Novel Quinazoline Ring Synthesis by Cycloaddition of *N*-Arylketenimines with *N*,*N*-Disubstituted Cyanamides

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The reaction of *N*-aryl-substituted ketenimines with *N*,*N*-disubstituted cyanamides or $(MeS)_2C{=}N{-}CN$ under high pressure afforded 4-(*N*,*N*-disubstituted amino) or 4-$(MeS)_2C{=}N$-substituted quinazoline derivatives, respectively. These products were formed by [4+2] cycloaddition between the aza-diene moieties of the *N*-aryl-substituted ketenimines and cyano groups. A 4-(unsubstituted amino)quinazoline derivative was synthesized by hydrolysis of the latter product.

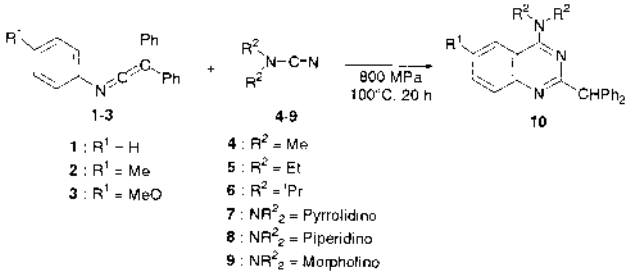
Key words quinazoline; ketenimine; cyanamide; high-pressure reaction; cycloaddition

It has been reported that ketenimines reacted with various kinds of reactants and became starting materials of various compounds.[1] Among them, the most attractive reactions were cycloaddition for the synthesis of heterocyclic rings. Intermolecular and intramolecular [4+2] or [2+2] cycloadditions of ketenimines were reported, and ketenimines can play the role of either the 2- or 4-atom component on cycloaddition.[2] When multiple-bond compounds that have electron-donating substituents were treated with *N*-aryl-substituted ketenimines, the [4+2] cycloaddition occurred at the C=C–N=C moieties of the ketenimines as aza-dienes. For example, 4-aminoquinoline derivatives were synthesized in the reaction of triphenylketenimine with *N*,*N*-disubstituted aminoacetylenes.[3] We also reported the cycloaddition of *N*-aryl-substituted ketenimines with enol ethers under high pressure to form quinoline derivatives in a previous paper.[4] Therefore it was expected that the cycloaddition of ketenimines would occur with *N*,*N*-disubstituted cyanamides because the cyanamides are regarded as electron-rich triple-bond compounds. However, to our knowledge there has been no report on the cycloaddition of ketenimines with the CN triple bond. In this paper, we describe the cycloaddition of *N*-aryl-substituted ketenimines with *N*,*N*-disubstituted cyanamides under high pressure.

When *N*-(*p*-tolyl)diphenylketenimine (**2**) was heated with *N*,*N*-dimethylcyanamide (**4**) in toluene under reflux, no cyclized product was obtained and **2** was recovered. Therefore the reaction of **2** with *N*,*N*-disubstituted cyanamides **4**—**9** was carried out under high-pressure conditions as reported for the reactions with enol ethers.[4] The ketenimine **2** was dissolved in pyrrolidine-1-carbonitrile (**7**) and the mixture was compressed under 800 MPa at 100 °C. The resulting crude product was purified with chromatography on silica gel to give 2-diphenylmethyl-6-methyl-4-pyrrolidinoquinazoline (**10f**) in 60% yield. The structure of **10f** was confirmed by comparison with spectral data of the compound prepared by cyclodesulfurization of 2,2-diphenyl-*N*-*p*-tolylthioacetamide with silver perchlorate in **7**,[5] followed by neutralization with base. The same high-pressure reactions of ketenimines **1**—**3** with *N*,*N*-disubstituted cyanamides **4**—**9** were carried out, and quinazoline derivatives (**10**) were obtained in the yields shown in Table 1. However, nitrile compounds such as acetonitrile or benzonitrile did not react with ketenimines under these reaction conditions.

The mechanism of quinazoline ring formation is explained by the occurrence of a [4+2] cycloaddition between the

Table 1. Reaction of Ketenimine with Cyanamide



Run	Ketenimine	Cyanamide	Quinazoline	R^1	NR^2_2	Yield of **10** (%)
1	**1**	**4**	**10a**	H	NMe_2	71
2	**2**	**4**	**10b**	Me	NMe_2	66
3	**3**	**4**	**10c**	OMe	NMe_2	47
4	**2**	**5**	**10d**	Me	NEt_2	65
5	**2**	**6**	**10e**	Me	$N(^iPr)_2$	44
6	**2**	**7**	**10f**	Me	Pyrrolidino	60
7	**2**	**8**	**10g**	Me	Piperidino	67
8	**2**	**9**	**10h**	Me	Morpholino	43

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C=C–N=C moieties of *N*-arylketenimines and the cyano groups of cyanamides, followed by aromatization to the quinazoline rings (Chart 1). This reaction mechanism is similar to the cycloaddition of ketenimines with ynamines[3] or enol ethers.[4]

It was reported that quinazoline compounds are found in natural products or used in medicines.[6] 4-Aminoquinazoline derivatives have various bioactivities such as an antimalarial effect.[7] Although quinazoline synthesis was performed by cyclization of the ketenimines **1**—**3** with *N*,*N*-disubstituted cyanamides **4**—**9** as described above, the substituents on the C-4 carbon of quinazolines (**10**) were restricted to *N*,*N*-disubstituted amino groups. To prepare 4-(*N*-unsubstituted amino)quinazolines by the cycloaddition of ketenimines with cyanamides, an *N*-unsubstituted cyanamide was used as a starting material. However, the cyanamides that had hydrogen atoms on the amino groups tautomerized to carbodiimides. Moreover, ketenimines reacted with free amino groups to afford amidine derivatives.[1] For these reasons, 4-(unsubstituted amino)quinazoline derivatives were not directly synthesized. Therefore the reactions of dimethyl *N*-cyanodithioiminocarbonate (**11**), which is regarded as an *N*-protected cyanamide, with ketenimines were investigated. A mixture of **1** and **11** was dissolved in toluene and the solution was compressed at 800 MPa. After the reaction, 4-[*N*-bis(methylthio)methylideneamino]quinazoline (**12**) was isolated in 55% yield from the reaction mixture. When hydrolysis of the $(MeS)_2C{=}N$–moiety of **12** was carried out with aqueous potassium hydroxide in methanol, the product showed disappearance of a methylthio group peak in the ^{1}H-NMR spectra and appearance of N–H absorption in the IR spectra. The C=N double bond of the $(MeS)_2C{=}N$–moiety in **12** was hydrolyzed and 4-amino-2-diphenylmethylquinazoline (**14**) was obtained in 53% yield. Although the hydrolysis of **12** also occurred under acidic conditions, the methanolysis product 2-diphenylmethyl-4-methoxyquinazoline (**15**) was formed in 47% yield as a main product as well as **14** in 40% yield (Chart 2).

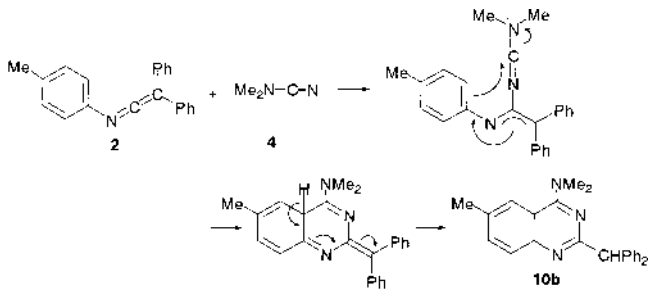

Chart 1

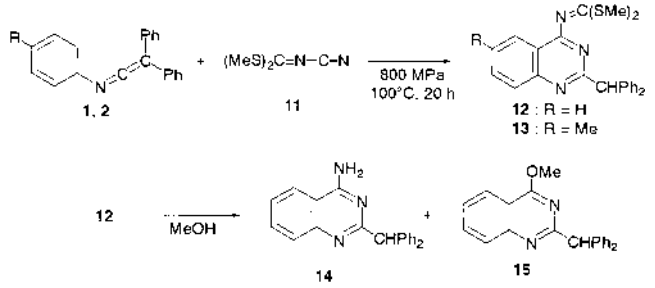

Chart 2

In conclusion, 4-(*N*,*N*-disubstituted amino)-2-substituted quinazoline derivatives were synthesized by the [4+2] cycloaddition of *N*-aryl-substituted ketenimines with *N*,*N*-disubstituted cyanamides under high pressure. A 4-aminoquinazoline derivative was synthesized by hydrolysis of a 4-[*N*-bis(methylthio)methylideneamino]quinazoline, which was prepared by the reaction of ketenimines with dimethyl *N*-cyanodithioiminocarbonate.

Experimental

Melting points were determined on a Mettler FP90 microscopic plate and are uncorrected. ^{1}H-NMR spectra were obtained with a Varian Gemini 300BB spectrometer, and chemical shifts are reported in parts per million relative to internal tetramethylsilane. ^{13}C-NMR spectra were obtained with JEOL LA-500 spectrometer, and chemical shifts are reported in parts per million relative to internal $CDCl_3$ (77 ppm). IR spectra were recorded on a JASCO FTIR-5300 spectrophotometer. The apparatus used for the high-pressure reaction was the same as that described previously.[8] Ketenimines **1**—**3** were prepared by the method described in a previous paper.[9]

General Procedure for the Reaction of *N*-Aryl-substituted Diphenylketenimines with *N*,*N*-Disubstituted Cyanamides under High Pressure A homogeneous mixture of a ketenimine (0.5 mmol) and a cyanamide (0.5 ml) in a sealed Teflon tube was compressed to 800 MPa, heated at 100 °C, and maintained for 20 h in a high-pressure apparatus. The resulting mixture was chromatographed on silica gel with dichloromethane : acetone : methanol (100 : 5 : 1) mixture as the eluent.

4-Dimethylamino-2-diphenylmethylquinazoline (**10a**): mp 149—150 °C (benzene–hexane). ^{1}H-NMR ($CDCl_3$) δ: 3.31 (6H, s, NMe_2), 5.62 (1H, s, 2-CH), 7.16—7.36 (7H, m, Ph), 7.47—7.49 (4H, m, Ph), 7.64 (1H, ddd, J=8.5, 6.9, 1.4 Hz, 6-H), 7.84 (1H, dd, J=8.5, 1.4 Hz, 5-H), 7.97 (1H, dd, J=8.5, 1.4 Hz, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 41.8 (q), 60.8 (d), 114.4 (s), 124.0 (d), 125.3 (d), 126.2 (d), 127.9 (d), 128.2 (d), 129.4 (d), 131.8 (d), 142.9 (s), 152.6 (s), 163.5 (s), 165.4 (s). IR (KBr) cm^{-1}: 1566, 1532, 1491, 1381, 750, 702. *Anal.* Calcd for $C_{23}H_{21}N_3$: C, 81.38; H, 6.24; N, 12.38. Found: C, 80.98; H, 6.22; N, 12.30.

4-Dimethylamino-2-diphenylmethyl-6-methylquinazoline (**10b**): mp 104—105 °C (benzene–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s, 6-Me), 3.27 (6H, s, NMe_2). 5.61 (1H, s, 2-CH), 7.17—7.29 (6H, m, Ph), 7.46—7.50 (5H, m, Ph, 7-H), 7.72 (1H, d, J=0.8 Hz, 5-H), 7.74 (1H, d, J=8.5 Hz, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 21.8 (q), 41.8 (q), 60.7 (d), 114.4 (s), 124.4 (d), 126.2 (d), 127.9 (d), 128.0 (d), 129.4 (d), 133.7 (s), 133.7 (d), 143.0 (s), 150.9 (s), 163.4 (s), 164.6 (s). IR (KBr) cm^{-1}: 1566, 1530, 1385, 1080, 833, 729, 698. *Anal.* Calcd for $C_{24}H_{23}N_3$: C, 81.55; H, 6.56; N, 11.89. Found C, 81.35; H, 6.75; N, 11.76.

4-Dimethylamino-2-diphenylmethyl-6-methoxyquinazoline (**10c**): Oil. ^{1}H-NMR ($CDCl_3$) δ: 3.26 (6H, s, NMe_2), 3.88 (3H, s, 6-MeO), 5.61 (1H, s, 2-CH), 7.18—7.29 (7H, m, Ph, 5-H), 7.34 (1H, dd, J=9.1, 2.7 Hz, 7-H), 7.47—7.50 (4H, m, Ph), 7.79 (1H, d, J=9.1 Hz, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 41.6 (q), 55.6 (q), 60.6 (d), 105.1 (d), 115.1 (s), 122.8 (d), 126.2 (d), 127.9 (d), 129.4 (d), 129.7 (d), 143.1 (s), 147.9 (s), 155.8 (s), 163.6 (s), 163.6 (s). IR (neat) cm^{-1}: 1570, 1530, 1399, 1225, 1032, 837, 700. Picrate: mp 190—192.5 °C (ethanol). *Anal.* Calcd for $C_{30}H_{26}N_6O_8$: C, 60.20; H, 4.38; N, 14.04. Found: C, 60.20; H, 4.32; N, 13.99.

4-Diethylamino-2-diphenylmethyl-6-methylquinazoline (**10d**): Oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (6H, t, J=7.0 Hz, Et), 2.46 (3H, s, 6-Me), 3.62 (4H, q, J=7.0 Hz, Et). 5.63 (1H, s, 2-CH), 7.14—7.28 (6H, m, Ph), 7.38—7.42 (4H, m, Ph), 7.47 (1H, d, J=8.5, 1.8 Hz, 7-H), 7.62 (1H, s, 1H, 5-H), 7.74 (1H, d, J=8.5 Hz, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 13.0 (q), 21.9 (q), 44.9 (t), 60.5 (d), 114.5 (s), 123.7 (d), 126.1 (d), 127.9 (d), 128.1 (d), 129.4 (d), 133.6 (s), 133.7 (d), 143.1 (s), 150.9 (s), 162.1 (s), 164.8 (s). IR (neat) cm^{-1}: 1562, 1524, 1348, 1086, 833, 698. Picrate: mp 176—177.5 °C (ethanol). *Anal.* Calcd for $C_{32}H_{30}N_6O_7$: C, 62.94; H, 4.95; N, 13.76. Found: C, 62.87; H, 4.93; N, 13.72.

4-Diisopropylamino-2-diphenylmethyl-6-methylquinazoline (**10e**): Oil. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (12H, d, J=6.6 Hz, $CHMe_2$), 2.45 (3H, s, 6-Me), 4.09 (2H, hep, J=6.6 Hz, 4-NCH), 5.71 (1H, s, 5-H), 7.15—7.32 (10H, m, Ph), 7.45 (1H, dd, J=8.5, 1.9 Hz, 7-H), 7.54 (1H, s, 5-H), 7.71 (1H, d, J=8.5 Hz, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 21.8 (q), 21.8 (q), 50.2 (d), 60.4 (d), 115.2 (s), 123.9 (d), 126.1 (d), 128.0 (d), 128.1 (d), 129.6 (d), 133.2 (s), 133.4 (d), 142.8 (s), 151.3 (s), 162.8 (s), 164.8 (s). IR (neat) cm^{-1}: 1559, 1526, 1379, 1152, 831, 698. Picrate: mp 205—208 °C (ethanol). *Anal.* Calcd for $C_{34}H_{34}N_6O_7$: C, 63.94; H, 5.37; N, 13.16. Found: C, 63.77; H, 5.33; N,

13.15.

2-Diphenylmethyl-6-methyl-4-pyrrolidinoquinazoline (**10f**): mp 154.6—155.5 °C (benzene–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.97—2.02 (4H, m), 2.45 (3H, s, 6-Me), 3.85—3.90 (4H, m), 5.57 (1H, s, 2-CH), 7.15—7.29 (6H, m, Ph), 7.45—7.51 (5H, m, Ph, 7-H), 7.72 (1H, d, J=8.5 Hz, 8-H), 7.88 (1H, s, 5-H). ^{13}C-NMR ($CDCl_3$) δ: 21.9 (q), 25.7 (t), 50.8 (t), 60.8 (d), 114.8 (s), 124.2 (d), 126.1 (d), 127.8 (d), 127.9 (d), 129.4 (d), 133.4 (s), 133.5 (d), 143.2 (s), 150.6 (s), 159.5 (s), 165.1 (s). IR (KBr) cm^{-1}: 1562, 1514, 1391, 1333, 835, 718, 698. *Anal.* Calcd for $C_{26}H_{25}N_3$: C, 82.29; H, 6.64; N, 11.07. Found: C, 82.29; H, 6.73; N, 11.04.

2-Diphenylmethyl-6-methyl-4-piperidinoquinazoline (**10g**): Oil. ^{1}H-NMR ($CDCl_3$) δ: 1.64—1.77 (6H, m), 2.47 (3H, s, 6-Me), 3.64 (4H, br s, N-CH_2), 5.63 (1H, s, 2-CH), 7.15—7.29 (6H, m, Ph), 7.45—7.51 (5H, m, Ph, 7-H), 7.58 (1H, s, 5-H), 7.76 (1H, d, J=8.5 Hz, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 21.8 (q), 24.8 (t), 26.0 (t), 50.9 (t), 60.6 (d), 114.9 (s), 123.9 (d), 126.2 (d), 127.9 (d), 128.1 (d), 129.4 (d), 134.0 (d), 134.4 (s), 143.0 (s), 150.6 (s), 164.6 (s), 164.8 (s). IR (neat) cm^{-1}: 1562, 1539, 1508, 1447, 1360, 833, 729, 698. Picrate: mp 199—200.4 °C (ethanol). *Anal.* Calcd for $C_{33}H_{30}N_6O_7$: C, 63.66; H, 4.86; N, 13.50. Found: C, 63.49; H, 4.82; N, 13.54.

2-Diphenylmethyl-6-methyl-4-morpholinoquinazoline (**10h**): mp 115.5—117 °C (CH_2Cl_2–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.48 (3H, s, 6-Me), 3.69—3.75 (4H, m, N-CH_2), 3.78—3.81 (4H, m, O-CH_2), 5.67 (1H, s, 2-CH), 7.16—7.29 (6H, m, Ph), 7.41—7.44 (4H, m, Ph), 7.53 (1H, dd, J=8.5, 1.9 Hz, 7-H), 7.58 (1H, s, 5-H), 7.80 (1H, d, J=8.5 Hz, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 21.8 (q), 50.3 (t), 60.6 (d), 66.7 (t), 114.8 (s), 123.4 (d), 126.3 (d), 128.0 (d), 128.5 (d), 129.3 (d), 134.4 (d), 135.1 (s), 142.8 (s), 150.8 (s), 164.4 (s), 164.9 (s). IR (neat) cm^{-1}: 1562, 1505, 1433, 1358, 1115, 700. Picrate: mp 190—192.5 °C (ethanol). *Anal.* Calcd for $C_{32}H_{28}N_6O_8$: C, 61.53; H, 4.52; N, 13.46. Found: C, 61.36; H, 4.36; N, 13.47.

General Procedure for the Reaction of *N*-Aryl-substituted Diphenylketenimines with Dimethyl *N*-Cyanodithioiminocarbonate under High Pressure A homogeneous mixture of ketenimine (**1** or **2**, 0.5 mmol) and dimethyl *N*-cyanodithioiminocarbonate (**11**, 366 mg, 2.5 mmol) in toluene (1 ml) in a sealed Teflon tube was compressed to 800 MPa, heated at 100 °C, and maintained for 20 h in a high-pressure apparatus. After the reaction, the solvent was evaporated and the resulting mixture was chromatographed on alumina with ethyl acetate : hexane (15 : 2) mixture as eluent.

4-[*N*-Bis(methylthio)methylideneamino]-2-diphenylmethylquinazoline (**12**): Yield 55%. mp 110—112 °C (benzene–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.55 (6H, s, MeS), 5.85 (1H, s, 2-CH), 7.17—7.30 (6H, m, Ph), 7.42—7.45 (4H, m, Ph), 7.51 (1H, ddd, J=8.2, 6.9, 1.1 Hz, 6-H), 7.79 (1H, ddd, J=8.2, 6.9, 1.4 Hz, 7-H), 7.94 (1H, d, J=8.2 Hz, 8-H), 8.20 (1H, dd, J=8.2, 1.4 Hz, 5-H). ^{13}C-NMR ($CDCl_3$) δ: 16.0 (q), 60.8 (d), 118.7 (s), 125.0 (d), 126.3 (d), 126.5 (d), 128.0 (d), 128.1 (d), 129.6 (d), 133.3 (d), 142.2 (s), 151.9 (s), 164.0 (s), 167.0 (s), 174.8 (s). IR (KBr) cm^{-1}: 1543, 1497, 1472, 1009, 924, 774, 700, 617. *Anal.* Calcd for $C_{24}H_{21}N_3S_2$: C, 69.36; H, 5.09; N, 10.11. Found: C, 69.36; H, 5.04; N, 9.99.

4-[*N*-Bis(methylthio)methylideneamino]-2-diphenylmethyl-6-methylquinazoline (**13**): Yield 37%. mp 122.4—123.4 °C (benzene–hexane). ^{1}H-NMR ($CDCl_3$) δ: 2.51 (3H, s, 6-Me), 2.45 (6H, s, MeS), 5.38 (1H, s, 2-CH), 7.15—7.21 (2H, m, Ph), 7.24—7.30 (4H, m, Ph), 7.41—7.44 (4H, m, Ph), 7.62 (1H, dd, J=8.5, 1.9 Hz, 7-H), 7.84 (1H, d, J=8.5 Hz, 8-H), 7.91 (1H, s, 5-H). ^{13}C-NMR ($CDCl_3$) δ: 16.0 (q), 21.8 (q), 60.7 (d), 118.4 (s), 123.7 (d), 126.3 (d), 127.8 (d), 128.0 (d), 129.6 (d), 135.5 (d), 136.5 (s), 142.4 (s), 150.4 (s), 163.7 (s), 166.2 (s), 173.9 (s). IR (KBr) cm^{-1}: 1553, 1478, 1414, 1188, 910, 831, 747, 700, 615. *Anal.* Calcd for $C_{25}H_{23}N_3S_2$: C, 69.89; H, 5.40; N, 9.78. Found: C, 69.87; H, 5.33; N, 9.76.

Hydrolysis of 12 The quinazoline (**12**, 50 mg, 0.12 mmol) was dissolved in methanol (10 ml) and aqueous potassium hydroxide (0.4 M, 5 ml) was added to the solution. The mixture was stirred at 80 °C for 2 h. Water was added to the reaction mixture and products were extracted with dichloromethane. The organic layer was dried with magnesium sulfate, and the solvent was evaporated. The residue was recrystallized from a benzene–hexane mixture. **14** was obtained in 53% yield.

4-Amino-2-diphenylmethylquinazoline (**14**): mp 164—165.5 °C (benzene–hexane). ^{1}H-NMR ($CDCl_3$) δ: 5.66 (1H, s, 2-CH), 6.03 (2H, br s, NH_2), 7.25—7.45 (12H, m, Ar), 7.67—7.73 (1H, m, Ar), 7.81 (1H, d, J=8.2 Hz, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 60.7 (d), 112.9 (s), 121.4 (d), 125.7 (d), 126.5 (d), 128.3 (d), 128.5 (d), 129.6 (d), 133.1 (d), 142.3 (s), 150.4 (s), 161.7 (s), 167.2 (s). IR (KBr) cm^{-1}: 3474, 3306, 1642, 1555, 1499, 1366, 702. *Anal.* Calcd for $C_{21}H_{17}N_3 \cdot 0.1H_2O$: C, 80.54; H, 5.54; N, 13.42. Found: C, 80.67; H, 5.41; N, 13.39.

The quinazoline (**12**, 100 mg, 0.24 mmol) and *p*-toluenesulfonic acid monohydrate (200 mg, 1.02 mmol) were dissolved in methanol (20 ml). The mixture was stirred at reflux for 3 h. Water was added to the reaction mixture and products were extracted with dichloromethane. The organic layer was dried with magnesium sulfate, and the solvent was evaporated. The resulting mixture was chromatographed on silica gel with dichloromethane : acetone : methanol (100 : 5 : 1) mixture as eluent. **14** and **15** were isolated in 40% and 47% yield, respectively.

2-Diphenylmethyl-4-methoxyquinazoline (**15**): mp 93—95 °C (hexane). ^{1}H-NMR ($CDCl_3$) δ: 4.10 (3H, s, MeO), 5.73 (1H, s, 2-CH), 7.19—7.32 (6H, m, Ph), 7.44—7.53 (5H, m, Ph, 7-H), 7.78 (1H, ddd, J=8.5, 7.1, 1.6 Hz, 6-H), 7.91 (1H, dd, J=8.5, 1.6 Hz, 5-H), 8.10 (1H, dd, J=8.5, 1.4 Hz, 8-H). ^{13}C-NMR ($CDCl_3$) δ: 54.2 (q), 60.8 (d), 114.9 (s), 123.3 (d), 126.5 (d), 126.5 (d), 127.6 (d), 128.1 (d), 129.4 (d), 133.4 (d), 142.3 (s), 151.4 (s), 166.3 (s), 137.1 (s). IR (KBr) cm^{-1}: 1620, 1568, 1497, 1453, 1375, 1107, 774. *Anal.* Calcd for $C_{22}H_{18}N_2O \cdot 0.1H_2O$: C, 80.51; H, 5.59; N, 8.54. Found: C, 80.58; H, 5.54; N, 8.51.

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