A ONE-POT AND SELECTIVE PREPARATION OF 2-(N-ALKYL-4-CHLOROBUTYL-AMINO)-4-CHLOROQUINAZOLINES

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Abstract —— A new and facile synthesis of 2-(N-alkyl-4-chlorobutylamino)-4-chloroquinazolines by the reaction of 2,4(1H,3H)-quinazolinedione with N-alkylpyrrolidines in phosphoryl chloride is described.

The chlorination of 2,4(1H,3H)-quinazolinedione (1) with phosphoryl chloride in the presence of triethylamine gave 4-chloro-2-diethylaminoquinazoline (3) instead of 2,4-dichloroquinazoline (2). On the other hand, when tripropylamine was used as a base in place of triethylamine, compound 1 was smoothly converted to 2.[1)]

To expand the studies of these reactions, N-alkylpyrrolidines (4) were used in place of triethyl- or tripropylamine as a base, and it was designed to convert the hydroxy group at 2-position in compound 1 to N-alkyl-4-chlorobutylamino group and to prepare 2-(N-alkyl-4-chlorobutylamino)-4-chloroquinazolines (5) in a one-pot selective preparation.

The reaction of 1 with phosphoryl chloride in the presence of N-methylpyrrolidine (4a) was carried out at 80-85 °C for 20 min to give 4-chloro-2-(N-methyl-4-chlorobutylamino)quinazoline (5a) as a yellow oil and 2 as colorless needles (mp 116-118 °C). (Literature[2)]; mp 118 °C).

To make further investigation into this reaction, the study was expanded to the use of other N-alkylpyrrolidines such as N-ethylpyrrolidine (4b), N-propylpyrrolidine (4c), N-butylpyrrolidine (4d), N-sec-butylpyrrolidine (4e) and N-tert-butylpyrrolidine (4f). The results were summarized in Table I.

As shown in Table I, it has become apparent that the reaction of 1 with phosphoryl chloride in the presence of N-alkylpyrrolidines proceeds by a von Braun type reaction[3)] through the formation of a quaternary ammonium salt, which decomposes to give the new tertiary amines, 2-(N-alkyl-4-chlorobutylamino)-4-chloroquinazolines (5).

There are two possible reaction pathways to decompose the quaternary ammonium

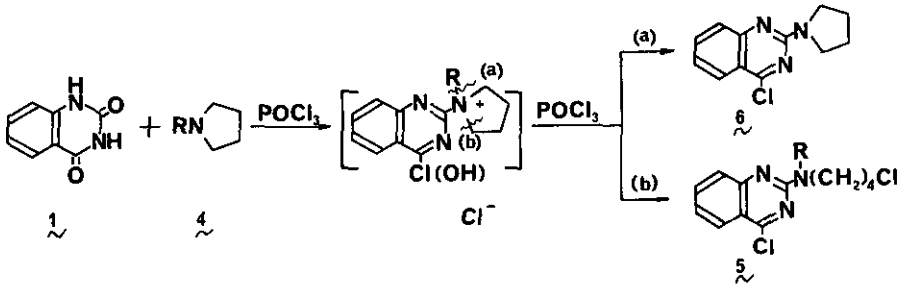
Table I Yields (%) of Isolated Products from the Reaction of 1 with $POCl_3$ in the Presence of 4

R	4	2	5
Me	4a	3.3	(5a) 77.3
Et	4b	17.9	(5b) 58.7
Pr	4c	19.5	(5c) 59.4
Bu	4d	48.5	(5d) 34.7
sec-Bu	4e	84.6	(5e) trace
tert-Bu	4f	88.5	(5f) trace

salt, (a): the cleavage of N-alkyl group, and (b): the cleavage of pyrrolidine ring. On the results of these studies, the isolated product was mainly 5, 4-chloro-2-pyrrolidinoquinazoline (6) was not isolated.

When the bulky N-alkylpyrrolidine such as 4e or 4f was used as a base in the phosphoryl chloride chlorination of 1, compound 2 was mainly obtained. However, when the amine such as 4a, 4b, 4c or 4d was used, both of 2 and 5 were obtained.

It was found that the products ratio depended on the bulkiness of N-alkylpyrrolidines used. The introduction of N-alkyl-4-chlorobutylamino group to quinazoline ring has not been reported in the literature.



1 4 6 5

General procedure ---- N-Alkylpyrrolidine (15 ml) was added to a mixture of 1 (5.0 g, 0.031 mol) and phosphoryl chloride (70 ml) and the mixture was stirred at 80-85°C for 20 min. After the excess of phosphoryl chloride and N-alkylpyrrolidine were evaporated off in vacuo, the residue was disolved in 100 ml of chloroform. The chloroform layer was washed with water, satd. $NaHCO_3$ aq., and then satd. NaCl aq. successively. After dring over $MgSO_4$, the chloroform layer was concentrated to

give a yellow oil. The residue was subjected to the silica gel column chromatography. The elution with tetrachloromethane gave 2-(N-alkyl-4-chlorobutylamino)-4-chloroquinazoline 5 as a yellow oil and 2 as colorless needles.

The results were summarized in Table II.

Table II 2-(N-Alkyl-4-chlorobutylamino)-4-chloroquinazoline

Compound No.	N_d^{20}	UV_{max}^{EtOH} nm(ε)	MS m/e(M^+)	PMR(δ: ppm in $CDCl_3$)
5a	1.6147	247(28700) 385(3300)	283,285,287.	1.57-1.92(4H,m,CH_2),3.16(3H, s,CH_3),3.37-3.19(4H,m,CH_2), 6.85-7.95(4H,m,Ar-H).
5b	1.5987	247(31900) 384(3200)	297,299,301.	1.19(3H,t,CH_3),1.59-1.98(4H, m,CH_2),3.37-3.88(6H,m,CH_2), 6.80-7.90(4H,m,Ar-H).
5c	1.5960	247(30600) 384(3100)	311,313,315.	0.91(3H,t,CH_3),1.30-2.13(6H, m,CH_2),3.34-3.72(6H,m,CH_2), 6.80-7.90(4H,m,Ar-H).
5d	1.5862	247(29400) 384(3100)	325,327,329.	0.93(3H,t,CH_3),1.40-2.15(8H, m,CH_2),3.32-3.85(6H,m,CH_2), 6.82-7.91(4H,m,Ar-H).

REFERENCES AND NOTES

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4) The structure of all new compounds was established from their analytical data of PMR, UV and MS spectra in addition to the elementalanalyses for C, H and N.

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