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THE REACTION OF 2-CHLORO-4-METHYLTHIOQUINAZOLINE WITH ALKYLAMINES IN DIMETHYLFORMAMIDE

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Abstract —— The reaction of 2-chloro-4-methylthioquinazoline with alkylamines in dimethylformamide afforded 2,4-bis(methylthio)-, 2-alkylamino-4-methylthio-, 4-alkylamino-2-chloro-, 4-alkylamino-2-methylthio-, and 2,4-bis(alkylamino)quinazoline. The relative easiness of displacement of the chlorine and/or the methylthio group in 2-chloro-4-methylthioquinazoline depended on the bulkiness of alkylamines.

In the course of researches on quinazoline derivatives showing herbicidal activity, the displacement reaction of 2-chloro-4-methylthioquinazoline[1](1) with alkylamines has been studied.

The reaction of 1 with ethylamine in dimethylformamide at 80-85°C for 20 min gave 2,4-bis(methylthio)quinazoline[2](2), 2-ethylamino-4-methylthioquinazoline (3a) as colorless needles (mp 79-80°C), 2-chloro-4-ethylaminoquinazoline[3](4a), 4-ethylamino-2-methylthioquinazoline (5a) as colorless needles (mp 149-150°C), and a trace amount of 2,4-bis(ethylamino)quinazoline[3](6a).

Compounds 3a and 5a had the same molecular formula, $C_{11}H_{13}N_3S$, and their PMR spectra indicated the presence of an ethylamino (δ: 1.12, 3.30-3.80 for 3a and 1.22, 3.40-3.87 for 5a) and a methylthio (δ: 2.56 for 3a and 2.57 for 5a).

In order to differentiate clealy the structures of 3a from 5a, these compounds were desulfurized with Raney nickel, respectively. Compound 3a afforded 2-ethylaminoquinazoline (7) as colorless needles (mp 96-97°C), on the other hand 5a gave 4-ethylaminoquinazoline (8) as colorless needles (mp 149-150°C).[3] From these data, the structure of 5a was confirmed to be 4-ethylamino-2-methylthioquinazoline, 7 and 3a were ascribed to 2-ethylaminoquinazoline and 2-ethylamino-4-methylthioquinazoline as isomeric compounds of 8 and 5a, respectively.

Compound 3a showed characteristic UV absorption maximum at 362 nm, on the other hand 5a had an absorption at 328 nm. By comparing their UV spectra, the isomeric relation between 2-alkylamino-4-methylthioquinazolines (3) and 4-alkylamino-2-methylthioquinazoline (5) can easily and unequivocally be differentiated.

To investigate the scope and limit of this type of reaction, the study was expanded to the use of other alkylamines (e.g., butylamine, dimethylamine, dipropylamine and diisopropylamine). The results were summarized in Table I and II.

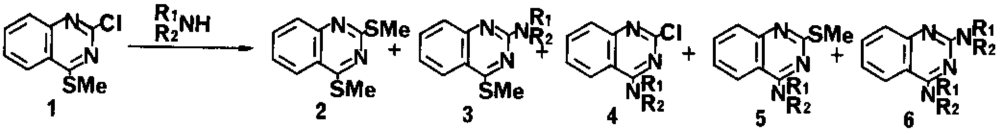


Table I The Reaction of 2-Chloro-4-methylthioquinazoline with Alkylamines

Amines	Reaction Conditions		Products and Yield (%)				
R^1R^2NH	Time (h)	Temp (°C)					
$EtNH_2$	1/3	85	2(2)	3a(38)	4a(54)	5a(3)	6a(1)
$BuNH_2$	1/3	85	2(6)	3b(34)	4b(33)	5b(9)	6b(3)
Me_2NH	1/3	85	2(5)	3c(26)	4c(35)	5c(13)	6c(1)
Pr_2NH	3	reflux	-	3d(92)	-	-	-
iso-Pr_2NH	3	reflux	-	-	-	-	-

Table II UV Absorption Maxima of 3 and 5 in Ethanol

3	nm(εmax)	5	nm(εmax)
3a	362(6570)	5a	328(8320)
3b	365(5340)	5b	330(6870)
3c	370(4420)	5c	337(7400)

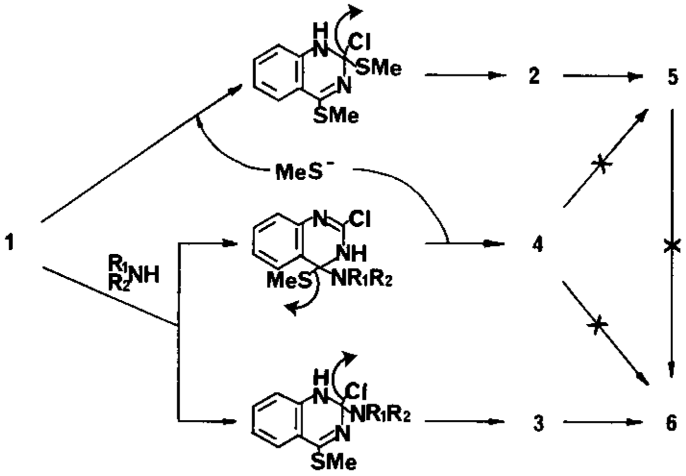
Primary amines or dimethylamine reacted with the chlorine at 2-position and/or the methylthio group at 4-position in quinazoline ring to afford 2- and/or 4-substituted quinazolines. Dipropylamine reacted with the chlorine at 2-position to give 2-dipropylamino-4-methylthioquinazoline 3d selectively. A more bulky amine, diisopropylamine, did not react with 1.

Results of these studies show that the reaction of 1 with alkylamines is affected to a great extent by the bulkiness rather than the basicity of alkylamines.

Some reactions were attempted to clarify the mechanism for the formation of the compounds 2-6. The reaction of 2 with butylamine in dimethylformamide at 80-

85°C gave mainly 5b. The reaction of 3b with butylamine gave chiefly 6b, however 4b did not react with butylamine or methylmercaptide anymore. Compound 5 did not react with butylamine.

On the basis of these results, a plausible mechanism for the reaction of 1 with alkylamines is shown in Chart 1.



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3) J.R.Geigy Akt.-Ges., Brit.Pat., 822069(1959). Chem.Abstr., 55, 2005d(1960).

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

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