

Carbon–Carbon Bond Cleavage of α -Hydroxybenzylheteroarenes Catalyzed by Cyanide Ion: Retro-Benzoin Condensation Affords Ketones and Heteroarenes and Benzyl Migration Affords Benzylheteroarenes and Arenecarbaldehydes

Yumiko SUZUKI, Yuki TAKEMURA, Ken-ichi IWAMOTO, Takeo HIGASHINO, and Akira MIYASHITA*

School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Shizuoka 422, Japan.
Received July 15, 1997; accepted September 18, 1997

4-(α -Benzyl- α -hydroxybenzyl)quinazoline (**4a**) underwent retro-benzoin condensation catalyzed by cyanide ion to give deoxybenzoin (**2a**) and quinazoline (**5a**). Similarly, several nitrogen-containing heteroarenes (**4**, **9**, **12**, **16–19**) having an α -hydroxybenzyl group at the α -position of the nitrogen underwent retro-benzoin type condensation to afford ketones (**2**) and heteroarenes (**5**). However, similar reaction of pyrazolopyrimidines (**13**, **14**, **15**) having an α -benzyl- α -hydroxybenzyl group resulted in benzyl migration, giving benzylpyrazolopyrimidines (**8**) and arenecarbaldehydes (**3**). Tetrabutylammonium cyanide (**11**, Bu₄CN) was a more effective cyanide ion donor than KCN (**10**). The retro-benzoin condensation was applied to the synthesis of 2-substituted quinazolines (**38**) from 2-chloro-4-arylquinazolines (**34**), using the aryl group as a protecting and electron-withdrawing group.

Key words retro-benzoin condensation; cyanide ion; α -hydroxybenzylheteroarene; ketone; tetrabutylammonium cyanide; 2-substituted quinazoline

We have shown that α -substituted benzoin (**1**) such as α -benzylbenzoin (**1a**) undergo carbon–carbon bond cleavage catalyzed by cyanide ion (CN⁻), resulting in the formation of the ketones (**2**) and benzaldehyde (**3a**).¹ This reaction is considered to proceed through a retro-benzoin condensation mechanism.² As shown in Chart 1, the known analogy between the chemical behavior of the C=O double bond of ketones and the C=N double bond of nitrogen-containing heteroarenes^{3,4} led us to the idea that, since the structure of benzoin is similar to that of nitrogen-containing heteroarenes having an α -aryl- or α -alkyl- α -hydroxybenzyl group at the α -position of the nitrogen, a retro-benzoin type condensation might also proceed in the heteroarenes. In the preceding communication,⁴ we reported the retro-benzoin condensation of heteroarenes. Here, we wish to report those results in detail and to extend the methodology to the synthesis of 2-substituted quinazolines.

When 4-(α -benzyl- α -hydroxybenzyl)quinazoline (**4a**) was treated with potassium cyanide (**10**, KCN) in *N,N*-dimethylformamide (DMF), the retro-benzoin condensation proceeded to afford the expected deoxybenzoin (**2a**) in 72% yield together with quinazoline (**5a**) and 4-

quinazolinecarbonitrile (**6**). As shown in Chart 2, several quinazolines (**4**) having an α -aryl- or α -alkyl- α -hydroxybenzyl group underwent the retro-benzoin condensation to give the corresponding ketones (**2**) and quinazoline (**5a**). In this retro-condensation, 4-quinazolinecarbonitrile (**6**) and 4-quinazolinecarboxamide (**7**) were simultaneously formed as by-products. Unexpectedly, 4-benzylquinazoline (**8a**) was also obtained in low yield (entries 2, 4). Further, carbon–carbon bond cleavage of the 2-phenylquinazoline derivative (**9c**) proceeded in the presence of potassium cyanide (**10**) in refluxing DMF for 1 h, resulting in the formation of the ketone (**2c**) and 2-phenylquinazo-

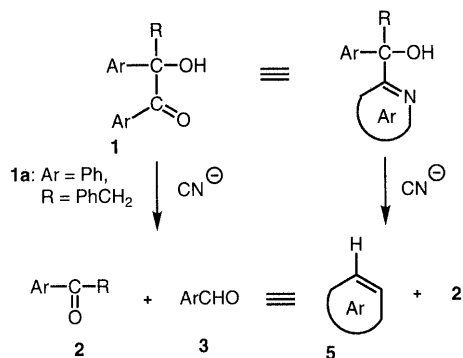
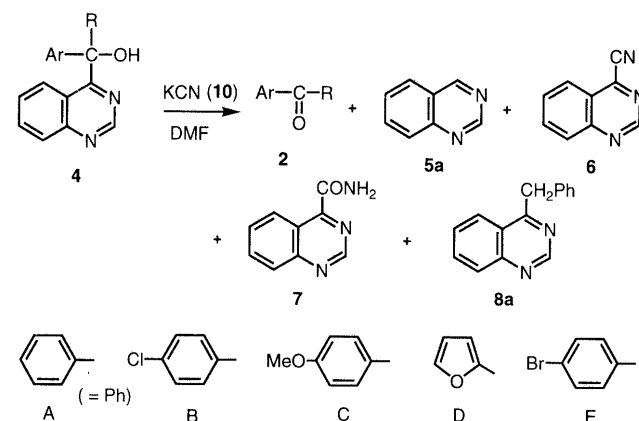


Chart 1



2 and 4;

a: Ar = A, R = PhCH₂, **b:** Ar = B, R = PhCH₂, **c:** Ar = C, R = PhCH₂,
d: Ar = D, R = PhCH₂, **e:** Ar = C, R = Ph, **f:** Ar = C, R = Me, **g:** Ar = A, R = Ph,
h: Ar = A, R = Me

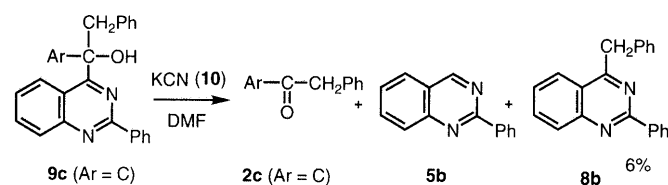


Chart 2

* To whom correspondence should be addressed.

Table 2. Retro-Benzoin Condensation of Heteroarenes (**12**–**19**) Catalyzed by Potassium Cyanide

Entry	Substrate: Heteroarene	Reaction conditions		Products; isolated yield (%)						
		Temp. (°C)	Time (h)	Ketone:	2	5	3	8	Recovery	
1	12a	80	1	2a	63	5c	36	—	8c	14
2	12b	80	1	2g	99	—	—	—	—	—
3	13a	Reflux	2	2a	32	5d	Trace	—	8d	57
4	13b	Reflux	1	—	—	—	—	3b	8d	44
5	13c	Reflux	1	—	—	—	—	3c	8d	68
6	14a	Reflux	1	—	—	—	—	3c	8e	99
7	15a	Reflux	1	—	—	—	—	3c	8f	95
8	15b	Reflux	1	2e	82	—	(37) ^a	—	—	—
9	15c	Reflux	1	2f	69	—	(70) ^a	—	—	—
10	16a	Reflux	1	2a	71	5g	83	—	—	16
11	16b	Reflux	1	2c	67	5g	73	—	—	—
12	17a	Reflux	1	2c	40	5h	35	3c	8h	31
13	17b	Reflux	2	2e	92	5h	67	—	—	—
14	18a	Reflux	3	2a	66	5i	36	—	—	—
15	19a	120	2	2a	73	5j	75	—	—	32

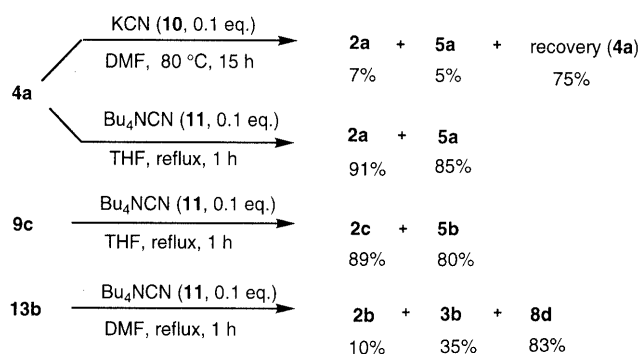
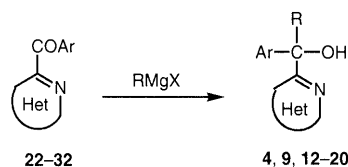
a) Yield of dimer **21**.

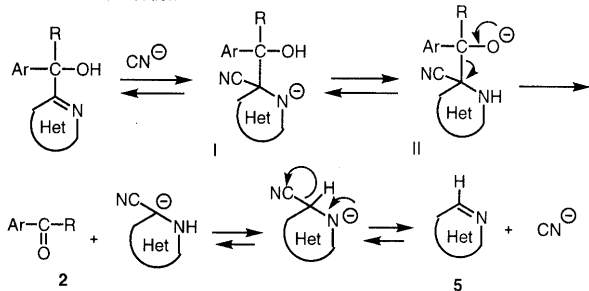
Chart 4



22a: Het = a, Ar = A, **22b**: Het = a, Ar = B, **22c**: Het = a, Ar = C, **22d**: Het = a, Ar = D,
23c: Het = b, Ar = C, **24a**: Het = c, Ar = A, **25a**: Het = d, Ar = A, **25b**: Het = d, Ar = B,
25c: Het = d, Ar = C, **26c**: Het = e, Ar = C, **27c**: Het = f, Ar = C, **28a**: Het = g, Ar = A,
28c: Het = g, Ar = C, **29c**: Het = h, Ar = C, **30a**: Het = i, Ar = A, **31a**: Het = j, Ar = A,
32a: Het = k, Ar = A

Chart 6

Retro-Benzoin Condensation



Benzyl Migration

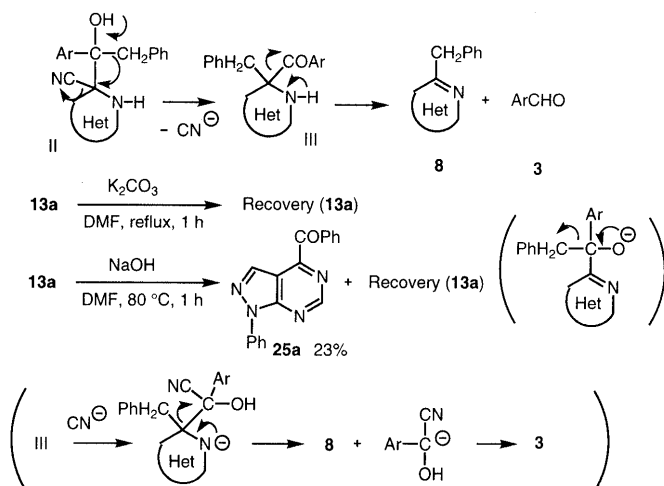


Chart 5

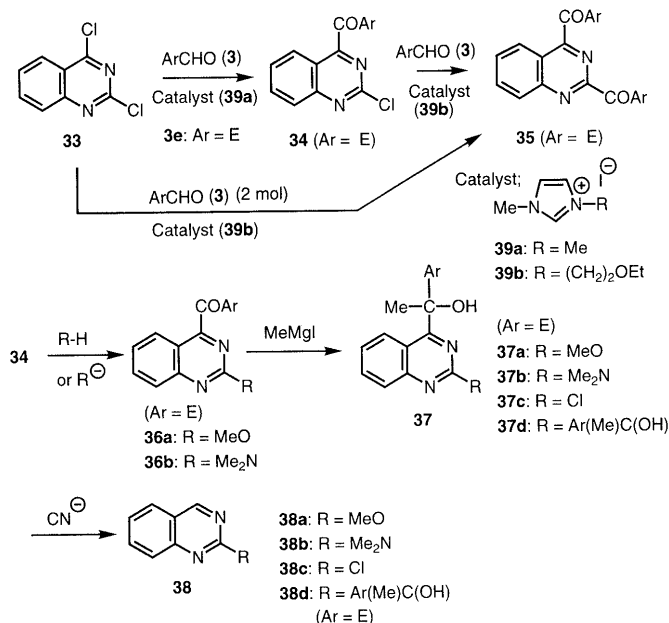
base instead of KCN. The treatment of **13a** with K_2CO_3 in refluxing DMF for 1 h resulted only in recovery of **13a**. By using NaOH, the ketone **25a** was obtained in 23% yield. This result indicates that the benzyl migration into heteroarene does not proceed solely by base action, and further supports the reaction pathway involving the formation of the adduct with cyanide ion. Because of the difficulty of formation of the aroyl anion, another possibility is that the release of the aroyl anion as the final step proceeds through the formation of the mandelonitrile anion. However, the details remain to be investigated. In the case of two carbon–carbon bond cleavages, the path of the reaction may depend on the nature of the heteroarene.

The starting heteroarenes having an α -aryl- or α -alkyl- α -hydroxybenzyl group were prepared by Grignard reaction from aroylheteroarenes (**22**–**32**).⁵⁾ Namely, treatment of aroylheteroarenes (obtained by catalytic aroylation) with Grignard reagent furnished α -aryl- or α -alkyl- α -hydroxybenzylheteroarenes (**4**, **9**, **12**–**20**) in good yields, as shown in Chart 6 and Table 3.

We applied this retro-benzoin condensation to the synthesis of 2-substituted quinazolines (**38**) from 2,4-dichloroquinazoline (**33**). In the literature, 2-substituted quinazolines have been obtained directly by substitution of 2-chloroquinazoline (**38c**) with nucleophiles, though it is difficult to prepare the starting 2-chloroquinazoline (**38c**).⁶⁾ 2,4-Dichloroquinazoline (**33**) reacted with equi-

Table 3. Synthesis of Heteroarenes Having an α -Substituted α -Hydroxybenzyl Group (**4**, **9**, **12**–**20**) from Aroylheteroarenes (**22**–**32**) by Grignard Reaction

Substrates		Product	Yield (%)
Aroylheteroarene	Grignard reagent		
22a	PhCH ₂ MgBr	4a	76
22b	PhCH ₂ MgBr	4b	81
22c	PhCH ₂ MgBr	4c	91
22d	PhCH ₂ MgBr	4d	70
22e	PhMgBr	4e	70
22f	MeMgI	4f	79
23c	PhCH ₂ MgBr	9c	100
24a	PhCH ₂ MgBr	12a	88
24a	PhMgBr	12b	83
25a	PhCH ₂ MgBr	13a	89
25b	PhCH ₂ MgBr	13b	100
25c	PhCH ₂ MgBr	13c	73
26c	PhCH ₂ MgBr	14a	99
27c	PhCH ₂ MgBr	15a	95
27c	PhMgI	15b	96
27c	MeMgBr	15c	97
28a	PhCH ₂ MgBr	16a	86
28c	PhCH ₂ MgBr	16b	61
29c	PhCH ₂ MgBr	17a	71
29c	PhMgBr	17b	100
30a	PhCH ₂ MgBr	18a	90
31a	PhCH ₂ MgBr	19a	65
32a	PhCH ₂ MgBr	20a	75



molar *p*-bromobenzaldehyde (**3e**) catalyzed by 1,3-dimethylimidazolium iodide to give 4-(*p*-bromobenzoyl)-2-chloroquinazolin-2(1H)-one (**34**) in 79% yield. 2,4-Bis(*p*-bromobenzoyl)quinazolin-2(1H)-one (**35**) was obtained when 2 mol eq of *p*-bromobenzaldehyde (**3e**) was used with 1-(2-ethoxyethyl)-3-methylimidazolium iodide⁷⁾ as the catalyst. The chloro group of **34** is easily replaced with nucleophiles to give 2-substituted 4-aryloquinazolines (**36**) owing to the electron-withdrawing effect of the aroyl group. This aroyl group could be readily removed by treating **36** with methylmagnesium iodide (MeMgI) followed by cyanide

ion. Subsequent reactions including retro-benzoin condensation furnished 2-substituted quinazolines (**38**) in good overall yields. Application of similar procedures to those described for **36** to **34** and **35** afforded 2-chloroquinazolin-2(1H)-one (**38c**) and 2-(α -methyl- α -hydroxy-4-bromobenzyl)quinazolin-2(1H)-one (**38d**) in good yields. These results indicate that the aroyl group, which was introduced onto nitrogen-containing heteroarenes at the α -position of the nitrogen, can be used as a protecting group and then easily removed by conversion to an α -hydroxybenzyl group, followed by retro-benzoin condensation.

In conclusion, based on the structural similarity between the C=O double bond of ketones and the C=N double bond of nitrogen-containing heteroarenes, we have found two pathways of carbon-carbon bond cleavage of heteroarenes; one is retro-benzoin condensation to afford ketones (**2**) and heteroarenes (**5**) and the other is benzyl migration to afford benzylheteroarenes (**8**) and arenecarbaldehydes (**3**). The heteroarenes (**4**, **9**, **12**–**19**) having an α -hydroxybenzyl group underwent retro-benzoin condensation, like α -substituted benzoin (**1**). We showed that this retro-benzoin condensation is applicable to the synthesis of 2-substituted quinazolines (**38**).

Experimental

All melting points are uncorrected. IR spectra were recorded on a JASCO A-102 diffraction grating IR spectrophotometer. ¹H-NMR spectra were measured at 60 MHz on a JEOL PMX60SI NMR spectrometer and at 270 MHz on a JEOL JNM-GSX270 FT-NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard, and coupling constants (*J*) are given in Hz.

Reaction of 4-(α -Benzyl- α -hydroxybenzyl)quinazolin-2(1H)-one (4a**) with KCN (**10**)** A solution of **4a** (328 mg, 1.0 mmol) and KCN (72 mg, 1.1 mmol) in DMF (10 ml) was stirred at 80 °C for 1 h. The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and AcOEt. The first fraction eluted with *n*-hexane-AcOEt (10:1) gave deoxybenzoin (**2a**) in 72% yield (141 mg), and the second fraction gave 4-quinazolinocarbonitrile (**6**)⁸⁾ in 3% yield (4 mg). The fraction eluted with *n*-hexane-AcOEt (5:1) gave quinazolin-2(1H)-one (**5a**) in 35% yield (45 mg), and the fraction eluted with *n*-hexane-AcOEt (1:1) gave 4-quinazolinocarbonitrile (**7**)⁸⁾ in 10% yield (17 mg).

A similar reaction using 0.1 mol eq of KCN at 80 °C for 15 h afforded a 7% yield of deoxybenzoin (**2a**, 17 mg), a 5% yield of quinazolin-2(1H)-one (**5a**,⁸⁾ 7 mg), and a 75% recovery of the starting **4a** (246 mg).

Retro-Benzoin Condensation of Quinazolines 4 Catalyzed by KCN General Procedure: A solution of a quinazolin-2(1H)-one (**4**, 1.0 mmol) and KCN (72 mg, 1.1 mmol) in DMF (10 ml) was stirred under appropriate conditions (reaction conditions are shown in Table 1). The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and AcOEt. In the cases of **4b** and **4d**, 4-benzylquinazolin-2(1H)-one (**8a**)⁹⁾ was obtained. These results are shown in Table 1.

Retro-Benzoin Condensation of 4-(α -Benzyl- α -hydroxy-4-methoxybenzyl)-2-phenylquinazolin-2(1H)-one (9c**) Catalyzed by KCN** A solution of **9c** (432 mg, 1.0 mmol) and KCN (72 mg, 1.1 mmol) in DMF (10 ml) was refluxed for 1 h with stirring. The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and AcOEt. The first fraction eluted with *n*-hexane-AcOEt (50:3) gave 4-benzyl-2-phenylquinazolin-2(1H)-one (**8b**) in 6% yield (17 mg), the second fraction gave 2-phenylquinazolin-2(1H)-one (**5b**) in 68% yield (141 mg), and the third fraction gave 4-methoxydeoxybenzoin (**2c**) in 77% yield (174 mg).

4-Benzyl-2-phenylquinazolin-2(1H)-one (**8b**): Slightly yellow granules (acetone-

n-hexane), mp 61–63 °C. *Anal.* Calcd for C₂₁H₁₆N₂: C, 85.11; H, 5.44; N, 9.45. Found: C, 84.71; H, 5.57; N, 9.33. ¹H-NMR (CDCl₃) δ: 4.68 (2H, s, CH₂), 7.20–7.53 (9H, m, aromatic H), 7.78–7.84 (1H, m, aromatic H), 8.07 (1H, d, *J*=9.8 Hz, C⁵-H or C⁸-H), 8.12 (1H, d, *J*=9.8 Hz, C⁵-H or C⁸-H), 8.65 (2H, d, *J*=7.8 Hz, aromatic H).

The structures of the produced ketones, deoxybenzoin (**2a**), 4-chlorodeoxybenzoin (**2b**), 4-methoxydeoxybenzoin (**2c**), 2-furyl benzyl ketone (**2d**), phenyl 4-methoxyphenyl ketone (**2e**), 4-methoxyacetophenone (**2f**), and benzophenone (**2g**), were confirmed by comparison of the spectral data and melting points with those of authentic samples.¹¹

Reaction of α -Aryl- or α -Alkyl- α -hydroxybenzylheteroarenes 12–19 with KCN General Procedure: A solution of an α -aryl or α -alkyl- α -hydroxybenzylheteroarene (**12–19**, 1 mmol) and KCN (72 mg, 1.1 mmol) in DMF (10 ml) was stirred under appropriate conditions (reaction conditions are shown in Table 2). The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane, AcOEt and/or CH₂Cl₂. These results are shown in Table 2.

The identities of 3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine (**5c**),^{10a} 2-phenylquinoxaline (**5g**),^{10b} 1-phenylphthalazine (**5h**),^{10c} 1-methylbenzimidazole (**5i**), benzothiazole (**5j**), and arenecarbaldehyde (**3**) were confirmed by comparison of the spectral data with those of authentic samples. Structural elucidation of the benzylheteroarenes (**8**) was based on the spectral data and elemental analyses.

4-Benzyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**8d**): Colorless needles (acetone-*n*-hexane), mp 100–101 °C (lit.,^{11a} 100–101 °C). ¹H-NMR (CDCl₃) δ: 4.43 (2H, s, CH₂), 7.20–7.67 (8H, m, aromatic H), 7.82 (1H, s, C³-H), 8.04–8.28 (2H, m, aromatic H), 9.00 (1H, s, C⁶-H).

4-Benzyl-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**8e**): Yellow oil (lit.,^{11a} picrate, mp 157–160 °C).

4-Benzyl-3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**8f**): Yellow prisms (acetone-*n*-hexane), mp 97–98 °C. *Anal.* Calcd for C₁₉H₁₆N₄: C, 75.98; H, 5.37; N, 18.65. Found: C, 75.95; H, 5.22; N, 18.87. ¹H-NMR (CDCl₃) δ: 2.71 (3H, s, Me), 4.51 (2H, s, CH₂), 7.23–7.34 (6H, m, aromatic H), 7.48–7.54 (2H, m, aromatic H), 8.16–8.19 (2H, m, aromatic H), 9.00 (1H, s, C⁶-H).

1-Benzyl-4-phenylphthalazine (**8h**): Slightly yellow needles (acetone-*n*-hexane), mp 126–128 °C (lit.,^{11b} 131–132 °C).

In the cases of the reactions of pyrazolopyrimidines **15b** and **15c**, 4,4'-bi(3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine) (**21**) was obtained. Yellow needles (acetone-*n*-hexane), mp 233–234 °C. *Anal.* Calcd for C₂₄H₁₈N₈: C, 68.89; H, 4.34; N, 26.78. Found: C, 68.53; H, 4.42; N, 26.54. ¹H-NMR (CDCl₃) δ: 2.54 (3H, s, Me), 7.36–7.42 (1H, m, aromatic H), 7.55–7.61 (2H, m, aromatic H), 8.25 (2H, dd, *J*=8.8 Hz, 1.0 Hz, aromatic H), 9.25 (1H, s, C⁶-H). ¹³C-NMR (CDCl₃) δ: 15.69 (q), 113.47 (s), 121.60 (d), 126.88 (d), 129.31 (d), 138.36 (s), 143.86 (s), 154.19 (s), 154.79 (d), 157.99 (s).

Reaction of 2-(α -Benzyl- α -hydroxybenzyl)pyridine (20a) with KCN A solution of **20a** (275 mg, 1.0 mmol) and KCN (72 mg, 1.1 mmol) in DMF (10 ml) was refluxed for 3 h with stirring. The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and AcOEt. The fraction eluted with *n*-hexane-AcOEt (1:1) afforded the recovered pyridine (**20a**) in quantitative yield.

Retro-Benzoin Condensation of 4-(α -Benzyl- α -hydroxybenzyl)quinazoline (4a) in the Presence of 0.1 Mol Eq of KCN A solution of **4a** (328 mg, 1.0 mmol) and KCN (10 mg, 0.15 mmol) in DMF (10 ml) was stirred at 80 °C for 15 h. The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and AcOEt. The fraction eluted with *n*-hexane-AcOEt (10:1) gave deoxybenzoin (**2a**) in 7% yield (17 mg). The fraction eluted with *n*-hexane-AcOEt (8:1) afforded the recovered starting **4a** in 75% yield (246 mg). The fraction eluted with *n*-hexane-AcOEt (5:1) gave quinazoline (**5a**) in 5% yield (7 mg).

Retro-Benzoin Condensation of 4-(α -Benzyl- α -hydroxybenzyl)quinazoline (4a) Catalyzed by Bu₄NCN (11) A solution of **4a** (326 mg, 1.0 mmol) and Bu₄NCN (27 mg, 0.1 mmol) in tetrahydrofuran (THF) (10 ml) was refluxed for 1 h. The reaction mixture was poured into ice-H₂O and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column

chromatography on SiO₂ with *n*-hexane and AcOEt. The fraction eluted with *n*-hexane-AcOEt (10:1) gave deoxybenzoin (**2a**) in 91% yield (179 mg). The fraction eluted with *n*-hexane-AcOEt (5:1) gave quinazoline (**5a**) in 85% yield (110 mg).

Retro-Benzoin Condensation of 4-(α -Benzyl- α -hydroxy-4-methoxybenzyl)-2-phenylquinazoline (9c) Catalyzed by Bu₄NCN (11) A solution of **9c** (432 mg, 1.0 mmol) and Bu₄NCN (11, 27 mg, 0.1 mmol) in THF (10 ml) was refluxed for 1 h. The reaction mixture was poured into ice-H₂O and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and AcOEt. The first fraction eluted with *n*-hexane-AcOEt (50:3) gave 2-phenylquinazoline (**5b**) in 80% yield (164 mg). The second fraction gave 4-methoxydeoxybenzoin (**2c**) in 89% yield (201 mg).

Retro-Benzoin Condensation of 4-(α -Benzyl- α -hydroxy-4-chlorobenzyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (13b) Catalyzed by Bu₄NCN A solution of **13b** (427 mg, 1.0 mmol) and Bu₄NCN (27 mg, 0.1 mmol) in DMF (10 ml) was refluxed for 1 h. The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and AcOEt. The fraction eluted with *n*-hexane-AcOEt (20:1) gave *p*-chlorobenzaldehyde (**3b**) in 35% yield (49 mg). The fraction eluted with *n*-hexane-AcOEt (15:1) gave 4-chlorodeoxybenzoin (**2b**) in 10% yield (23 mg). The fraction eluted with *n*-hexane-AcOEt (10:1) afforded the recovered starting **13b** in 2% yield (8 mg), and the next fraction gave 4-benzyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**8d**) in 83% yield (237 mg).

Reaction of 4-(α -Benzyl- α -hydroxybenzyl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (13a) with NaOH A solution of **13a** (392 mg, 1.0 mmol) and NaOH (40 mg, 1.0 mmol) in DMF (10 ml) was heated at 80 °C for 1 h. The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and AcOEt. The fraction eluted with *n*-hexane-AcOEt (10:1) afforded the recovered starting **13a** in quantitative yield. The fraction eluted with *n*-hexane-AcOEt (10:3) afforded the ketone **25a** in 23% (53 mg) yield.

The reaction of **13a** and K₂CO₃ in refluxing DMF for 1 h afforded the recovered starting **13a** in quantitative yield.

Grignard Reaction of Aroylheteroarenes (22–32); Synthesis of α -Alkyl- or α -Aryl- α -hydroxybenzylheteroarenes (4, 9, 12–20) General Procedure: Grignard reagent (7.5 mmol in 10 ml of Et₂O) was added dropwise to a stirred solution of aroylheteroarene (**22–32**, 5 mmol) in THF (30 ml). The resulting mixture was stirred at room temperature for 1 h, then poured into NH₄Cl-NH₃-H₂O, and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane, AcOEt and/or CHCl₃. 4-Aroylquinazolines (**22a–d**), 4-aryol-2-phenylquinazoline (**23c**), 7-aryoltriazolopyrimidine (**24a**), 4-aryolpyrazolopyrimidines (**25a–c**, **26c**, **27c**), 2-aryolquinoxalines (**28a**, **28c**), 1-aryolphthalazine (**29c**), 2-benzoyl-1-methylbenzimidazole (**30a**), and 2-benzoylbenzothiazole (**31a**) were prepared by reported procedures.⁵

The yields are shown in Table 3, and the spectral data, appearance, and elemental analyses are shown in Tables 4 and 5.

Aroylation of 2,4-Dichloroquinazoline (33). 4-(*p*-Bromobenzoyl)-2-chloroquinazoline (34) Sodium hydride (60% in oil, 1320 mg, 33 mmol) was added to a solution of **33** (4.98 g, 25 mmol), *p*-bromobenzaldehyde (**3e**, 5.55 g, 30 mmol), and 1,3-dimethylimidazolium iodide (**39a**, 1.86 g, 8.3 mmol) in THF (80 ml), and the mixture was refluxed for 5 h with stirring. The reaction mixture was poured into ice-H₂O and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and CHCl₃. The fraction eluted with *n*-hexane-CHCl₃ (1:1) gave **34** in 79% yield (6.89 g). Colorless needles (*n*-hexane-CH₂Cl₂), mp 180–181 °C. *Anal.* Calcd for C₁₅H₈BrClN₂O: C, 51.83; H, 2.32; N, 8.06. Found: C, 51.80; H, 2.26; N, 7.92. MS *m/z*: 348 (M⁺). IR (KBr) cm⁻¹: 1665 (CO). ¹H-NMR (CDCl₃) δ: 7.72–7.65 (3H, m, aromatic H), 7.85 (2H, d, *J*=8.8 Hz, aromatic H), 8.13–7.99 (3H, m, aromatic H).

2,4-Bis(*p*-bromobenzoyl)quinazoline (35) Sodium hydride (60% in oil, 280 mg, 7 mmol) was added to a solution of **33**¹² (597 mg, 3 mmol), *p*-bromobenzaldehyde (**3e**, 1.22 g, 6.6 mmol), and 1-(2-ethoxyethyl)-3-methylimidazolium iodide⁷ (**39b**, 282 mg, 1 mmol) in THF (10 ml), and

Table 4. Formulae, Melting Points, MS Data, and Elemental Analyses for α -Aryl- or α -Alkyl- α -hydroxybenzylheteroarenes **4**, **9**, **12**—**20**

Compd.	Melting point (°C)	Appearance (Recrystallization solvent)	Formula	Analysis (%); Calcd(Found)			MS (<i>m/z</i>)
				C	H	N	
4a	117—118	Colorless prisms (MeOH)	C ₂₂ H ₁₈ N ₂ O	80.96 (80.80)	5.56 (5.55)	8.58 (8.44)	
4b	156	Yellow needles (MeOH)	C ₂₂ H ₁₇ N ₂ OCl	73.23 (73.05)	4.75 (4.64)	7.76 (7.64)	
4c	145—146	Colorless needles (acetone–MeOH)	C ₂₃ H ₂₀ N ₂ O ₂	77.51 (77.46)	5.66 (5.65)	7.86 (7.85)	
4d	139—140	Colorless columns (MeOH)	C ₂₀ H ₁₆ N ₂ O ₂	75.93 (75.81)	5.10 (5.08)	8.86 (8.88)	
4e	195—196	Colorless needles (CH ₂ Cl ₂ –MeOH)	C ₂₂ H ₁₈ N ₂ O ₂	77.17 (77.04)	5.30 (5.34)	8.18 (7.92)	
4f	141—142	Colorless needles (acetone– <i>n</i> -hexane)	C ₁₇ H ₁₆ N ₂ O ₂	72.84 (72.98)	5.75 (5.85)	9.99 (10.03)	
9c	146.5—147.5	Colorless needles (acetone– <i>n</i> -hexane)	C ₂₉ H ₂₄ N ₂ O ₂	80.53 (80.34)	5.59 (5.58)	6.48 (6.47)	
12a	130	Colorless needles (acetone– <i>n</i> -hexane)	C ₂₄ H ₁₉ N ₅ O	73.27 (73.21)	4.87 (4.83)	17.80 (17.94)	
12b	203—205	Yellow prisms (acetone– <i>n</i> -hexane)	C ₂₃ H ₁₇ N ₅ O	72.81 (72.63)	4.52 (4.41)	18.46 (18.69)	
13a	113—114	Colorless granules (acetone– <i>n</i> -hexane)	C ₂₅ H ₂₀ N ₄ O	76.51 (76.52)	5.14 (5.02)	14.28 (14.26)	
13b	91—92	Colorless prisms (Et ₂ O– <i>n</i> -hexane)	C ₂₅ H ₁₉ N ₄ OCl	70.34 (70.16)	4.49 (4.37)	13.12 (13.05)	
13c	106—107	Colorless columns (acetone– <i>n</i> -hexane)	C ₂₆ H ₂₂ N ₄ O ₂	73.92 (73.88)	5.25 (5.22)	13.26 (13.15)	
14a	79—80	Colorless needles (acetone– <i>n</i> -hexane)	C ₂₁ H ₂₀ N ₄ O ₂				FAB-MS; 361 (M ⁺ + 1)
15a	170	Colorless prisms (acetone– <i>n</i> -hexane)	C ₂₇ H ₂₄ N ₄ O ₂	74.29 (74.10)	5.54 (5.44)	12.84 (12.96)	
15b	124—125.5	Colorless granules (Et ₂ O– <i>n</i> -hexane)	C ₂₆ H ₂₂ N ₄ O ₂	73.92 (73.92)	5.25 (5.20)	13.26 (13.17)	
15c	118—119	Slightly yellow needles (acetone–MeOH)	C ₂₁ H ₂₀ N ₄ O ₂	69.98 (69.90)	5.59 (5.68)	15.55 (15.48)	
16a	170	Colorless prisms (acetone– <i>n</i> -hexane)	C ₂₈ H ₂₂ N ₂ O	83.56 (83.49)	5.51 (5.48)	6.96 (6.86)	
16b	165—166.5	Colorless prisms (acetone– <i>n</i> -hexane)	C ₂₉ H ₂₄ N ₂ O ₂	80.53 (80.44)	5.59 (5.82)	6.48 (6.23)	
17a	163—164	Colorless prisms (acetone– <i>n</i> -hexane)	C ₂₉ H ₂₄ N ₂ O ₂	80.53 (80.56)	5.59 (5.87)	6.48 (6.43)	
17b		Amorphous powder	C ₂₈ H ₂₂ N ₂ O ₂				FAB-MS; 419 (M ⁺ + 1)
18a	136—139	Colorless needles (benzene)	C ₂₂ H ₂₀ N ₂ O				EI-MS (HR): Calcd, 328.15756 (M ⁺) Observed, 328.15751
19a	105—115	Colorless needles (acetone– <i>n</i> -hexane)	C ₂₁ H ₁₇ NOS				FAB-MS; 332 (M ⁺ + 1)
20a	104—105	Colorless needles (acetone– <i>n</i> -hexane)	C ₁₉ H ₁₇ NO	82.88 (82.76)	6.22 (6.43)	5.09 (5.02)	

the mixture was refluxed for 1 h with stirring. The reaction mixture was poured into ice–H₂O and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and CHCl₃. The fraction eluted with CHCl₃ gave **35** in 86% yield (1.27 g). Yellow needles (*n*-hexane–acetone), mp 184—186 °C. *Anal.* Calcd for C₂₂H₁₂Br₂N₂O₂: C, 53.26; H, 2.44; N, 5.65. Found: C, 52.97; H, 2.41; N, 5.60. IR (KBr) cm⁻¹: 1670 (CO). ¹H-NMR (CDCl₃) δ: 7.64 (2H, d, *J* = 8.3 Hz, aromatic H), 7.65 (2H, d, *J* = 8.3 Hz, aromatic H), 7.78—7.84 (1H, m, aromatic H), 7.88 (2H, d, *J* = 8.3 Hz, aromatic H), 8.03 (2H, d, *J* = 8.3 Hz, aromatic H), 8.06—8.12 (1H, m, aromatic H), 8.17 (1H, d, *J* = 8.3 Hz, C⁵-H), 8.30 (1H, d, *J* = 8.3 Hz, C⁸-H). ¹³C-NMR (CDCl₃) δ: 121.79 (s), 125.91 (d), 129.23 (s), 129.96 (d), 130.39 (s), 130.53 (d), 131.76 (d), 132.13 (d), 132.22 (d), 132.53 (d), 133.70 (s), 133.96 (s), 135.55 (d), 150.92 (s), 156.91 (s), 164.10 (s), 189.87 (s, CO), 191.28 (s, CO).

Compound **35** was also obtained by arylation of **34** with **3e** catalyzed by imidazolium salt **39b**. However, the diarylated compound **35** could not be obtained by arylation of **33** or **34** with **3e** catalyzed by the imidazolium salt **39a**.

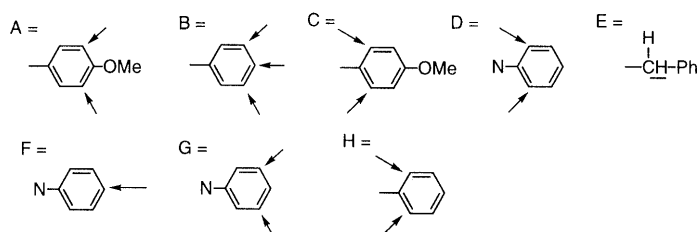
Synthesis of 2-Substituted 4-(*p*-Bromobenzoyl)quinazoline (**36**). 4-(*p*-

Bromobenzoyl)-2-methoxyquinazoline (**36a**) A solution of **34** (2.18 g, 6.3 mmol) in MeONa [prepared from 2.25 g of Na (98 mmol) with 200 ml of MeOH] was refluxed for 100 min. The reaction mixture was concentrated, then the residue was taken up in H₂O and extracted with CHCl₃. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and CHCl₃. The fraction eluted with *n*-hexane–CHCl₃ (1 : 2) gave **36a** in 71% yield (1.50 g). Colorless needles (MeOH), mp 166—167 °C. *Anal.* Calcd for C₁₆H₁₁BrN₂O₂: C, 56.00; H, 3.23; N, 8.16. Found: C, 56.02; H, 3.47; N, 7.90. IR (KBr) cm⁻¹: 1670 (CO). ¹H-NMR (CDCl₃) δ: 4.17 (3H, s, OMe), 7.48—7.42 (1H, m, aromatic H), 7.64 (2H, d, *J* = 8.8 Hz, aromatic H), 7.95—7.82 (5H, m, aromatic H).

4-(*p*-Bromobenzoyl)-2-dimethylaminoquinazoline (36b**)** A solution of **34** (834 mg, 2.4 mmol) in dimethylamine solution (50% in H₂O, 20 ml) was refluxed for 100 min. The reaction mixture was poured into ice–H₂O, and extracted with CHCl₃. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and CHCl₃. The fraction eluted with *n*-hexane–CHCl₃ (1 : 1) gave **36b** in 96% yield (816 mg). Colorless plates (*n*-hexane–CH₂Cl₂), mp 183—185 °C. *Anal.* Calcd for C₁₇H₁₄Br-

Table 5. IR and ¹H-NMR Data for α -Aryl- or α -Alkyl- α -hydroxybenzylheteroarenes **4**, **9**, **12**–**20**

Compd.	IR (KBr) cm ⁻¹	¹ H-NMR (CDCl ₃) δ :
4a	3270 (OH)	3.93 (2H, s, CH ₂), 5.73 (1H, s, OH), 6.52–8.13 (14H, m, aromatic H), 9.01 (1H, s, C ² -H)
4b	3200 (OH)	3.89 (2H, s, CH ₂), 5.66 (1H, s, OH), 6.53–8.17 (13H, m, aromatic H), 9.03 (1H, s, C ² -H)
4c	3200 (OH)	3.72 (3H, s, OMe), 3.89 (2H, s, CH ₂), 5.81 (1H, s, OH), 6.51–8.13 (13H, m, aromatic H), 8.99 (1H, s, C ² -H)
4d	3370 (OH)	3.70 (1H, d, <i>J</i> = 13 Hz, E), 3.98 (1H, d, <i>J</i> = 13 Hz, E), 6.27–8.23 (12H, m, aromatic H), 8.93 (1H, s, C ² -H)
4e	3180 (OH)	3.72 (3H, s, OMe), 6.74 (2H, s, A), 6.85 (1H, s, OH), 7.08–8.11 (13H, m, aromatic H), 9.23 (1H, s, C ² -H)
4f	3200 (OH)	2.00 (3H, s, Me), 3.76 (3H, s, OMe), 6.36 (1H, s, OH), 7.81 (2H, d, <i>J</i> = 9 Hz, A), 7.20–8.19 (6H, m, aromatic H), 9.32 (1H, s, C ² -H)
9c	3330 (OH)	3.63 (3H, s, OMe), 3.94 (2H, s, CH ₂), 5.81 (1H, s, OH), 6.60–8.45 (18H, m, aromatic H)
12a	3520 (OH)	3.96 (1H, d, <i>J</i> = 14 Hz, E), 4.43 (1H, d, <i>J</i> = 14 Hz, E), 5.75 (1H, s, OH), 6.96–7.72 (11H, m, aromatic H), 7.83–8.33 (4H, m, aromatic H), 9.00 (1H, s, C ⁵ -H)
12b	3390 (OH)	6.38 (1H, s, OH), 7.13–7.64 (13H, m, aromatic H), 8.18–8.35 (2H, m, D), 9.18 (1H, s, C ⁵ -H)
13a	3300–3500 (OH)	3.69 (1H, d, <i>J</i> = 14 Hz, E), 4.05 (1H, d, <i>J</i> = 14 Hz, E), 4.03 (1H, s, OH), 6.80–7.78 (13H, m, aromatic H), 7.99–8.20 (2H, m, D), 8.25 (1H, s, C ³ -H), 8.92 (1H, s, C ⁶ -H)
13b	3370 (OH)	3.73 (1H, d, <i>J</i> = 14 Hz, E), 3.96 (1H, s, OH), 4.03 (1H, d, <i>J</i> = 14 Hz, E), 6.96–7.54 (10H, m, aromatic H), 7.66 (2H, d, <i>J</i> = 9 Hz, aromatic H), 8.16 (2H, d, <i>J</i> = 8 Hz, D), 8.34 (1H, s, C ³ -H), 9.01 (1H, s, C ⁶ -H)
13c	3400 (OH)	3.71 (1H, d, <i>J</i> = 14 Hz, E), 3.76 (3H, s, OMe), 4.02 (1H, d, <i>J</i> = 14 Hz, E), 4.09 (1H, s, OH), 6.74–7.70 (12H, m, aromatic H), 8.03–8.23 (2H, m, D), 8.26 (1H, s, C ³ -H), 8.94 (1H, s, C ⁶ -H)
14a	3520 (OH)	3.74 (1H, d, <i>J</i> = 13 Hz, E), 3.77 (3H, s, OMe), 3.96 (1H, d, <i>J</i> = 13 Hz, E), 4.06 (3H, s, NMe), 4.41 (1H, s, OH), 6.85 (2H, d, <i>J</i> = 9 Hz, A), 6.90–6.93 (2H, m, H), 7.09–7.12 (3H, m, B), 7.57 (2H, d, <i>J</i> = 9 Hz, C), 8.07 (1H, s, C ³ -H), 8.85 (1H, s, C ⁶ -H)
15a	3520 (OH)	2.29 (3H, s, Me), 3.77 (3H, s, OMe), 3.82 (2H, s, CH ₂), 4.77 (1H, s, OH), 6.72–7.53 (12H, m, aromatic H), 8.03–8.26 (2H, m, D), 8.84 (1H, s, C ⁶ -H)
15b	3360 (OH)	1.80 (3H, s, Me), 3.75 (3H, s, OMe), 6.18 (1H, s, OH), 6.77 (2H, d, <i>J</i> = 9 Hz, A), 7.13–7.67 (10H, m, aromatic H), 8.13 (2H, d, <i>J</i> = 8 Hz, D), 8.97 (1H, s, C ⁶ -H)
15c	3430 (OH)	2.03 (3H, s, Me), 2.05 (3H, s, Me), 3.79 (3H, s, OMe), 5.83 (1H, s, OH), 6.85 (2H, d, <i>J</i> = 9 Hz, A), 7.25 (2H, d, <i>J</i> = 9 Hz, C), 7.31–7.37 (1H, m, F), 7.49–7.55 (2H, m, G), 8.11–8.15 (2H, m, D), 9.05 (1H, s, C ⁶ -H)
16a	3320 (OH)	3.65 (1H, d, <i>J</i> = 14 Hz, E), 3.78 (1H, d, <i>J</i> = 14 Hz, E), 5.10 (1H, s, OH), 6.78–7.30 (15H, m, aromatic H), 7.77–7.80 (2H, m, aromatic H), 8.08–8.12 (2H, m, aromatic H)
16b	3160 (OH)	3.62 (1H, d, <i>J</i> = 14 Hz, E), 3.73 (1H, d, <i>J</i> = 14 Hz, E), 3.79 (3H, s, OMe), 4.99 (1H, s, OH), 6.69 (2H, d, <i>J</i> = 9 Hz, A), 6.83 (2H, d, <i>J</i> = 8 Hz, aromatic H), 6.90–7.34 (10H, m, aromatic H), 7.76–7.81 (2H, m, aromatic H), 8.05–8.13 (2H, m, aromatic H)
17a	3225 (OH)	3.78 (3H, s, OMe), 3.95 (1H, d, <i>J</i> = 13.2 Hz, E), 4.11 (1H, d, <i>J</i> = 13.2 Hz, E), 5.32 (1H, s, OH), 6.81–6.88 (4H, m, aromatic H), 7.01–7.10 (3H, m, aromatic H), 7.42 (2H, d, <i>J</i> = 8.8 Hz, C), 7.53–7.56 (3H, m, aromatic H), 7.64–7.75 (4H, m, aromatic H), 8.04 (1H, dd, <i>J</i> = 8.3, 2.0 Hz, C ⁵ -H or C ⁸ -H), 8.24 (1H, dd, <i>J</i> = 8.3, 2.0 Hz, C ⁵ -H or C ⁸ -H)
17b	3300 (OH)	3.25 (3H, s, OMe), 5.23 (1H, s, OH), 6.82 (2H, d, <i>J</i> = 8.8 Hz, A), 7.24–7.36 (4H, m, aromatic H), 7.43–7.48 (3H, m, aromatic H), 7.54–7.60 (4H, m, aromatic H), 7.67–7.78 (3H, m, aromatic H), 7.86 (1H, dd, <i>J</i> = 8.3 Hz, C ⁵ -H or C ⁸ -H), 8.08 (1H, d, <i>J</i> = 8.3 Hz, C ⁵ -H or C ⁸ -H)
18a	3380 (OH)	3.44 (3H, s, NMe), 3.80 (2H, br s, CH ₂), 6.40 (1H, s, OH), 6.82–7.88 (14H, m, aromatic H)
19a	3400 (OH)	3.39 (3H, s, OH), 3.52 (1H, d, <i>J</i> = 14 Hz, E), 4.08 (1H, d, <i>J</i> = 14 Hz, E), 6.99–8.12 (14H, m, aromatic H)
20a	3340 (OH)	3.61 (2H, s, CH ₂), 5.34 (1H, s, OH), 6.92–7.65 (13H, m, aromatic H), 8.22–8.40 (1H, m, C ⁶ -H)



N₃O: C, 57.32; H, 3.96; N, 11.80. Found: C, 57.33; H, 4.21; N, 11.73. IR (KBr) cm⁻¹: 1671 (CO). ¹H-NMR (CDCl₃) δ : 3.27 (6H, s, N(Me)₂), 7.17–7.11 (1H, m, aromatic H), 7.72–7.60 (5H, m, aromatic H), 7.87 (2H, d, *J* = 8.8 Hz, aromatic H).

Synthesis of 2-Substituted 4-(α -Methyl- α -hydroxy-*p*-bromobenzyl)-quinazoline (37). **4-(α -Methyl- α -hydroxy-*p*-bromobenzyl)-2-methoxyquinazoline (37a)** A solution of MeMgI (8.4 mmol in 10 ml of Et₂O) was added dropwise to a solution of **36a** (1.4 g, 4.1 mmol) in THF (20 ml). The resulting mixture was stirred at room temperature for 1 h, then poured into NH₄Cl–NH₃–H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane

and CHCl₃. The fraction eluted with *n*-hexane–CHCl₃ (1:2) gave **37a** in 88% yield (1.30 g). Slightly yellow needles (CHCl₃–*n*-hexane), mp 123–125 °C. MS *m/z*: 359, 361 (M⁺ + 1). IR (KBr) cm⁻¹: 3150–3500 (OH). ¹H-NMR (CDCl₃) δ : 2.08 (3H, s, Me), 4.20 (3H, s, OMe), 5.80 (1H, s, OH), 7.22–7.15 (1H, m, C⁶-H or C⁷-H), 7.30 (2H, d, *J* = 8.5 Hz, aromatic H), 7.44 (2H, d, *J* = 8.5 Hz, aromatic H), 7.72–7.62 (2H, m, aromatic H), 7.84 (1H, dd, *J* = 7.8, 1.5 Hz, C⁸-H).

4-(α -Methyl- α -hydroxy-*p*-bromobenzyl)-2-dimethylaminoquinazoline (37b) A solution of MeMgI (18 mmol in 6 ml of THF) was added dropwise to a solution of **36b** (1.42 g, 4.0 mmol) in THF (20 ml). The resulting mixture was stirred at room temperature for 2 h. The reaction mixture was poured into NH₄Cl–NH₃–H₂O and extracted with AcOEt.

The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and CHCl₃. The fraction eluted with *n*-hexane-CHCl₃ (1:2) gave **37b** in 85% yield (1.26 g). Slightly yellow needles (CHCl₃-*n*-hexane), mp 210–212 °C. *Anal.* Calcd for C₁₈H₁₈BrN₃O: C, 58.08; H, 4.87; N, 11.29. Found: C, 57.88; H, 4.58; N, 11.09. IR (KBr) cm⁻¹: 3150–3400 (OH). ¹H-NMR (CDCl₃) δ: 2.05 (3H, s, Me), 3.37 (6H, s, N(Me)₂), 6.52 (1H, s, OH), 6.94–6.88 (1H, m, aromatic H), 7.28 (2H, d, *J* = 8.8 Hz, aromatic H), 7.34 (1H, d, *J* = 8.3 Hz, C⁵-H), 7.44 (2H, d, *J* = 8.8 Hz, aromatic H), 7.55–7.48 (1H, m, aromatic H), 7.60 (1H, d, *J* = 8.3 Hz, C⁸-H).

4-(α -Methyl- α -hydroxy-*p*-bromobenzyl)-2-chloroquinazoline (37c) A solution of MeMgI (9.4 mmol in 10 ml of Et₂O) was added dropwise to a solution of **34** (1.62 g, 4.7 mmol) in THF (20 ml). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into NH₄Cl-NH₃-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and CHCl₃. The fraction eluted with *n*-hexane-CHCl₃ (1:2) gave **37c** in 64% yield (1.09 g). Colorless needles (acetone-*n*-hexane), mp 165–166 °C. *Anal.* Calcd for C₁₆H₁₂BrClN₂O: C, 52.85; H, 3.33; N, 7.70. Found: C, 52.84; H, 3.18; N, 7.63. IR (KBr) cm⁻¹: 3404 (OH). ¹H-NMR (CDCl₃) δ: 2.10 (3H, s, Me), 5.31 (1H, s, OH), 7.29 (2H, d, *J* = 8.8 Hz, aromatic H), 7.49–7.39 (3H, m, aromatic H), 7.86–7.79 (2H, m, aromatic H), 7.99 (1H, dd, *J* = 8.3, 1.5 Hz, C⁸-H).

2,4-Bis(α -methyl- α -hydroxy-*p*-bromobenzyl)quinazoline (37d) A solution of MeMgI (6 mmol in 10 ml of Et₂O) was added dropwise to a solution of **35** (992 mg, 2.0 mmol) in THF (20 ml). The resulting mixture was stirred at room temperature for 1 h. The reaction mixture was poured into NH₄Cl-NH₃-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and CHCl₃. The fraction eluted with *n*-hexane-CHCl₃ (10:1) gave **37d** in 64% yield (678 mg). Recrystallization of **37d** from MeOH gave the epimers (A, B).

A (38%): Colorless granules (Et₂O-*n*-hexane), mp 126–127 °C. FAB-MS *m/z*: 529 (M⁺ + 1, C₂₄H₂₀⁷⁹Br⁸¹BrN₂O₂). IR (KBr) cm⁻¹: 3400 (OH). ¹H-NMR (CDCl₃) δ: 2.10 (3H, s, Me), 2.14 (3H, s, Me), 5.34 (1H, s, OH), 5.76 (1H, s, OH), 7.16 (2H, d, *J* = 8.8 Hz, aromatic H), 7.37–7.48 (5H, m, aromatic H), 7.66 (2H, d, *J* = 8.8 Hz, aromatic H), 7.78–7.84 (2H, m, aromatic H), 8.04 (1H, d, *J* = 8.5 Hz, C⁸-H). ¹³C-NMR (CDCl₃) δ: 28.86 (q, Me), 29.41 (q, Me), 75.96 (s), 76.34 (s), 119.73 (s), 121.32 (s), 121.93 (s), 126.69 (d), 127.54 (d), 127.69 (d), 128.96 (d), 131.21 (d), 131.84 (d), 134.14 (d), 144.04 (s), 145.25 (s), 150.35 (s), 165.74 (s), 172.89 (s).

B (26%): Colorless prisms (acetone-*n*-hexane), mp 192–193 °C. *Anal.* Calcd for C₂₄H₂₀Br₂N₂O₂: C, 54.57; H, 3.82; N, 5.30. Found: C, 54.81; H, 3.52; N, 5.20. IR (KBr) cm⁻¹: 3375 (OH). ¹H-NMR (CDCl₃) δ: 2.05 (3H, s, Me), 2.14 (3H, s, Me), 5.32 (1H, s, OH), 5.75 (1H, s, OH), 7.20 (2H, d, *J* = 8.8 Hz, aromatic H), 7.37–7.47 (5H, m, aromatic H), 7.64 (2H, d, *J* = 8.8 Hz, aromatic H), 7.78–7.86 (2H, m, aromatic H), 8.04 (1H, d, *J* = 8.3 Hz, C⁸-H). ¹³C-NMR (CDCl₃) δ: 28.81 (q, Me), 29.48 (q, Me), 75.95 (s), 76.44 (s), 119.74 (s), 121.28 (s), 121.91 (s), 126.69 (d), 127.52 (d), 127.67 (d), 127.71 (d), 128.97 (d), 131.18 (d), 131.81 (d), 134.13 (d), 144.12 (s), 145.26 (s), 150.37 (s), 165.75 (s), 172.88 (s).

Synthesis of 2-Substituted Quinazolines (38) by Retro-Benzoin Condensation. 2-Methoxyquinazoline (38a) A mixture of **37a** (718 mg, 2.0 mmol) and KCN (143 mg, 2.2 mmol) in DMF (10 ml) was stirred at 80 °C for 1 h. The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and CHCl₃. The fraction eluted with *n*-hexane-CHCl₃ (2:1) gave *p*-bromoacetophenone (**2h**) in 83% yield (332 mg). Colorless needles (*n*-hexane). ¹H-NMR (CDCl₃) δ: 2.56 (3H, s, Me), 7.54 (2H, d, *J* = 8.0 Hz, aromatic H), 7.80 (2H, d, *J* = 8.0 Hz, aromatic H). The fraction eluted with *n*-hexane-CHCl₃ (1:1) gave **38a** in 86% yield (275 mg). Colorless needles (CH₂Cl₂-*n*-hexane), mp 58 °C (lit.,¹³ 58 °C). MS *m/z*: 160 (M⁺).

2-Dimethylaminoquinazoline (38b) A mixture of **37b** (372 mg, 1.0 mmol) and KCN (143 mg, 2.2 mmol) in DMF (5 ml) was refluxed for 2.5 h. The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and CHCl₃. The fraction eluted with *n*-hexane-CHCl₃ (2:1) gave *p*-bromoacetophenone (**2h**) in 56% yield

(112 mg). The fraction eluted with *n*-hexane-CHCl₃ (1:1) gave **38b** in 93% yield (161 mg). Colorless oil. ¹H-NMR (CDCl₃) δ: 3.31 (6H, s, N(Me)₂), 7.20–7.14 (1H, m, aromatic H), 7.67–7.56 (3H, m, aromatic H), 8.99 (1H, s, C⁴-H). Picrate of **38b**: Orange columns (MeOH), mp 240 °C. *Anal.* Calcd for C₁₆H₁₄N₆O₇: C, 47.77; H, 3.51; N, 20.89. Found: C, 47.58; H, 3.55; N, 20.78. The same reaction using Bu₄NCN (**11**, 242 mg, 1 mmol) in place of KCN as the catalyst in refluxing dioxane for 3 h gave **38b** in 91% yield (158 mg).

2-Chloroquinazoline (38c) A mixture of **37c** (545 mg, 1.5 mmol) and Bu₄NCN (80 mg, 0.3 mmol) in THF (8 ml) was refluxed for 2.5 h. The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and AcOEt. The fraction eluted with *n*-hexane-AcOEt (15:1) gave *p*-bromoacetophenone (**2h**) in 89% yield (265 mg). The fraction eluted with *n*-hexane-AcOEt (10:1) gave **38c** in 39% yield (95 mg). Slightly yellow powder (acetone-*n*-hexane), mp 107–109 °C (lit.,¹⁴ 107.5–108 °C).

2-(α -Methyl- α -hydroxy-*p*-bromobenzyl)quinazoline (38d) A mixture of **37d** (528 mg, 1.0 mmol) and Bu₄NCN (27 mg, 0.1 mmol) in THF (10 ml) was refluxed for 20 min. The reaction mixture was poured into ice-H₂O and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with *n*-hexane and CHCl₃. The fraction eluted with *n*-hexane-CHCl₃ (1:1) gave *p*-bromoacetophenone (**2h**) in 89% yield (177 mg). The fraction eluted with *n*-hexane-CHCl₃ (1:2) gave **38d** in 98% yield (324 mg). Yellow prisms (acetone-*n*-hexane), mp 94–94.5 °C. *Anal.* Calcd for C₁₆H₁₃BrN₂O: C, 58.38; H, 3.98; N, 8.51. Found: C, 58.35; H, 4.07; N, 8.43. IR (KBr) cm⁻¹: 3440 (OH). ¹H-NMR (CDCl₃) δ: 2.07 (3H, s, Me), 5.84 (1H, s, OH), 7.41 (2H, d, *J* = 8.3 Hz, aromatic H), 7.61–7.69 (3H, m, aromatic H), 7.91–7.97 (2H, m, aromatic H), 8.05 (1H, d, *J* = 7.8 Hz, aromatic H).

References and Notes

- Miyashita A., Suzuki Y., Okumura Y., Iwamoto K., Higashino T., *Chem. Pharm. Bull.*, **46**, 6–11 (1998).
- a) Ide W. S., Buck J. S., *Org. React.*, **4**, 269–304 (1948); b) Kuebrich J. P., Schowen R. L., Wang M., Lupes M. E., *J. Am. Chem. Soc.*, **93**, 1214–1220 (1971), and references cited therein.
- a) Higashino T., Goi M., Hayashi E., *Chem. Pharm. Bull.*, **22**, 2493–2501 (1974); b) Higashino T., Matsushita Y., Takemoto M., Hayashi E., *ibid.*, **31**, 3951–3958 (1983); c) Yamanaka H., Ohba S., *Heterocycles*, **31**, 895–909 (1990).
- Miyashita A., Suzuki Y., Takemura Y., Iwamoto K., Higashino T., *Heterocycles*, **45**, 1–5 (1997).
- a) Miyashita A., Matsuda H., Iijima C., Higashino T., *Chem. Pharm. Bull.*, **38**, 1147–1152 (1990); b) *Idem*, *ibid.*, **40**, 43–48 (1992); c) Miyashita A., Matsuda H., Suzuki Y., Iwamoto K., Higashino T., *ibid.*, **42**, 2017–2022 (1994); d) Higashino T., Takemoto M., Miyashita A., Hayashi E., *ibid.*, **33**, 1395–1399 (1985); e) Miyashita A., Suzuki Y., Nagasaki I., Ishiguro C., Iwamoto K., Higashino T., *ibid.*, **45**, 1254–1258 (1997).
- 2-Substituted quinazolines are usually prepared by reaction of 2-chloroquinazoline with nucleophiles or by ring-closure.^{a)} 2-Chloroquinazoline is prepared by chlorination of 2-hydroxyquinazoline. However, the synthesis of 2-hydroxyquinazoline is not easy. In contrast, 2,4-dihydroxyquinazoline^{b)} and 2,4-dichloroquinazoline are readily prepared.
a) Stefanovic G., Lorenc L. J., Mihailovic M. L., *Rec. Trav. Chim.*, **80**, 149–157 (1961) [*Chem. Abstr.*, **55**, 24764c (1961)]; b) Lange N. A., Sheibley F. E., *Org. Synth., Coll. Vol.*, **2**, 79–80 (1943).
- The catalytic ability of this azolium salt will be reported elsewhere.
- Higashino T., *Yakugaku Zasshi*, **80**, 245–250 (1960).
- Higashino T., *Chem. Pharm. Bull.*, **10**, 1043–1047 (1962).
- a) Higashino T., Katori T., Hayashi E., *Chem. Pharm. Bull.*, **27**, 2431–2436 (1979); b) Hayashi E., Iijima C., *Yakugaku Zasshi*, **86**, 571–576 (1966); c) Hayashi E., Oishi E., *ibid.*, **86**, 576–584 (1966).
- a) Higashino T., Iwai Y., Hayashi E., *Yakugaku Zasshi*, **94**, 666–671 (1974); b) Hayashi E., Oishi E., Tezuka T., Ema K., *ibid.*, **88**, 1333–1337 (1968).
- Scarborough H. C., Lawes B. C., Minielli J. L., Compton J. L., *J. Org. Chem.*, **27**, 957–961 (1962).
- Adachi K., *Yakugaku Zasshi*, **75**, 1426–1429 (1955).
- Chapman N. B., Russell-Hill D. Q., *J. Chem. Soc.*, **1956**, 1563–1572.