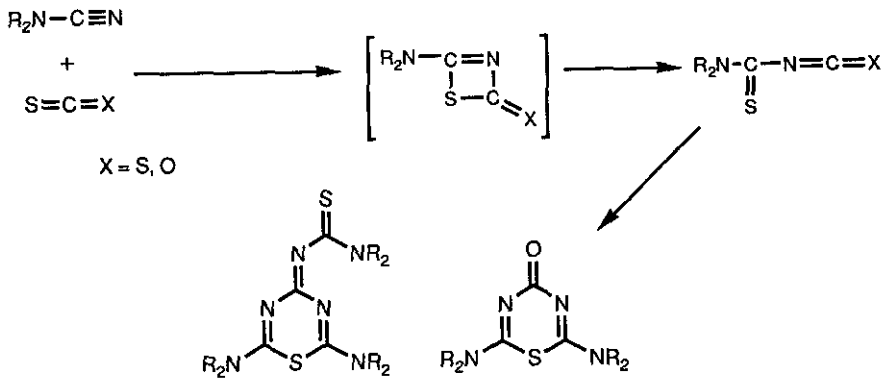
SYNTHESIS OF NOVEL 4-ARYLAMINO-2-DIALKYLAMINO-QUINAZOLINES UNDER HIGH PRESSURE

Akihiro Oishi,* Masahiko Yasumoto,* Midori Goto,
Tohru Tsuchiya , Isao Shibuya, and Yoichi Taguchi

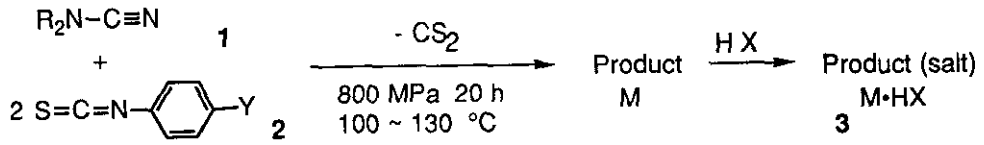
National Institute of Materials and Chemical Research, Higashi 1-1, Tsukuba, Ibaraki 305, Japan

Abstract - Novel 4-arylamino-2-dialkylaminoquinazolines (salt) were obtained in good yields by reaction of dialkylcyanamides with 4-substituted phenyl isothiocyanates at 800 MPa .
The molecular structure of 6-chloro-4-(4'-chlorophenylamino)-2-dimethylaminoquinazoline 2"-chlorobenzoate (**3 e**) was determined by X-ray crystallographic analysis.

We have been studying the reactions of dialkylcyanamides (**1**) with heterocumulenes, which have C-S double bond, and we have reported that the reactions of **1** with carbon disulfide or carbon oxosulfide at 500 ~ 800 MPa give novel 1,3,5-thiadiazine derivatives.[1,2] These reactions do not occur at ambient pressure. In these reactions, we assumed that thiocarbamoyl isothiocyanates and thiocarbamoyl isocyanates were formed as intermediates. The process is shown in Scheme 1.
During the course of our study we found that **1** react with 4-substituted phenyl isothiocyanates (**2**), which were other type of heterocumulenes with C-S double bond, to give novel 4-arylamino-2-dialkylaminoquinazoline salts (**3**) in good ~ moderate yields.[3] In this paper, we describe result of the reactions of **1** with **2** , X-ray crystallographic analysis of 6-chloro-4-(4'-chlorophenylamino)-2-dimethylaminoquinazoline 2"-chlorobenzoate (**3 e**), and mechanism of affording **3**.



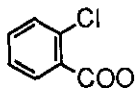
1,3,5-Thiadiazine Scheme 1.



Scheme 2.

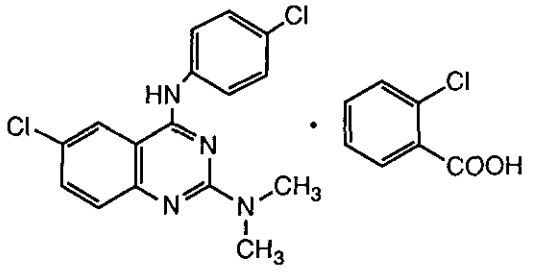
The reaction conditions and yields are summarized in Table 1. Each of the compounds was given in good ~ moderate yield.

Table 1. Reaction conditions and Yields of **3**

Run	R_2N of **1**	Y of **2**	X	Reaction conditions [a] Molar ratio (**1**:**2**)	Reaction conditions [a] Temperature (°C)	Product	Yield (%) [b]
1	Me_2N–	H	Cl	1:1	100	**3a**	86
2		H	Cl	3:1	130	**3b**	78
3		H	Cl	3:1	130	**3c**	62
4		H	Cl	3:1	130	**3d**	51
5	Me_2N–	Cl		1:1	100	**3e**	74

a) 800 MPa, 20 h. b) Isolated yield based on **2**.

From our previous study,[1,2] the products were expected to be 1,3,5-thiadiazine derivatives (**1**:**2** = 2:1 or 3:1 adducts), but elemental and mass analyses indicated that the products were not thiadiazine derivatives. It was found that the products are composed from one molecule of **1** and two molecules of **2** with elimination of one molecule of CS_2. Unfortunately, the products were poorly soluble in solvents such as methanol and chloroform, their nmr spectra could not be measured. To confirm the molecular structure, the X-ray crystallographic analysis of **3e** was carried out. Figure 1 shows molecular structure of **3e**. It was found that **3e** had a quinazoline ring.



3e

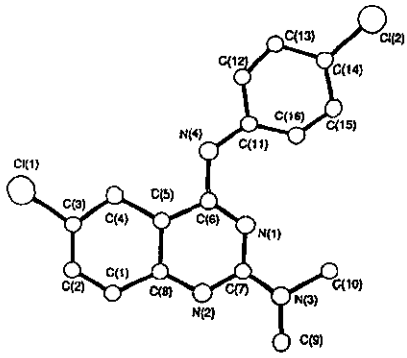


Figure 1. The molecular structure of quinazoline part of **3e**.

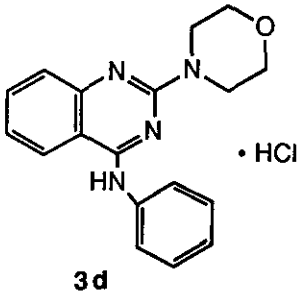
Next we examined effects of reaction pressure and temperature. The results are shown in Table 2. Yields were determined by hplc analysis. At atmospheric pressure, **3d** was not obtained (Run 1).

Table 2. Effects of Pressure and Temperature on the Yield of **3d**[a)]

Run	Pressure (MPa)	Temperature (°C)	Yield[b)] (%)
1	0.1	100	0
2	200	100	16.1
3	400	100	37.0
4	800	100	66.5
5	800	40	0.7
6	800	70	8.5
7	800	130	78.5

a) **1d** 2 mmol, **2a** 2 mmol, reaction time 20 h.

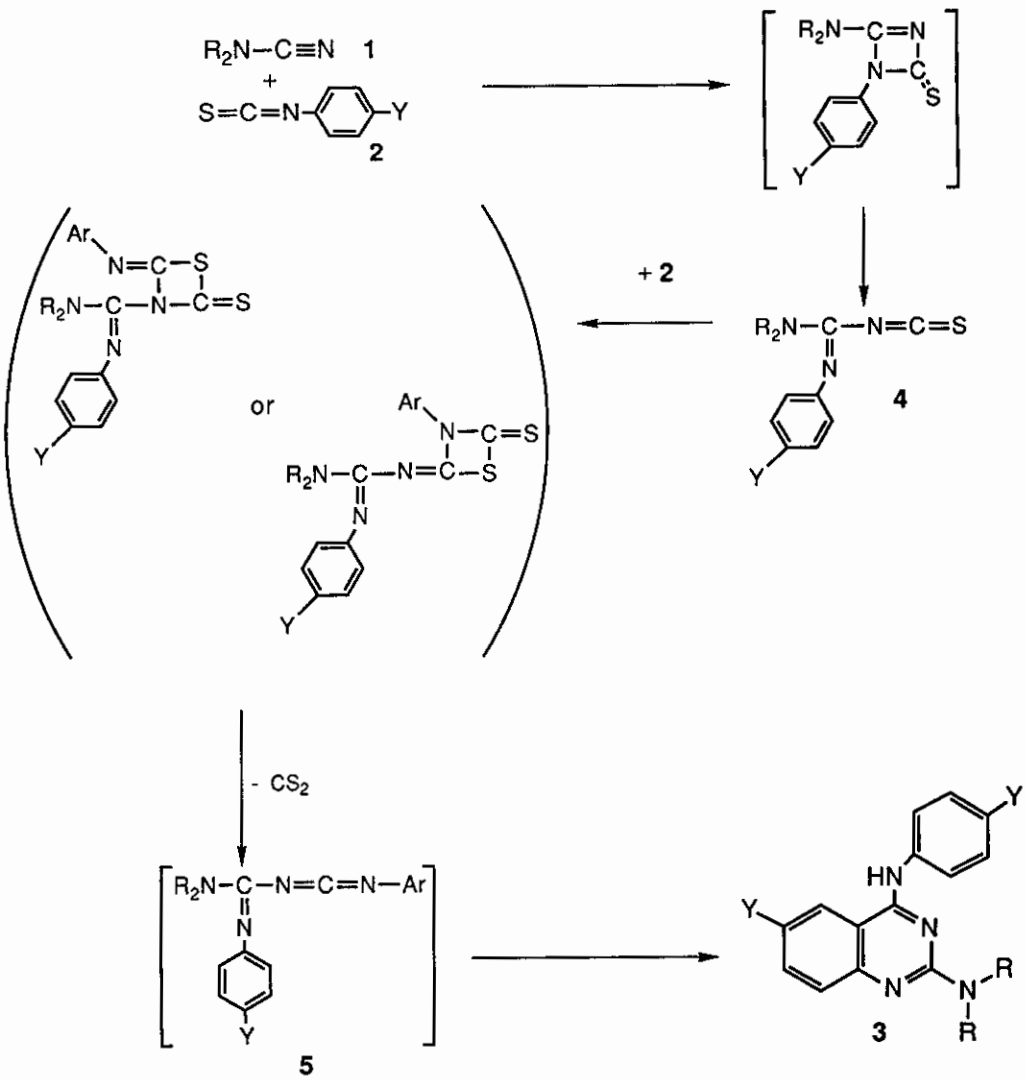
b) Determined by hplc.



3d

At 100 °C, the yield increased proportionally as reaction pressure rose. At 40 °C, 800 MPa, **3d** was little obtained (Run 5). The yield increased dramatically as reaction temperature rose, but it was saturated around at 100 °C. These results suggest that formation of **3** needs applied pressure and increasing of yields of **3** needs higher temperature.

Although the mechanism of the reaction is not clear yet, the process of pathway affording **3** clearly involves repeated cycloaddition-retroaddition, as shown in the previous works dealing with CS_2[1,4] and COS,[2] followed by migration of either ortho-hydrogen in phenyl group. The pathway affording



Scheme 3.

3 was summarized in Scheme 3. In this case, imidoyl isothiocyanates (**4**) are formed at the initial stage. It is described that **4** react with **2** to give 4-arylamino-2-dialkylaminoquinazolines.[5] Similarly *N*-aryl-*N'*-(*N*-aryldialkylaminoimidoyl)carbodiimide (**5**), which is afforded by cycloaddition and elimination of CS_2 from **4**, forms quinazoline ring. A similar formation of quinazoline ring from *N*-phenyl-*N'*-(*N*-phenylbenzimidoyl)carbodiimide at ordinary pressure is also known.[6]

The reaction is useful for convenient preparation of **3**. Previous methods for preparing **3** are reported by the substitution of chlorine in 2,4-dichloroquinazoline,[7] 4-chloroquinazoline[8] with reactive amines, by the reaction of chloroformamidines with phenylcyanamides,[9] and by the reaction of imidoyl isothiocyanates with substituted phenyl isothiocyanates.[5]

In conclusion, we described that novel 4-arylamino-2-dialkylaminoquinazolines (salt) were obtained in good yields by reaction of 4-substituted phenyl isothiocyanate with dialkylcyanamides under high pressure. This synthetic method is useful for preparing quinazoline rings.

EXPERIMENTAL SECTION

Melting points were determined by a Mettler FP82 apparatus. Ir spectra were recorded on a JASCO FT/IR 5300 spectrophotometer. Mass spectra were measured with a SHIMADZU GCMS-QP2000A mass spectrometer. Hplc were performed with a SHIMADZU LC-5A Liquid chromatography with a HITACHI L-4000 UV Detector using a Inertsil ODS column. Triphenylbenzene was used as an internal standard. High pressure reaction apparatuses used were original.[10] Reagents and solvents were purchased and used without any purification.

Reaction of dialkylcyanamides (1) with 4-substituted phenyl isothiocyanate (2); General procedure. A mixture of **1** and **2** was sealed in a flexible tube. The tube was placed in a reaction vessel and pressurized at 800 MPa for 20 h. The reaction mixture was washed with diisopropyl ether (20 ml). A mixture of this residue and a solution of concentrated hydrochloric acid (1 ml) in ethanol (10 ml) was heated under reflux for 0.5 h and allowed to cool to room temperature. The precipitate that formed was collected, washed with acetone and was dried under a reduced pressure. And then the product was recrystallized from acetonitrile. Reaction conditions and the yields of the products are shown in Table 1.

2-Dimethylamino-4-phenylaminoquinazoline hydrochloride (3a). White powder ; mp 288 °C; ms m/z 265 [(M^+ - Cl);100%], 250, 235, 220,77; ir (KBr) 1639, 1605, 1555, 1395, 766, 756 cm^{-1}; Anal. Calcd for $C_{16}H_{17}N_4Cl$: C, 63.88; H, 5.70; N, 18.63. Found: C, 63.74; H, 5.63; N, 18.43.

4-Phenylamino-2-(1-pyrrolidinyl)quinazoline hydrochloride (3b). White flake ; mp >300 ° C; ms m/z 291 (M^+ - Cl), 262(100%), 220, 77; ir (KBr) 1642, 1605, 1553, 1420, 768, 756 cm^{-1}; Anal. Calcd for $C_{18}H_{19}N_4Cl$: C, 66.14; H, 5.86; N, 17.15. Found: C, 65.97; H, 5.80; N, 17.00.

4-Phenylamino-2-piperidinoquinazoline hydrochloride (3c). White powder ; mp 250 °C; ms m/z 305 [(M^+ - Cl);100%], 276, 262, 250, 221, 77; ir (KBr) 1638, 1601, 1553, 1414, 764 cm^{-1}; Anal. Calcd for $C_{19}H_{21}N_4Cl$: C, 66.95; H, 6.21; N, 16.44. Found : C, 66.68; H, 6.19; N, 16.28.

2-Morpholino-4-phenylaminoquinazoline hydrochloride (3d). White flake ; mp 267 °C;ms m/z 307 (M^+ - Cl), 276(100%), 262, 250, 220, 138, 77; ir (KBr) 1640, 1603, 1551, 1416, 1121, 764 cm^{-1} ; Anal. Calcd for $C_{18}H_{19}N_4OCl$: C, 63.06; H, 5.58; N, 16.35. Found: C, 62.82; H, 5.52; N, 16.48.

6-Chloro-4-(4'-chlorophenylamino)-2-dimethylaminoquinazoline 2"-chlorobenzoate (3e). Experimental procedure was same as described above with the exception of dealing with a 2-chlorobenzoic acid instead of a hydrochloric acid. White prism ; mp 189 °C; ms m/z 333 [(M^+ - 2-ClC_6H_4COOH); 100%], 318, 304, 289, 255, 111[(2-ClC_6H_4)+], 75; ir (KBr) 1649, 1603, 1588, 1547, 1491, 1431, 1389, 829, 752 cm^{-1}; Anal. Calcd for $C_{23}H_{19}N_4O_2Cl_3$: C, 56.40; H, 3.91; N, 11.44. Found: C, 56.38; H, 3.85; N, 11.42.

X-Ray Analysis of 3e. Crystal data $C_{16}H_{14}N_4Cl_2$•2-ClC_6H_4COOH, *Mw* = 489.8, monoclinic, *space group* $P2_1/a$, a = 12.75(1), b = 29.83(1), c = 13.71(1) Å, β = 108.06(3), V = 4690(6) Å^3, Z = 8, D_C = 1.31 g cm^{-3}. Cell parameters and data collection were performed with graphite monochromated Cu-K_a(λ = 1.5418 Å) radiation on an Enrauf-Nonius CAD4 diffractometer. Crystal size: (0.1 × 0.1 × 0.5 mm). The empirical corrections for absorption (Y scan) were done.

6500 reflections were obtained in the range $4° \leq 2\theta \leq 120°$ and scan width $Dw = (1.4 + 0.15\tan\theta)$. 1924 independent reflections ($|F_0| \geq 3\sigma|F_0|$) were used for the analysis. The structure was solved by MULTAN 78 program.[11] The structure was refined by full matrix least-squares methods. The final agreement factors were $R = 0.16$ ($\omega = 1.0$). All computations were performed on a FACOM M-380 computer using UNICS III system.[12]

REFERENCES AND NOTES

1. T. Tsuchiya, M. Yasumoto, I. Shibuya, and M. Goto, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1218.
2. M. Yasumoto, T. Tsuchiya, Y. Taguchi, I. Shibuya, K. Yonemoto, and M. Goto, *Chem. Lett.*, **1991**, 1229.
3. The free base of the products M could not be crystallized. But dealing with acid, the product (salt) could be easy purified. And crystal of **3 e** for X-ray crystallography was obtained.
4. T. Tsuchiya, M. Yasumoto, I. Shibuya, Y. Taguchi, K. Yonemoto, and M. Goto, *Chem. Lett.*, **1990**, 1423.
5. S. Stankovsky and A. Martvon, *Collect. Czech. Chem. Commun.*, 1980, **45**, 1079.
6. J. Goerdeler and H. Lohmann, *Chem. Ber.*, 1977, **110**, 2996.
7. B. Tadeusz and D. Wojciech, *Diss. Pharm. Pharmacol.*, 1970, **22**, 117.
8. H. C. Scaraborough, B. C. Lawes, J. L. Minelli, and J. L. Compton, *J. Org. Chem.*, 1962, **27**, 957.
9. W. Ried, N. Kothe, R. Schweitzer, and A. Hole, *Chem. Ber.*, 1976, **109**, 2921.
10. M. Kurabayashi, K. Yanagiya, and M. Yasumoto, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 3413.
11. P.Main, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declerg, and M. M. Woolfson, "MULTAN 78. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data." Univs. of York, England, and Louvain, Belgium (1978).
12. T. Sakurai and K. Kobayashi, *Rikagaku Kenkyusho Hokoku*, 1979, **55**, 69.

Received, 13th May, 1994