Reaction of *N*-Substituted Cyclic Amines with 2,4-Dichloroquinazoline, 2,4-Dichloropyrimidine, and its 5-Methyl Derivative

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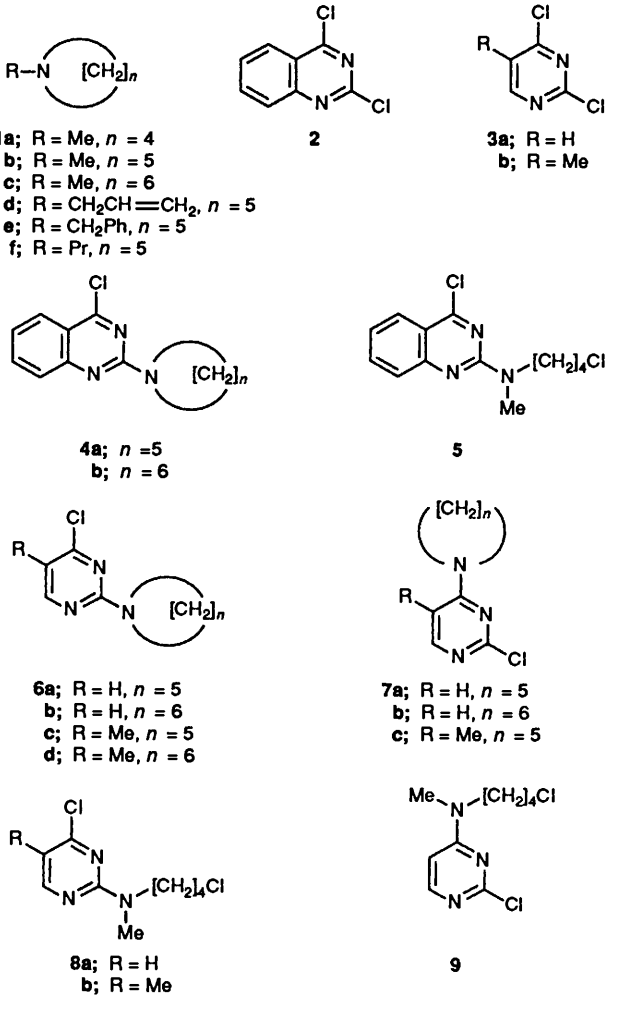
The reaction of *N*-substituted cyclic amines with 2,4-dichloroquinazoline **2** and 2,4-dichloro-5-methylpyrimidine **3b** afforded 2-amino-4-chloroquinazolines and 2-amino-4-chloro-5-methylpyrimidines, respectively. However, the reaction of these amines with 2,4-dichloropyrimidine **3a** afforded not only 2-amino-4-chloropyrimidines but also the isomeric 4-amino-2-chloropyrimidines. The regioselectivity of these reactions was considered to be determined by the steric nature of the substrates **2**, **3a** and **3b**.

In our previous paper, we described how the reaction of quinazoline-2,4(1*H*,3*H*)-dione with *N*-substituted cyclic amines in combination with phosphoryl trichloride afforded 4-chloro-2-(cyclic amino)quinazolines regioselectively.[1] Moreover, we reported that 2,4-dichloroquinazoline **2** was considered as an intermediate in the reaction. We have now found that the reaction of compound **2** with *N*-methylpiperidine **1b** in 1,4-dioxane afforded 4-chloro-2-piperidinoquinazoline **4a**. In order to elucidate the regioselectivity of the reaction, we focused on the reaction of *N*-substituted cyclic amines (**1a–f**) with 2,4-dichloropyrimidine **3a** and 2,4-dichloro-5-methylpyrimidine **3b**. This paper describes the reactions of cyclic amines **1a–f** with substrates **2**, **3a** and **3b**.

When compound **2** was allowed to react with *N*-methylpiperidine **1b** (1.2 mol equiv.) in 1,4-dioxane at 100 °C for 1 h, 4-chloro-2-piperidinoquinazoline **4a** was isolated in 92% yield. The structure of the product **4a** was confirmed by comparison with an authentic sample prepared by the method described in our previous paper.[1] In order to elucidate the scope and limitation of this type of reaction, the reaction of compound **2** with other cyclic amines was examined. The results are summarized in Table 1. In the case of six- or seven-membered cyclic amines (**1b–e**), the reaction proceeded regioselectively, and only quinazoline derivatives (**4a** or **4b**), in which cyclic amines were substituted at the 2-position of quinazoline, were isolated. On the other hand, the reaction of compound **2** with five-membered cyclic amine **1a** afforded 4-chloro-2-[*N*-(4-chlorobutyl)-*N*-methylamino]quinazoline **5**. These results were in good accord with those of the reaction of quinazoline-2,4(1*H*,3*H*)-dione with *N*-substituted cyclic amines in combination with phosphoryl trichloride.[1]

It is well known that the 4-position of the quinazoline **2** is more reactive than the 2-position toward nucleophilic attack by primary or secondary amines.[2] The above reaction, however, indicates that the 2-position of compound **2** is more reactive than the 4-position for the attack by tertiary amines. In order to elucidate the regioselectivity of the above reaction, the reaction of substrates **1a–f** with 2,4-dichloropyrimidine **3a** and 2,4-dichloro-5-methylpyrimidine **3b** was examined.

The reaction of the methylpyrimidine **3b** with *N*-methylpiperidine **1b** afforded 4-chloro-5-methyl-2-piperidinopyrimidine **6c** in 84% yield. The structure of compound **6c** was confirmed by comparison with an authentic sample prepared by chlorination of 5-methyl-2-piperidinopyrimidin-4(3*H*)-one.[3] The structure of product **6c** was further confirmed by comparison of its NMR spectra with those of 2-chloro-5-methyl-4-piperidinopyrimidine **7c**, which was prepared by the reaction of dichloride **3b** with piperidine. The ^1H and ^{13}C



NMR assignments of regioisomers **6c** and **7c** were made based on C–H COSY, COLOC, and LSPD spectra and the data are shown in Tables 2 and 3. In the UV spectra, regioisomers **6c** and **7c** showed an absorption maximum at 325 and 289 nm, respectively. The results of the reaction of dichloride **3b** with other *N*-substituted cyclic amines are summarized in Table 1. In the case of *N*-substituted six- or seven-membered cyclic amines, 4-chloro-2-(cyclic amino)-5-methylpyrimidines (**6c** or **6d**) were obtained. However, in the case of *N*-substituted five-membered cyclic amine **1a**, 4-chloro-2-[*N*-(4-chlorobutyl)-*N*-methyl-

Table 1 Reaction of *N*-substituted cyclic amines (**1a–f**) with 2,4-dichloroquinazoline **2**, 2,4-dichloropyrimidines **3a**, or 2,4-dichloro-5-methylpyrimidine **3b** in 1,4-dioxane

Amine	Dichloride	Reaction temp. (°C)	Reaction time (*t*/h)	Product	Isolation yield (%)
1a	**2**	100	0.5	**5**	43
1b	**2**	100	1	**4a**	92
1c	**2**	100	1	**4b**	87
1d	**2**	120	6	**4a**, **2**[a]	12, 77[a]
1e	**2**	120	12	**4a**, **2**[a]	8, 72[a]
1a	**3a**	120	1	**8a**, **9**	5, 80
1b	**3a**	120	1.5	**6a**, **7a**	24, 76
1c	**3a**	120	2	**6b**, **7b**	34, 60
1d	**3a**	120	6	**6a**, **7a**, **3a**[a]	43, 31, 16[a]
1e	**3a**	120	12	**6a**, **7a**, **3a**[a]	22, 20, 49[a]
1f	**3a**	120	4	**6a**, **7a**, **3a**[a]	40, 38, 14[a]
1a	**3b**	100	4	**8b**	78
1b	**3b**	100	4	**6c**	84
1c	**3b**	120	2	**6d**	83
1d	**3b**	120	12	**6c**, **3b**[a]	19, 74[a]
1e	**3b**	120	36	**6c**, **3b**[a]	4, 87[a]

[a] Recovered.

Table 2 ^{1}H and ^{13}C NMR chemical shifts (δ) of compound **6c** in $CDCl_3$, and results of COLOC experiments[a]

	^{1}H			
^{13}C	1.54–1.67 (3′-, 4′-, 5′-H)	2.12 (5-Me)	3.73 (2′-, 6′-H)	8.04 (6-H)
160.6 (C-4)		^3J	^3J[b]	^3J
160.4 (C-2)				^3J
158.7 (C-6)		^3J		^1J
115.3 (C-5)		^2J		^2J
44.7 (C-2′, -6′)			^1J	
25.6 (C-3′, -5′)	^1J		^2J	
24.6 (C-4′)	^1J		^3J	
15.1 (5-Me)		^1J		^3J

[a] ^2J, ^3J and ^4J indicate long-range coupling through two, three and four bonds, respectively. [b] Change of the multiplicity was observed in LSPD experiment irradiated at δ 3.73.

Table 3 ^{1}H and ^{13}C NMR chemical shifts (δ) of compound **7c** in $CDCl_3$, and results of COLOC experiments[a]

	^{1}H			
^{13}C	1.62–1.74 (3′-, 4′-, 5′-H)	2.19 (5-Me)	3.49 (2′-, 6′-H)	7.88 (6-H)
165.3 (C-4)		^3J	^3J[b]	^3J
159.0 (C-6)		^3J		^1J
157.6 (C-2)				^3J
114.9 (C-5)		^2J		^2J
48.3 (C-2′, -6′)			^1J	
25.7 (C-3′, -5′)	^1J		^2J	
24.3 (C-4′)	^1J		^3J	
17.3 (5-Me)		^1J		^3J

[a] ^2J, ^3J and ^4J indicate long-range coupling through two, three and four bonds, respectively. [b] Change of the multiplicity was observed in LSPD experiment irradiated at δ 3.49.

amino]-5-methylpyrimidine **8b** was obtained. The UV spectra of products **6c**, **6d** and **8b** showed an absorption maximum at ~320 nm (Table 4) and suggested that the amino groups were substituted at the 2-position of the pyrimidine ring.

On the other hand, the reaction of the piperidine **1b** with dichloropyrimidine **3a** afforded not only 4-chloro-2-piperidinopyrimidine **6a** but also its regioisomer 2-chloro-4-piperidinopyrimidine **7a** in 24 and 76% yield, respectively. The structure of the products **6a** and **7a** was confirmed by comparison with authentic samples, which were prepared by chlorination[4] of 2-piperidinopyrimidin-4(3*H*)-one and by the reaction[5] of dichloride **3a** with piperidine, respectively. These structures were further confirmed by the UV absorption maximum, at 315 and 290 nm respectively, which were in good accord with those of compounds **6c** and **7c**, respectively.

The reaction of dichloride **3a** with other *N*-substituted six- or seven-membered cyclic amines also afforded not only 2-chloro-4-(cyclic amino)-5-methylpyrimidine (**6a** or **6b**) but also the regioisomeric 4-chloro-2-(cyclic amino)-5-methylpyrimidine (**7a** or **7b**). In the case of *N*-methyl five-membered cyclic amine **1a**, 4-chloro-2-[*N*-(4-chlorobutyl)-*N*-methylamino]pyrimidine **8a** and 2-chloro-4-[*N*-(4-chlorobutyl)-*N*-methylamino]pyrimidine **9** were obtained. The results are summarized in Table 1 and the structure of the products was assigned by their UV and ^{1}H NMR spectral data (Tables 4 and 5).

It was reported that the reactivity of the 2-position of dichloride **3a** relative to the 4-position increases as the solvent polarity and the nucleophilicity of the primary and secondary amines are decreased.[6] In the above reaction of compound **3a** with tertiary amines, the ratios of 2-amino-4-chloropyrimidines to 4-amino-2-chloropyrimidines increased with the increased bulk of the *N*-substituent and the ring size of the cyclic amines (**8a**/**9**, **6a**/**7a** and **6b**/**7b**).

The 4-position of compound **3a** is considered to be more hindered than the 2-position by the presence of a hydrogen atom at the 5-position. Therefore, the increase of these ratios is explained by the steric hindrance between *N*-substituted cyclic amines and the hydrogen atom at the 5-position of compound **3a**.

On the other hand, compound **2** has a hydrogen atom at the 5-position (*peri*-position) and compound **3b** has a methyl group at the 5-position. Owing to the presence of these groups, the 4-position of compounds **2** and **3b** is considered to be more hindered than that of compound **3a**. The steric interaction between these groups and the *N*-substituted cyclic amines is considered to be a main reason for the regioselective attack by the cyclic amines on the 2-position of substrates **2** and **3b**.

In conclusion, the regioselectivity of the reaction of compound **2**, **3a** or **3b** with the *N*-substituted cyclic amines are reasonably explained by the steric hindrance between the *N*-substituted cyclic amines and the substituent at the 5-position of the substrate **2**, **3a** or **3b**. The reaction of compounds **2** and **3b** with the *N*-substituted cyclic amines offers a new synthetic

Table 4 Physical data for 2-amino-4-chloropyrimidines (**6a–d, 8a, 8b**) and 4-amino-2-chloropyrimidines (**7a–c, 9**)

Compound	M.p. (°C)	Recrystallization solvent	*m/z*	λ_{max} (EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1})	Formula	Found (%) (Requires) C	H	N
6a[a]	oil		197 (M^+), 96 (base)	315 (2 300), 251 (22 800)	$C_9H_{12}ClN_3$	54.5 (54.69	6.2 6.12	21.2 21.26)
6b	oil		211 (M^+), 70 (base)	318 (2 400), 251 (22 200)	$C_{10}H_{14}ClN_3 \cdot 0.1H_2O$	56.3 (56.26	6.6 6.70	19.5 19.68)
6c	oil		211 (M^+), 204 (base)	325 (2 500), 250 (25 600)	$C_{10}H_{14}ClN_3$	56.45 (56.74	6.5 6.67	19.8 19.85)
6d	oil		225 (M^+, base), 164	327 (2 000), 251 (20 400)	$C_{11}H_{16}ClN_3$	58.4 (58.53	7.1 7.14	18.5 18.62)
7a[b]	81–82	hexane	197 (M^+, base), 218	290 (4 800), 254 (17 900)	$C_9H_{12}ClN_3$	54.8 (54.69	6.1 6.12	21.3 21.26)
7b	oil		211 (M^+), 232 (base)	290 (4 700), 253 (16 900)	$C_{10}H_{14}ClN_3$	56.7 (56.74	6.6 6.67	19.6 19.85)
7c[c]	61–62	hexane	283 (M^+), 206 (base)	289 (7 000), 262 (10 600)	$C_{10}H_{14}ClN_3$	56.7 (56.74	6.5 6.67	19.9 19.58)
8a	oil		233 (M^+), 91 (base)	316 (2 700), 248 (23 100)	$C_9H_{13}Cl_2N_3$	46.3 (46.17	5.5 5.60	17.8 17.95)
8b	oil		247 (M^+), 206 (base)	324 (2 700), 248 (24 300)	$C_{10}H_{15}Cl_2N_3$	48.3 (48.40	6.0 6.09	16.9 16.93)
9	oil		233 (M^+), 91 (base)	289 (4 400), 251 (15 600)	$C_9H_{13}Cl_2N_3$	46.35 (46.17	5.6 5.60	17.7 17.95)

[a] Ref. 4. [b] Ref. 5. [c] Ref. 7.

Table 5 ^{1}H NMR spectral data for 2-amino-4-chloropyrimidines (**6a–d, 8a, 8b**) and 4-amino-2-chloropyrimidines (**7a–c, 9**). Chemical shifts (δ) and coupling constant (Hz, in parentheses)

Compound	5-H	6-H	Others
6a	6.43 (d, *J* 5.1)	8.12 (d, *J* 5.1)	1.54–1.74 (6 H, m, CH_2CH_2), 3.77 (4 H, t, *J* 5.4, NCH_2)
6b	6.44 (d, *J* 5.1)	8.13 (d, *J* 5.1)	1.52–1.84 (8 H, m, CH_2CH_2), 3.73 (4 H, t, *J* 6.0, NCH_2)
6c		8.04 (s)	1.54–1.74 (6 H, m, CH_2CH_2), 2.13 (3 H, s, 5-Me), 3.73 (4 H, t, *J* 5.3, NCH_2)
6d		8.05 (s)	1.52–1.88 (8 H, m, CH_2CH_2), 2.14 (3 H, s, 5-Me), 3.70 (4 H, t, *J* 5.9, NCH_2)
7a	6.38 (d, *J* 6.2)	7.97 (d, *J* 6.2)	1.57–1.77 (6 H, m, CH_2CH_2), 3.52–3.72 (4 H, m, NCH_2)
7b	6.29 (d, *J* 6.2)	7.97 (d, *J* 6.2)	1.48–1.86 (8 H, m, CH_2CH_2), 3.36–3.86 (4 H, m, NCH_2)
7c		7.89 (s)	1.62–1.74 (6 H, m, CH_2CH_2), 3.43–3.53 (4 H, m, NCH_2)
8a	6.47 (d, *J* 5.1)	8.13 (d, *J* 5.1)	1.72–1.88 (4 H, m, CH_2CH_2), 3.13 (3 H, s, NMe), 3.53–3.72 (4 H, m, NCH_2 and CH_2Cl)
8b		8.05 (s)	1.68–1.85 (4 H, m, CH_2CH_2), 2.14 (3 H, s, 5-Me), 3.11 (3 H, s, NMe), 3.56–3.70 (4 H, m, NCH_2 and CH_2Cl)
9	6.30 (d, *J* 6.1)	8.01 (d, *J* 6.1)	1.68–1.88 (4 H, m, CH_2CH_2), 3.06 (3 H, s, NMe), 3.50–3.74 (4 H, m, NCH_2 and CH_2Cl)

method for 4-chloro-2-(cyclic amino)quinazolines and 4-chloro-2-(cyclic amino)-5-methylpyrimidines.

Experimental

M.p.s were measured with a Yamato capillary melting point apparatus, model MP-21, and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AM-300 spectrometer for solutions in $CDCl_3$, and tetramethylsilane was used as internal reference. Mass spectra were determined with an Hitachi M-80B spectrometer. Analytical and preparative TLC (PLC) were performed on silica gel 60 F_{254} precoated plates (No. 5717 and No. 5715, respectively; Merck).

Reaction of Compounds **2**, **3a** *and* **3b** *with Several* N-*Substituted Cyclic Amines*.—The results are summarized in Table 1. As a typical example, the reaction of dichloride **2** with amine **1b** is described below. A mixture of compound **2** (0.40 g, 2.0 mmol) and amine **1b** (0.24 g, 2.4 mmol) in 1,4-dioxane (5.0 cm^3) was heated at 100 °C for 1 h. After being cooled to room temperature, the mixture was concentrated under reduced pressure. Upon PLC with hexane–AcOEt (5:1) as developing solvent, followed by recrystallization from MeCN, the residue gave compound **4a** (046 g, 92%) as crystals, m.p. 73–75 °C.

Preparation of 4-*Chloro*-2-*piperidinopyrimidine* **6a**.—A mixture of 2-piperidinopyrimidin-4(3*H*)-one[4] (0.18 g, 1.0 mmol) and phosphoryl trichloride (0.31 g, 2.0 mmol) was heated at 100 °C for 1 h. After being cooled to room temperature, the mixture was dissolved in $CHCl_3$ (10 cm^3) and poured into ice–water. After being neutralized with 2 mol dm^{-3} NaOH, the organic layer was separated, washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. Upon PLC [hexane–AcOEt (5:1)] the residue gave compound **6a** (0.17 g, 86%) as an oil.

Preparation of 4-*Chloro*-5-*methyl*-2-*piperidinopyrimidine* **6c**.—A mixture of 5-methyl-2-piperidinopyrimidin-4(3*H*)-one[3] (0.19 g, 1.0 mmol) and phosphoryl trichloride (0.31 g, 2.0 mmol) was heated at 100 °C for 30 min. After being cooled to room temperature, the mixture was dissolved in $CHCl_3$ (10 cm^3) and poured into ice–water. After being neutralized with 2 mol dm^{-3} NaOH, the organic layer was separated, washed with water, dried over $MgSO_4$, and evaporated under reduced pressure. Upon PLC (hexane–AcOEt (5:1)] the residue gave compound **6c** (0.20 g, 93%) as an oil.

Preparation of 2-*Chloro*-5-*methyl*-4-*piperidinopyrimidine* **7c**.—A solution of piperidine (0.34 g, 4.4 mmol) in 1,4-dioxane (3.0 cm^3) was added dropwise to an ice-cooled solution of 2,4-

dichloro-5-methylpyrimidine **3b** (0.33 g, 2.0 mmol) in 1,4-dioxane (3.0 cm^3). The mixture was stirred at room temperature for 2 h and then evaporated under reduced pressure. Upon PLC [hexane–AcOEt (3:1)] the residue gave compound **7c** (0.35 g, 83%) as crystals.

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