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A CONVENIENT SYNTHESIS OF 4-AMINOQUINAZOLINE DERIVATIVES

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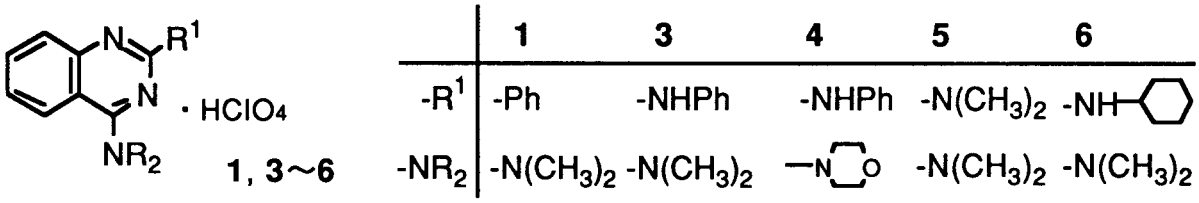
Abstract - 4-(*N*,*N*-Disubstituted amino)-2-substituted quinazoline derivatives (**1** - **9**) were newly synthesized through cyclodesulfurization of *N*-thiocarbonyl-arylamines with silver perchlorate in the presence of *N*,*N*-disubstituted cyanamides.

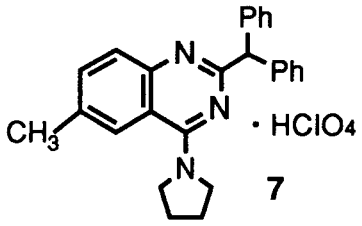
It has been reported that 4-aminoquinazoline derivatives have various bioactivities such as antimalarial effects,[1] inhibitors of the gastric (H^+/K^+)-ATPase,[2] atrial natriuetic peptide receptor modulators,[3] insecticidal and acaricidal activities.[4] Although their some synthetic methods are also known,[5-7] there is a strong demand to develop novel and convenient their synthetic methods in order to research on such functionalities further. Meanwhile, we have been developing the organic synthesis through desulfurization of various thiocarbonyl compounds by silver salt.[8-12] We here wish to report on a synthetic method of 4-(*N*,*N*-disubstituted amino)-2-substituted quinazoline derivatives through cyclodesulfurization of *N*-thiocarbonylarylamines, such as 1-aryl-3-substituted 2-thiourea, 1-aryl-3-disubstituted 2-thiourea, and *N*-thioacylarylamine with silver perchlorate in the presence of *N*,*N*-disubstituted cyanamide.

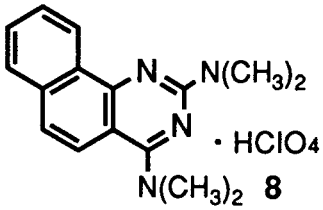
We first examined the reaction of thiobenzanilide with 2.4 eq mol of silver perchlorate in the presence of excess dimethylcyanamide at 130 ^{o}C for 1 h. The resulting crude product was purified by recrystallization from methanol to give 4-(*N*,*N*-dimethylamino)-2-phenylquinazolinium perchlorate (**1**) in 85% yield, while neutralization of **1** with aq. NaOH afforded known 4-(*N*,*N*-dimethylamino)-2-phenylquinazoline (**2**).[5] Other 4-(*N*,*N*-disubstituted amino)-2-substituted quinazolinium perchlorates (**3** - **8**) were obtained as the same manner by the treatment of an *N*-thiocarbonylarylamine with silver perchlorate in the presence of a

N,*N*-disubstituted cyanamide, respectively.

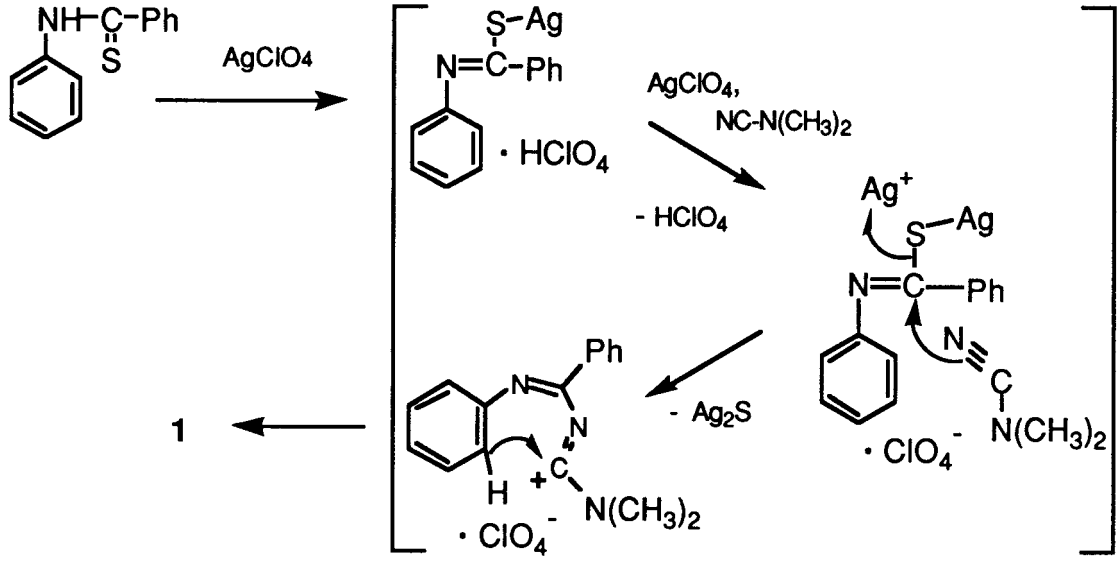
In ^{13}C NMR spectra of **1**, **3** - **8**, they had commonly two signals around 150 and 160 ppm, assignable to 2-C and 4-C of quinazolinium ring, and in their IR spectra three strong absorptions in the range from 1540 to 1640 cm^{-1}, assignable to C=C or C=N bond, and an absorption around 1110 cm^{-1} (perchlorate) also appeared, respectively. This fact showed that they have the same skeletal structure.







A plausible mechanism to form **1** was speculated as shown below. Thiobenzanilide and silver perchlorate initially form an adduct, and then it is simultaneously subjected to attack of another silver ion on the sulfur atom and nucleophilic addition of dimethylcyanamide to the imino carbon to afford quinazoline ring with eliminating Ag_2S. This mechanism can be considered to be similar as the reaction of *N*-phenylbenzimidoyl chloride with $TiCl_4$ in *N*,*N*-disubstituted cyanamide.[5, 13]



In conclusion, it was thus found that 4-(*N*,*N*-disubstituted amino)-2-substituted quinazoline derivatives are

newly synthesized in one pot through cyclodesulfurization of *N*-thiocarbonylarylamines by silver perchlorate in the presence of *N*,*N*-disubstituted cyanamides.

EXPERIMENTAL

Materials. Silver perchlorate, 1,3-diphenyl-2-thiourea, thiobenzanilide, and *N*,*N*-disubstituted cyanamides were purchased from the usual suppliers and used as they were. Diphenylacetothiocarbo-4'-toluide was prepared by treating the corresponding carboamide with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson Reagent). 1-Aryl-3-substituted 2-thioureas and 1-aryl-3-disubstituted 2-thioureas were obtained by the reaction of arylisothiocyanate with primary or secondary amines.

Melting points were determined by a Mettler FP82 apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR 5300 spectrophotometer using KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300BB spectrometer using TMS as an internal standard.

4-(*N*,*N*-Dimethylamino)-2-phenylquinazolinium perchlorate (**1**).

To a dimethylcyanamide solution (4 mL) of thiobenzanilide (213 mg, 1 mmol) silver perchlorate (500 mg, 2.4 mmol) was added and the mixture was heated to 130 ºC for 1 h. After removing silver sulfide by filtration and evapolating dimethylcyanamide, the resulting residue was recrystallized from methanol to give **1**. Yield 297 mg (85%), mp 218 °C; ^{1}H NMR δ = 3.69 (*s*, 6H, $N(CH_3)_2$), 7.68 - 7.80 (*m*, 4H), 7.98 - 8.07 (*m*, 2H), 8.25 - 8.43 (*m*, 3H); ^{13}C NMR δ = 42.51 ($N(CH_3)_2$), 111.84, 119.40, 126.85, 128.06, 129.11, 129.27, 131.28, 133.55, 135.50, 141.14, 154.81, 161.33; IR ν 3260, 1620, 1606, 1566, 1375, 1111, 769 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_3O_4Cl$: C, 54.94; H, 4.61; N, 12.01. Found: C, 55.12; H, 4.65; N, 11.91.

According to the above-mentioned method, in a disubstituted cyanamide (4 mL) an *N*-thiocarbonylarylamine (1 mmol) was treated with silver perchlorate (2.4 mmol) to give 4-(*N*,*N*-disubstituted amino)-2-substituted quinazolinium perchlorates (**3** - **8**). The *N*,*N*-disubstituted cyanamide, *N*-thiocarbonylarylamine, the yield, and their characterization data are shown below.

4-(*N*,*N*-Dimethylamino)-2-anilinoquinazolinium perchlorate (**3**).

Dimethylcyanamide, 1,3-diphenyl-2-thiourea, yield 248 mg (68%), mp 194 °C; ^{1}H NMR δ = 3.49 (*s*, 6H), 7.21 - 7.26 (*m*, 1H), 7.42 - 7.64 (*m*, 6H), 7.81 - 7.87 (*m*, 1H), 8.22 - 8.25 (*m*, 1H), 10.02 (*s*, 1H), 12.09 (*br s* 1H); ^{13}C NMR δ = 35.46, 42.29, 110.63, 117.75, 122.62, 124.02, 125.15, 128.06, 129.19,

134.94, 137.09, 141.14, 149.64, 162.05; IR ν 3325, 1635, 1593, 1564, 1386, 1105, 756 cm^{-1}. Anal. Calcd for $C_{16}H_{17}N_4O_4Cl$: C, 52.68; H, 4.70; N, 15.36. Found: C, 52.69; H, 4.69; N, 15.70.

2-Anilino-4-morpholinoquinazolinium perchlorate (**4**).

Morpholine-4-carbonitrile, 1,3-diphenyl-2-thiourea, yield 354 mg (87%), mp 281 °C; ^{1}H NMR δ = 3.77 - 3.80 (*m*, 4H), 4.03 - 4.06 (*m*, 4H), 7.22 - 7.30 (*m*, 1H), 7.41 - 8.03 (*m*, 8H), 10.18 (*s*, 1H), 12.28 (*br s*, 1H); ^{13}C NMR δ = 49.43, 65.88, 110.32, 118.29, 122.97, 124.17, 125.43, 127.22, 128.91, 129.26, 135.21, 136.91, 150.44, 162.85; IR ν 3339, 1631, 1593, 1541, 1358, 1114, 758 cm^{-1}. Anal. Calcd for $C_{18}H_{19}N_4O_5Cl$: C, 53.14; H, 4.71; N, 13.77. Found: C, 53.31; H, 4.68; N, 13.75.

2,4-Bis(*N*,*N*-dimethylamino)quinazolinium perchlorate (**5**).

Dimethylcyanamide, dimthylthiocarbamoylanilide, yield 215 mg (68%), mp 293 °C; ^{1}H NMR δ = 3.26 (s, 6H), 3.47 (s, 6H), 7.38 - 7.42 (m, 1H), 8.16 - 8.19 (m, 1H), 11.52 (s, 1H); ^{13}C NMR δ = 37.86, 42.30, 110.00, 117.69, 123.99, 128.08, 134.87, 141.69, 151.12, 161.07; IR ν 3298, 1637, 1601, 1556, 1383, 1109, 761 cm^{-1}. Anal. Calcd for $C_{12}H_{17}N_4O_4Cl$: C, 45.50; H, 5.41; N, 17.69. Found: C, 45.26; H, 5.25; N, 17.92.

4-(*N*,*N*-Dimethylamino)-2-cyclohexylaminoquinazolinium perchlorate (**6**).

Dimethylcyanamide, 1-cyclohexyl-3-phenyl-2-thiourea, yield 340 mg (92%), mp 190 °C; ^{1}H NMR δ = 1.30 - 1.93 (*m*, 10H), 3.47 (*s*, 6H), 3.87 (*br s*, 1H), 7.35 - 7.81 (*m*, 3H), 8.16 - 8.18 (*m*, 1H), 8.44 (*br s*, 1H), 11.59 (*br s*, 1H); ^{13}C NMR δ = 24.38, 24.93, 31.92, 42.01, 49.18, 50.10, 117.25, 123.49, 128.02, 134.71, 141.16, 150.65, 161.83; IR ν 3337, 2932, 1637, 1599, 1562, 1394, 1113, 760 cm^{-1}. Anal. Calcd for $C_{16}H_{23}N_4O_4Cl$: C, 51.82; H, 6.25; N, 1511. Found: C, 51.89; H, 6.28; N, 15.07.

2-Diphenylmethyl-4-pyrrolidino-6-methylquinazolinium perchlorate (**7**).

Pyrrolidine-1-carbonitrile, Diphenylthioaceto-4-toluide, yield 360 mg (75%), mp 223 °C; ^{1}H NMR δ = 1.97 - 2.01 (*m*, 4H), 2.50 (*s*, 3H), 3.95 (*br s*, 4H), 5.63 (*s*, 1H), 7.25 - 7.47 (*m*, 11H), 7.65 - 7.77 (*m*, 2H), 8.16 (*s*, 1H); ^{13}C NMR δ = 21.09, 24.72, 51.75, 56.79, 113.01, 121.22, 126.12, 127.22, 128.51, 129.11, 136.07, 136.39, 140.45, 158.14, 161.51; IR ν 3256, 1612, 1582, 1554, 1336, 1113, 739 cm^{-1}. Anal. Calcd for $C_{26}H_{26}N_3O_4Cl$: C, 65.06; H, 5.46; N, 8.76. Found: C, 65.25; H, 5.22; N, 8.75.

2,4-Bis(*N*,*N*-dimethylamino)-7,8-benzoquinazolinium perchlorate (**8**).

Dimethylcyanamide, 1,1-dimethyl-3-(1-naphthyl)-2-thiourea, yield 205 mg (56%), mp 286 °C; ^{1}H NMR δ = 3.35 (*s*, 6H), 3.46 (*s*, 6H), 7.77 - 7.88 (*m*, 3H), 8.01 - 8.11 (*m*, 2H), 8.75 - 8.78 (*m*, 1H); ^{13}C NMR δ =

35.91, 37.98, 41.84, 106.43, 122.57, 123.13, 123.76, 127.15, 128.46, 130.21, 134.96, 152.19, 162.20; IR ν 3398, 2935, 1637, 1593, 1562, 1379, 1091, 769 cm^{-1}. Anal. Calcd for $C_{16}H_{19}N_4O_4Cl$: C, 52.54; H, 4.96; N, 15.32. Found: C, 52.77; H, 4.93; N, 15.11.

4-(*N*,*N*-Dimethylamino)-2-phenylquinazoline (2) by neutralization of 1.

Chloroform (10 mL), 2M aq. NaOH (10 mL), and **1** (700 mg, 2 mmol) were mixed and stirred vigorously for 10 min. After removing the organic solvent from chloroform layer, the resulting residue was recrystallized from hexane to give **2**. Yield 440 mg (88%); mp 70 °C (lit.,[5] 67 - 69 °C). The IR spectrum of **2** was completely superimposed on that of an authentic sample.[5] IR ν 3063, 2955, 2878, 1564, 1529, 1381, 760, 702 cm^{-1}.

2,4-Bis(*N*,*N*-dimethylamino)-7,8-benzoquinazoline (9).

By the same way as the above, **8** (370 mg, 1 mmol) was neutralized with 2M aq. NaOH and recrystallized from hexane to give **9**. Yield 250 mg (93%), mp 95 °C; ^{1}H NMR δ = 3.24 (*s*, 6H), 3.33 (*s*, 6H), 7.24 - 7.32 (*m*, 1H), 7.53 - 7.63 (*m*, 2H), 7.69 - 7.77 (*m*, 2H), 9.06 - 9.09 (*m*, 1H); ^{13}C NMR δ = 36.96, 41.83, 106.70, 119.28, 122.87, 125.34, 125.75, 127.35, 128.64, 130.46, 135.29, 154.01, 159.50, 165.63; IR 3046, 2941, 1556, 1504, 1398, 1371, 1035, 968, 765 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_4$: C, 72.23; H, 6.81; N, 21.03. Found: C, 72.23; H, 7.06; N, 21.02.

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