Reaction of Quinazoline-2,4(1*H*,3*H*)-dione with *N*-Substituted Cyclic Amines in Combination with Phosphoryl Trichloride

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The reaction of quinazoline-2,4(1*H*,3*H*)-dione with *N*-allyl, *N*-benzyl and *N*-methyl cyclic amines in combination with phosphoryl trichloride in the presence of tripropylamine in 1,4-dioxane afforded 4-chloro-2-(cycloalkylamino)quinazolines. In the case of *N*-substituted pyrrolidines, 4-chloro-2-(*N*-substituted 4-chlorobutylamino) quinazolines were also obtained.

One of us reported that 2-(4-allylpiperazin-1-yl)-4-pentyloxyquinazoline exhibited antidementic activity.[1] For the preparation of the above compound, one of the key intermediates, 2-(4-allylpiperazin-1-yl)-4-chloroquinazoline **1a**, was synthesized in five steps from anthranilic acid derivatives, and it became necessary to prepare compound **1a** by a more convenient synthetic method. We found that the reaction of quinazoline-2,4(1*H*,3*H*)-dione **2** with 1,4-diallylpiperazine **3a** in combination with phosphoryl trichloride affords compound **1a** with no cleavage of the piperazine ring. This paper describes the reaction of dione **2** with several *N*-substituted cyclic amines in combination with phosphoryl trichloride.

When the reaction of dione **2** (1 mol equiv.) with 1,4-diallylpiperazine **3a** (2 mol equiv.) in combination with phosphoryl trichloride (3 mol equiv.) in the presence of tripropylamine (2 mol equiv.) was carried out in 1,4-dioxane at 100 °C for 1 h, compound **1a** was obtained in 64% yield. The structure of the product **1a** was confirmed by comparison of an authentic sample[1] prepared from 2-ethylthioquinazolin-4(3*H*)-one. The structure was further confirmed by comparison of the UV and NMR spectra of product **1a** with those of 4-(4-allylpiperazin-1-yl)-2-chloroquinazoline **4**, which was prepared from 2,4-dichloroquinazoline **5** and 1-allylpiperazine **6**. The UV spectra of compounds **1a** and **4** showed the absorption maximum at 379 and 331 nm, respectively, and these wavelengths are in good agreement with those of the absorption maximum of 4-chloro-2-(dialkylamino)quinazolines (380 nm) and 2-chloro-4-(dialkylamino)quinazoline (330 nm).[2c] The ^{1}H and ^{13}C NMR assignments of compounds **1a** and **4**, which were made based on decoupling experiments on aromatic protons, C–H COSY, and COLOC spectra, also supported their assigned structures. The data are shown in Tables 1 and 2.

In the absence of 1,4-dioxane as solvent, the reaction mixture solidified after being cooled to room temperature, and this resulted in difficulty in isolating the product **1a**. The yield of compound **1a** decreased considerably in the absence of tripropylamine (32% yield). This increase in the yield of compound **1a** by addition of tripropylamine is most likely due to trapping of allyl chloride, which is considered to be formed in the course of the reaction, with the additional tertiary amine.

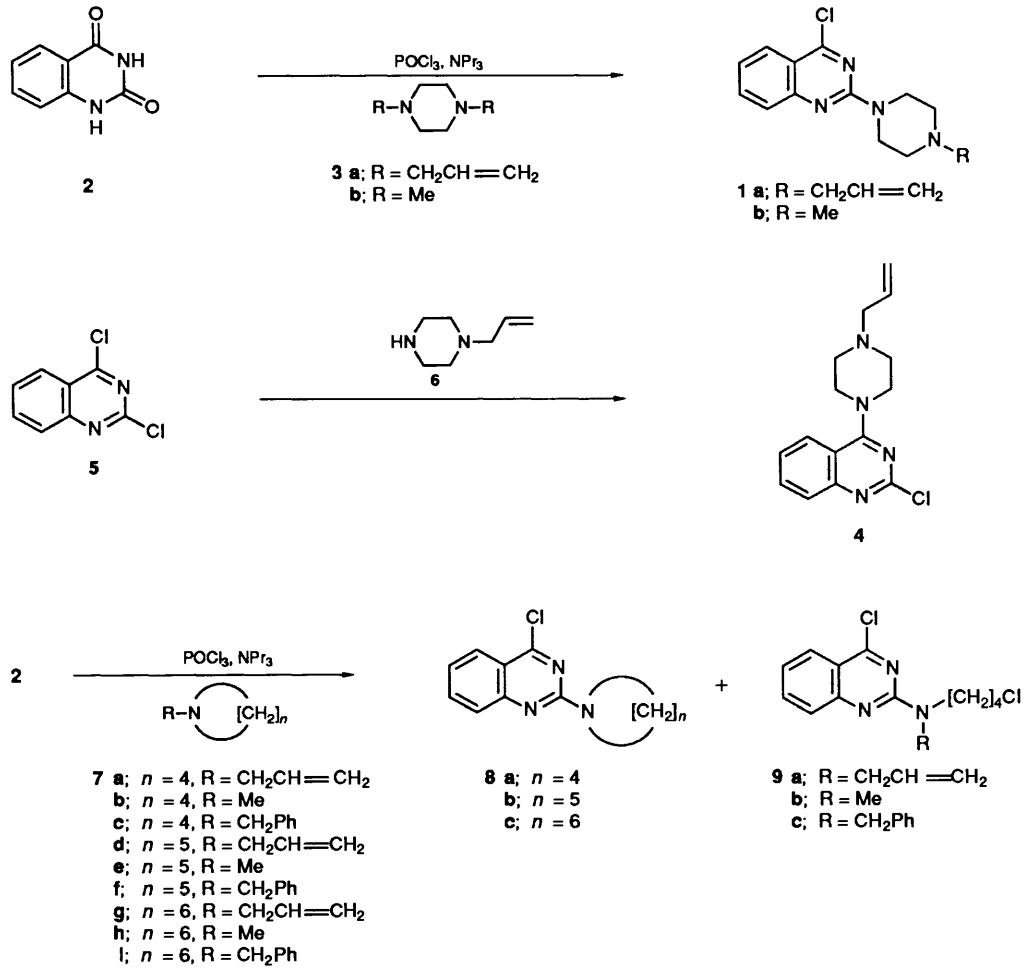
In order to clarify the scope and limitations of the above reaction, the combination of dione **2** with other cyclic amines (**3b** or **7a–i**) in the presence of phosphoryl trichloride was examined. The results are summarized in Table 3. In the case of six- or seven-membered cyclic amines (**3b**, **7d–i**), the reaction proceeded similarly to the above reaction, and only quinazoline derivatives (**1b**, **8b** or **8c**), in which cyclic amines were substituted at the 2-position, were isolated. On the other hand, five-membered cyclic amines (**7a–c**) afforded not only 4-chloro-2-pyrrolidinoquinazoline **8a** but also the 4-chloro-2-(*N*-substituted 4-chlorobutylamino)quinazolines **9a–c** (Scheme 1). The quotients of products **8a**/**9a–c** depended on the *N*-substituent groups as shown in Table 3: benzyl > allyl > methyl. The structures **8** and **9** were assigned based on their UV and ^{1}H NMR spectral data (Tables 4 and 5) and these data were quite similar to those of compounds **1a**.

Miki reported that the reaction of dione **2** with *N*-substituted cyclic amines in phosphoryl trichloride afforded 4-chloro-2-[(*N*-chloroalkyl)amino]quinazolines.[2a,2c] Moreover, he concluded that the dichloride **5** was not an intermediate in the

Table 1 ^{1}H and ^{13}C NMR chemical shifts, their assignment, and results of COLOC experiments of compound **1a** in $CDCl_3$[a]

	^{1}H									
^{13}C	2.55 (3′-, 5′-H)	3.06 (1″-H)	3.97 (2′-, 6′-H)	5.18 (3″-H)	5.23 (3″-H)	5.91 (2″-H)	7.22 (6-H)	7.54 (8-H)	7.65 (7-H)	7.95 (5-H)
162.49 (C-4)								^4J		^3J
157.51 (C-2)			^3J							
153.54 (C-8a)									^3J	^3J
134.63 (C-7)									^1J	^3J
134.46 (C-2″)		^2J		^2J	^2J					
125.97 (C-5)									^3J	^1J
125.77 (C-8)							^3J	^1J		
123.07 (C-6)							^1J			
116.38 (C-3″)		^3J		^1J	^1J					
116.02 (C-4a)							^3J	^3J		
61.67 (C-1″)				^3J	^3J					
52.82 (C-3′, -5′)	^3J	^3J	^2J							
43.97 (C-2′, -6′)	^2J		^3J							

[a] ^2J, ^3J and ^4J indicate long-range coupling through two, three and four bonds, respectively.



Scheme 1

Table 2 ^{1}H and ^{13}C NMR chemical shifts, their assignment, and results of COLOC experiments of compound **4** in $CDCl_3$[a]

	^{1}H									
^{13}C	2.63 (3′-, 5′-H)	3.07 (1″-H)	3.89 (2′-, 6′-H)	5.19 (3″-H)	5.23 (3″-H)	5.89 (2″-H)	7.39 (6-H)	7.69 (7-H)	7.78 (8-H)	7.84 (5-H)
165.03 (C-4)			^3J						^4J	^3J
156.24 (C-2)										
153.29 (C-8a)								^3J	^2J	^3J
134.29 (C-2″)		^2J		^2J	^2J					
133.05 (C-6)								^1J		^3J
127.75 (C-5)							^3J		^1J	
125.08 (C-7)							^1J			
125.03 (C-8)										^1J
118.30 (3-C″)		^3J		^1J	^1J					
114.47 (C-4a)							^3J		^3J	
61.39 (C-1″)				^3J	^3J					
52.67 (C-3′, -5′) ^3J		^3J	^2J							
49.45 (C-2′, -6′) ^2J			^3J							

[a] ^2J, ^3J and ^4J indicate long-range coupling through two, three and four bonds, respectively.

reaction, based on the observed complete recovery of compound **5** in its reaction with *N*-methylpyrrolidine **7b** in phosphoryl trichloride at 20–25 °C.[2b,2d] Nevertheless, when the reaction of dichloride **5** with *N*-methylpiperidine **7e** was carried out in a mixture of phosphoryl trichloride and 1,4-dioxane in the presence or in the absence of tripropylamine at 100 °C, we obtained compound **8b** in 87% and 79% yield, respectively. Furthermore, reaction of the dichloride **5** with *N*-methylpyrrolidine **7b** at 100 °C in phosphoryl trichloride partially decomposed by water, which was considered to be produced in the course of the chlorination of dione **2** to dichloride **5**, afforded compound **9b** in 30% yield. These results suggested that dichloride **5** was an intermediate in the synthesis of compounds **1**, **8** and **9** (Scheme 2).

It is well known that the 4-position of the dichloride **5** is more reactive than the 2-position for nucleophilic attack by primary or secondary amines.[3] Moreover, it was reported that *N*-substituted cyclic amines reacted at the 4-position of compound **5** in acetone.[4] The above reaction, however, indicated that the 2-position of compound **5** is reactive to attack by tertiary amines.

Further study is necessary to elucidate these interesting phenomena.

In conclusion, the reaction of quinazoline-2,4(1*H*,3*H*)-dione **2** with *N*-substituted six- or seven-membered cyclic amines in combination with phosphoryl trichloride is a useful method for the preparation of 4-chloro-2-(cycloalkylamino)quinazolines.

Table 3 Reactions of quinazoline-2,4(1*H*,3*H*)dione **2** with *N*-substituted cyclic amines in combination with phosphoryl trichloride in a solution of 1,4-dioxane

Amine	Reaction time (t/h)	Product	Isolation yield (%)	Quotient **8**/**9**
3a	1	**1a**	64	
3b	2	**1b**	74	
7a	1	**8a, 9a**	21, 27	0.78
7b	1	**8a, 9b**	3, 37	0.11
7c	2	**8a, 9c**	19, 2	9.50
7d	1	**8b**	56	
7e	1	**8b**	96	
7f	2	**8b**	26	
7g	1	**8c**	54	
7h	1	**8c**	73	
7i	2	**8c**	25	

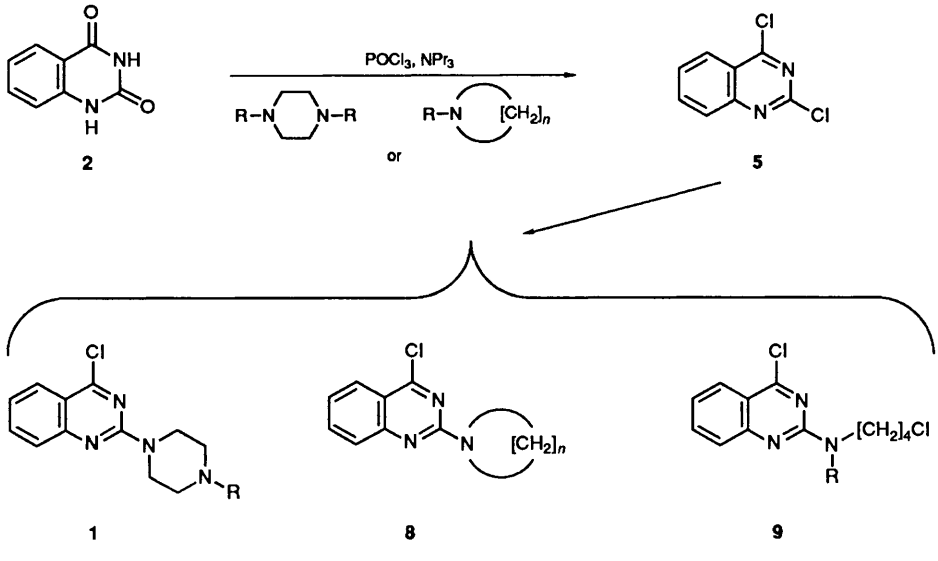
Experimental

M.p.s were measured with a Yamato capillary melting point apparatus, model MP-21, and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer in $CDCl_3$ and tetramethylsilane was used as an internal reference. *J*-Values are given in Hz. Analytical and preparative TLC were performed on silica gel 60 F_{254} precoated plates (No. 5717 and No. 5715, respectively, Merck).

Reaction of Dione **2** *with Several* N-*substituted Cyclic Amines in Combination with Phosphoryl Trichloride.*—The results are summarized in Table 4. As a typical example, the reaction of dione **2** with the diamine **3a** in combination with phosphoryl trichloride is described below. Phosphoryl trichloride (0.92 g, 6.0 mmol) was added to an ice-cooled mixture of quinazoline-2,4(1*H*,3*H*)-dione **2** (0.32 g, 2.0 mmol), 1,4-diallylpiperazine **3a** (0.67 g, 4.0 mmol), and tripropylamine (0.57 g, 4.0 mmol) in a solution of 1,4-dioxane (5 cm^3) and the mixture was heated at 100 °C for 1 h. After being cooled to room temperature, the reaction mixture was dissolved in $CHCl_3$ (30 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.

Table 4 Physical, spectral and analytical data for 2-amino-4-chloroquinazolines **1**, **8** and **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
1a	65–68	MeCN	288 (M^+), 96 (base)	379 (2 800), 248 (31 900)	$C_{15}H_{17}ClN_4$	62.50 (62.39)	5.96 (5.93)	19.49 (19.40)
1b	84–86	MeCN	262 (M^+), 70 (base)	379 (3 300), 248 (36 800)	$C_{13}H_{15}ClN_4$	59.54 (59.43)	5.71 (5.75)	21.29 (21.32)
8a	93–95	MeCN	233 (M^+), 204 (base)	383 (3 000), 248 (28 900)	$C_{12}H_{12}ClN_3$	61.68 (61.67)	5.20 (5.18)	18.02 (17.98)
8b	73–75	MeCN	247 (M^+, base), 164	384 (2 800), 249 (28 700)	$C_{13}H_{14}ClN_3$	63.13 (63.03)	5.71 (5.70)	17.01 (16.96)
8c	oil		261 (M^+, base), 218	386 (2 900), 248 (28 600)	$C_{14}H_{16}ClN_3$	64.17 (64.24)	6.14 (6.16)	15.98 (16.05)
9a	oil		309 (M^+), 232 (base)	381 (3 300), 248 (33 000)	$C_{15}H_{17}Cl_2N_3$	58.14 (58.05)	5.56 (5.52)	13.56 (13.55)
9b	oil		283 (M^+), 206 (base)	383 (3 200), 248 (31 600)	$C_{13}H_{15}Cl_2N_3$	54.69 (54.94)	5.33 (5.32)	14.57 (14.79)
9c	oil		359 (M^+), 91 (base)	382 (3 200), 249 (38 300)	$C_{19}H_{19}Cl_2N_3$	63.54 (63.34)	5.49 (5.32)	11.47 (11.66)



Scheme 2

Table 5 ^{1}H NMR spectral data for 2-amino-4-chloroquinazolines **1**, **8** and **9**. Chemical shifts and coupling constant (Hz, in parentheses).

Compound	5-H ($J_{5,6}$, $J_{5,7}$)	6-H ($J_{5,6}$, $J_{6,7}$, $J_{6,8}$)	7-H ($J_{6,7}$, $J_{7,8}$, $J_{5,7}$)	8-H ($J_{7,8}$, $J_{6,8}$)	Others
1a	7.95 (8.3, 1.4)	7.22 (8.3, 6.8, 1.1)	7.64 (6.8, 8.5, 1.4)	7.54 (8.5, 1.1)	2.55 (4 H, t, *J* 5.1, 3′- and 5′-H_2), 3.06 (2 H, dt, *J* 6.6 and 1.5, 1″-H_2), 3.97 (4 H, t, *J* 5.1, 2′- and 6′-H_2), 5.20 (1 H, dt, *J* 10.2 and 1.5, 3″-H), 5.22 (1 H, dt, *J* 17.0 and 1.5, 3″-H), 5.91 (1 H, ddt, *J* 17.0, 10.2, and 6.6, 2″-H)
1b	7.94 (8.3, 1.4)	7.21 (8.3, 6.8, 1.1)	7.65 (6.8, 8.5, 1.4)	7.54 (8.5, 1.1)	2.34 (3 H, s, NMe), 2.49 (4 H, t, *J* 5.1, 3′- and 5′-H_2), 3.96 (4 H, t, *J* 5.1, 2′-, and 6′-H_2)
8a	7.95 (8.3, 1.4)	7.18 (8.3, 6.7, 1.2)	7.64 (6.7, 8.5, 1.4)	7.56 (8.5, 1.2)	2.01 (4 H, t, *J* 6.8, 3′- and 4′-H_2), 3.68 (4 H, t, *J* 6.8, 2′- and 5′-H_2)
8b	7.93 (8.4, 1.5)	7.18 (8.4, 6.7, 1.2)	7.63 (6.7, 8.6, 1.4)	7.52 (8.6, 1.2)	1.60–1.70 (6 H, m, 3′-, 4′- and 5′-H_2), 3.89 (4 H, t, *J* 5.2, 2′- and 6′-H_2)
8c	7.93 (8.3, 1.4)	7.16 (8.3, 6.5, 1.4)	7.62 (6.5, 8.6, 1.4)	7.57 (8.6, 1.4)	1.52–1.97 (8-H, m, 3′-, 4′-, 5′- and 6′-H_2), 3.84 (4 H, t, *J* 6.0, 2′- and 7′-H_2)
9a	7.96 (8.4, 1.4)	7.21 (8.4, 6.7, 1.2)	7.65 (6.7, 8.5, 1.4)	7.56 (8.5, 1.2)	1.77–1.91 (4 H, m, CH_2CH_2), 3.63 (2 H, t, *J* 6.3, NCH_2), 3.72 (2 H, t, *J* 6.7, CH_2Cl), 4.34 (2 H, dt, *J* 5.6 and 1.3, NCH_2CH) 5.17 (1 H, ddt, *J* 10.2, 1.5 and 1.3, CH_2), 5.21 (1 H, ddt, *J* 8.5, 1.5 and 1.3, CH_2), 5.91 (1 H, ddt, *J* 17.1, 10.2 and 5.6, $CHCH_2$)
9b	7.95 (8.3, 1.5)	7.20 (8.3, 6.8, 1.3)	7.65 (6.8, 8.4, 1.5)	7.56 (8.4, 1.3)	1.78–1.84 (4 H, m, CH_2CH_2), 3.25 (3 H, s, NMe), 3.62 (2 H, t, *J* 6.2, NCH_2), 3.78 (2 H, t, *J* 6.7, CH_2Cl)
9c	7.98 (8.4, 1.4)	7.23 (8.4, 6.8, 1.2)	7.67 (6.8, 8.6, 1.4)	7.56 (8.6, 1.2)	1.79–1.83 (4 H, m, CH_2CH_2), 3.59 (2 H, t, *J* 6.3, NCH_2), 3.70 (2 H, t, *J* 6.8, CH_2Cl), 5.00 (2 H, s, CH_2Ph), 7.25–7.31 (5 H, m, Ph)

Upon preparative TLC (PLC) with hexane–AcOEt (10:1) as developing solvent, followed by recrystallization from MeCN, the residue gave compound **1a** (0.37 g, 64%) as crystals, m.p. 65–68 °C.

Preparation of 4-(4-*Allylpiperazin*-1-*yl*)-2-*chloroquinazoline* **4**.—A solution of 1-allylpiperazine **3a** (0.76 g, 6.0 mmol) in toluene (10 cm^3) was added to a solution of 2,4-dichloroquinazoline **5** (1.00 g, 5.0 mmol) in toluene (10 cm^3). Aq. sodium hydroxide (0.40 g in 2 cm^3) was added and the mixture was stirred at room temperature for 30 min. The organic layer was separated, washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from AcOEt–hexane to give the *title* compound **4** (0.66 g, 46%) as needles, m.p. 90–92 °C (Found: C, 62.5; H, 6.0; N, 19.5. $C_{15}H_{17}ClN_4$ requires C, 62.39; H, 5.93; N, 19.40%); $\delta_H(CDCl_3)$ 2.63 (4 H, t, *J* 5.0, 3′- and 5′-H_2), 3.07 (2 H, dt, *J* 6.6 and 1.2, 1″-H_2), 3.89 (4 H, t, *J* 5.0, 2′- and 6′-H_2), 5.20 (1 H, dt, *J* 10.2 and 1.2, 3″-H), 5.23 (1 H, dt, *J* 17.0 and 1.2, 3″-H), 5.89 (1 H, ddt, *J* 17.0, 10.2, and 6.6, 2″-H), 7.40 (1 H, ddd, *J* 8.4, 6.9 and 1.4, 6-H), 7.69 (1 H, ddd, *J* 8.4, 6.9 and 1.4, 7-H), 7.77 (1 H, dd, *J* 8.4 and 1.4, 8-H) and 7.84 (1 H, dd, *J* 8.4 and 1.4, 5-H); λ_{max}(EtOH)/nm 216 (32 000) and 331 (9 700); *m*/*z* 288 (M^+).

Reaction of 2,4-*Dichloroquinazoline* **5** *with* N-*Methylpiperidine* **7e** *in the presence of Phosphoryl Trichloride*.—Phosphoryl trichloride (0.92 g, 6.0 mmol) was added to an ice-cooled solution of 2,4-dichloroquinazoline **5** (0.40 g, 2.0 mmol), *N*-methylpiperidine **7e** (0.40 g, 4.0 mmol), and tripropylamine (0.57 g, 4.0 mmol) in 1,4-dioxane (5 cm^3), and the mixture was heated at 100 °C for 1 h. After being cooled to room temperature, the reaction mixture was dissolved in $CHCl_3$ (30 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 with hexane–AcOEt (10:1) as developing solvent, followed by recrystallization from MeCN, the residue gave compound **8b** (0.43 g, 87%) as crystals, m.p. 73–75 °C.

Reaction of 2,4-*Dichloroquinazoline* **5** *with* N-*Methylpyrrolidine* **7b** *in the Presence of Phosphoryl Trichloride*.—Water (0.18 cm^3, 10 mmol) was added to ice-cooled phosphoryl trichloride (8 cm^3), and the mixture was stirred at room temperature for 0.5 h. 2,4-Dichloroquinazoline **5** (1.0 g, 5.0 mmol) and *N*-methylpyrrolidine **7b** (3 cm^3) were added to the mixture and the resulting mixture was stirred at 100 °C for 0.5 h. After being cooled to room temperature, the reaction mixture was dissolved in $CHCl_3$ (70 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 with hexane–AcOEt (5:1) as developing solvent, the residue gave compound **9b** (0.35 g, 30%) as an oil. The IR and ^{1}H NMR spectra of the product were identical with those of 4-chloro-2-[*N*-(4-chlorobutyl)-*N*-methylamino]quinazoline **9b** obtained directly from dione **2**.

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