underline{H}_2Cl$)	292(M+) 294(M+2)	37.07	2.77	36.68	2.76
8e	-$(CH_2)_4$-		S	CH_2Cl	$C_{11}H_{10}N_2BrClS$	136 - 138	44	2.05 (m, 8H, -$(C\underline{H}_2)_4$-), 4.65 (s, 2H, $C\underline{H}_2Cl$)	318(M+) 320(M+2)	41.60	3.17	42.07	2.93
8f	-$(CH_2)_4$-		S	$CHCl_2$	$C_{11}H_9N_2BrCl_2S$	152 - 154	53	1.95 (m, 8H, -$(C\underline{H}_2)_4$-), 6.80 (s, 2H, $C\underline{H}Cl_2$)	352(M+) 354(M+2)	37.52	2.58	37.88	2.69
8g	-C(CH_3)CH=C(CH_3)N-		S	CH_2Cl	$C_{12}H_9N_3BrClS$	165 - 166	42	2.92 (s, 3H, ^{7}C-$C\underline{H}_3$), 3.10 (s, 3H, ^{9}C-$C\underline{H}_3$), 7.10 (s, 1H, Ar-$\underline{H}$), 4.61 (s, 2H, $C\underline{H}_2Cl$)	343(M+) 345(M+2)	42.06	2.65	42.20	2.44

EXPERIMENTAL

General procedure for the synthesis of 4-bromo-5-carbethoxy-2-(substituted)6-(substituted amino)pyrimidines (3)

To a saturated solution of dry hydrogen bromide in 1,4-dioxane (30 mL), 10 mmol of *N*-cyanovinylamidine[5,6] was added and the resulting mixture was stirred at 15-20°C for 2 h. Reaction mixture was allowed to stand at rt for 1 h. and then poured into crushed ice. 4-Bromopyrimidines were obtained as pale yellow colored solids, which were filtered and purified by recrystallisation (n-hexane) to give pure 4-bromopyrimidine **(3).**

General procedure for the synthesis of condensed 4-bromo-2-(substituted)pyrimidines(8)

To a mixture of 10 of mmol 2-aminonitrile[13] and 10 mmol of halogenoacetonitrile was added 30 mL of saturated solution of dry hydrogen bromide gas in 1,4-dioxane. Resultant mixture was stirred at 15-20°C for 2 h and allowed to stand at rt for 1 h. The reaction mixture was poured into crushed ice. The condensed 4-bromopyrimidines were obtained as pale yellow solids, which were filtered and recrystallised from n-hexane.

REFERENCES

1. A. H. Amin, D. R. Mehta, and S. S. Samarth, 'Progress in Drug Research', Vol. 14, ed. by E. Zucker, Birkhauser Verlag, Basel, 1970, p. 218.
2. W. L. F. Armarego, *Adv. Heterocycl. Chem.*, 1979, **24**,1.
3. A. M. Thompson, D. K. Murray, W. L. Elliot, D. W. Fry, H. D. Nelson, H. Showalter, B. J. Roberts, P. W. Vimart, and W. A. Denny, *J. Med. Chem.*,1997, **40**, 3915.
4. D. J. Brown, 'Comprehensive Heterocyclic Chemistry', ed. by A. R. Katritzky and C. Y. Rees, Pergamon Press, Oxford, 1984, **3,** p. 139.
5. C. J. Shishoo, M. B. Devani, V. S. Bhadti, S. Ananthan, and G. V. Ullas, *Tetrahedron Lett.*, 1984, **25**, 1291.
6. C. J. Shishoo, M. T. Chhabria, T. P. Gandhi, and R. Bangaroo, *Arzneim. Forsch. / Drug Res.*, 1997, **45**, 35.
7. F. Johnson and R. Madronero, *Adv. Heterocyclic Compound,* 1966, **6**, 95.
8. E. N. Zil'berman, *Russ. Chem. Rev.*, 1962, **31**, 615.
9. R. Bonnett, 'The Chemistry of Carbon-Nitrogen double bond', ed. by S. Patai, Interscience, NewYork, 1970, p. 597.

10. S. Yanagida, T. Fujita, M. Ohoka, I. Katagiri, and S. Komori, *Bull. Chem. Soc. Japan,* 1973, **46**, 292.
11. C. J. Shishoo, M. B. Devani, V. S. Bhadti, S. Ananthan, and G. V. Ullas, *Tetrahedron Lett.*, 1983, **24**, 4611.
12. A. I. Vogel, 'A Textbook of Practical Organic Chemistry', 5th ed., English Language Book Society, London, 1989, p. 437.
13. The required 2-aminonitriles were synthesized according to the reported procedure, 2-aminobenzonilonitrile (Aldrich Chemical Inc.), 2-amino-3-cyano-4,5,6,7-tetrahydrobenzo(*b*)thiophene,[14] 2-amino-3-cyano-4,5-dimethylthiophene,[14] 2-amino-3-cyano-4,5-diphenyl-furan,[15] 3-amino-2-cyano-4,6-dimethylthieno(2,3-*b*)pyridine.[16]
14. K. Gewald, E. Schinke, and M. Bottcher, *Chem. Ber.*, 1966, **99**, 94.
15. K. Gewald, *Chem. Ber.*, 1966, **99**, 1002.
16. K. Gewald and M. Hentschel, *J. Prakt. Chem.*, 1974, **316**, 1030.

Received, 7th June, 1999