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.
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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, Bu_4NCN) 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-aroylquinazolines (34), using the aroyl 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 benzoins (**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 benzoins 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 delivative (**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-

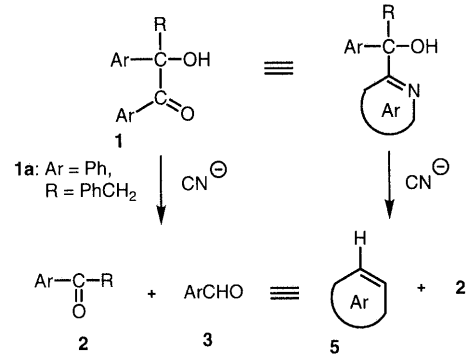


Chart 1

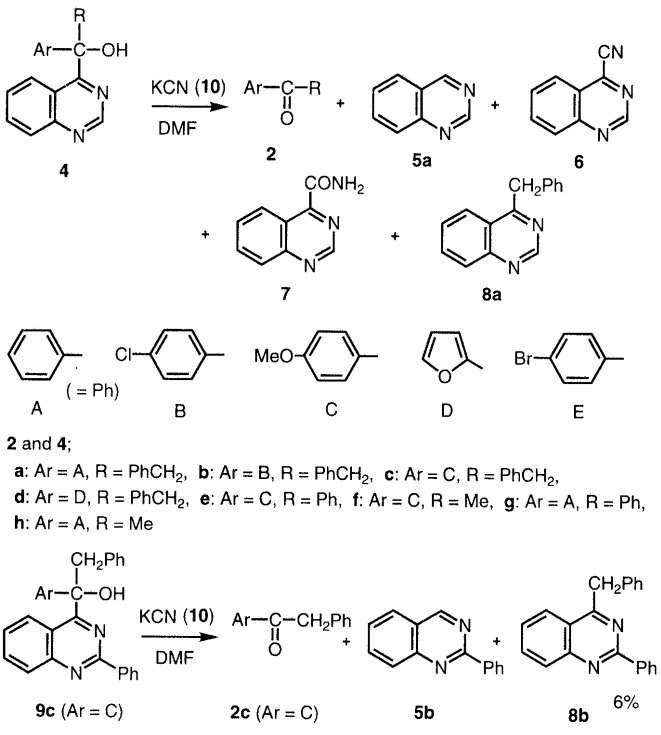


Chart 2

* To whom correspondence should be addressed.

Table 1. Retro-Benzoin Condensation of Quinazolines (**4**) Catalyzed by Potassium Cyanide (**10**)

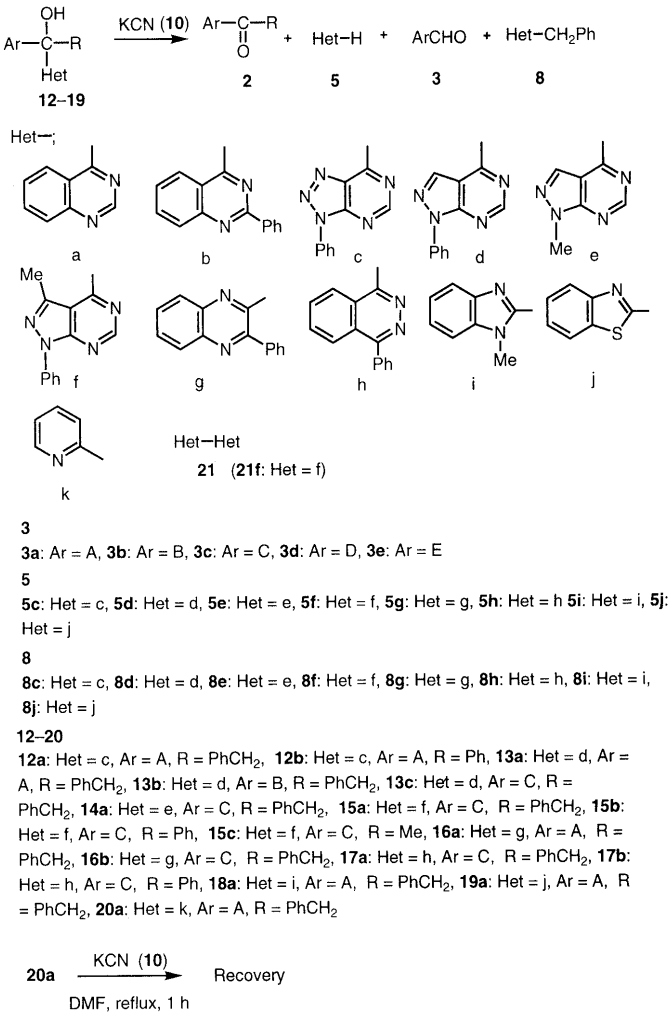
Entry	Substrate: Quinazoline; **4**	Products; isolated yield (%)						
		Ketone;	Quinazoline derivatives **2**	**5**	**6**	**7**	**8**	Recovery
1	**4a**	**2a**	72	35	3	—	—	—
2	**4b**	**2b**	68	—	9	10	9	1
3	**4c**	**2c**	78	6	—	27	—	6
4	**4d**	**2d**	59	15	—	14	5	22
5	**4e**	**2e**	64	—	3	12	—	31
6	**4f**	**2f**	70	55	Trace	13	—	—

line (**5b**). This reaction also unexpectedly gave 4-benzyl-2-phenylquinazoline (**8b**) in 6% yield. These results are summarized in Chart 2 and Table 1.

The retro-benzoin condensation of other heteroarenes having different ring systems (**12**—**20**) was then examined. As shown in Chart 3 and Table 2, triazolopyrimidines (**12**), quinoxalines (**16**), and phthalazines (**17**) having an α-aryl- or α-alkyl-α-hydroxybenzyl group at the α-position of the ring-nitrogen underwent the retro-condensation to give ketones (**2**), together with the corresponding heteroarenes (**5**) and/or derivatives such as benzylheteroarenes (**8**). The retro-condensation was also observed in benzimidazole (**18**) and benzothiazole (**19**). However, on similar treatment of pyrazolopyrimidines (**13**—**15**) having an α-benzyl-α-hydroxybenzyl group, benzyl migration instead of the retro-condensation proceeded, giving benzylpyrazolopyrimidines (**8d**—**8f**) and arenecarbaldehydes (**3**). In contrast, the pyrazolopyrimidines **15b** and **15c**, which lack an α-benzyl-α-hydroxybenzyl group, but have an α-hydroxybenzyl moiety, underwent retro-benzoin condensation to give the ketones (**2e**, **2f**) in good yields. However, in this reaction, the dimer (**21**) was obtained instead of the heteroarene (**5f**), because further reaction proceeded, catalyzed by cyanide ion. Namely, the dimer (**21**) may be produced through benzoin-type condensation of **5f** catalyzed by cyanide ion followed by oxidation. On the other hand, the pyridine (**20a**) failed to undergo retro-benzoin condensation or benzyl migration, because cyanide ion could not add to the C=N double bond due to low electrophilicity.

The retro-benzoin condensation required equimolar KCN. Namely, when 0.1 mol eq of KCN was used in the retro-condensation of **4a**, only a 7% yield of the ketone (**2a**) was obtained. Under the conditions used, cyanide ion was consumed by several further reactions involving the heteroarenes (**5**), such as the formation of heteroarenecarbonitriles and heteroarenecarboxamides.

It was found that tetrabutylammonium cyanide (**11**, Bu_4NCN) is a highly effective cyanide ion donor in this retro-benzoin condensation. As shown in Chart 4, compound **4a** was successfully cleaved in the presence of 0.1 mol eq of Bu_4NCN, resulting in the formation of the ketone **2a** (91%) together with quinazoline **5a** (85%). A similar result was obtained in the case of **9c**. In these reactions, heteroarenes (**5a**, **5b**) were obtained in good yields. However, when the retro-condensation was applied to **13b**, the main product was the benzylpyrazolopyrimidine (**8d**), as in the reaction using KCN.



3
3a: Ar = A, **3b**: Ar = B, **3c**: Ar = C, **3d**: Ar = D, **3e**: Ar = E

5
5c: Het = c, **5d**: Het = d, **5e**: Het = e, **5f**: Het = f, **5g**: Het = g, **5h**: Het = h **5i**: Het = i, **5j**: Het = j

8
8c: Het = c, **8d**: Het = d, **8e**: Het = e, **8f**: Het = f, **8g**: Het = g, **8h**: Het = h, **8i**: Het = i, **8j**: Het = j

12–20
12a: Het = c, Ar = A, R = $PhCH_2$, **12b**: Het = c, Ar = A, R = Ph, **13a**: Het = d, Ar = A, R = $PhCH_2$, **13b**: Het = d, Ar = B, R = $PhCH_2$, **13c**: Het = d, Ar = C, R = $PhCH_2$, **14a**: Het = e, Ar = C, R = $PhCH_2$, **15a**: Het = f, Ar = C, R = $PhCH_2$, **15b**: Het = f, Ar = C, R = Ph, **15c**: Het = f, Ar = C, R = Me, **16a**: Het = g, Ar = A, R = $PhCH_2$, **16b**: Het = g, Ar = C, R = $PhCH_2$, **17a**: Het = h, Ar = C, R = $PhCH_2$, **17b**: Het = h, Ar = C, R = Ph, **18a**: Het = i, Ar = A, R = $PhCH_2$, **19a**: Het = j, Ar = A, R = $PhCH_2$, **20a**: Het = k, Ar = A, R = $PhCH_2$

20a —KCN (10), DMF, reflux, 1 h→ Recovery

Chart 3

Plausible reaction pathways are shown in Chart 5. The retro-benzoin condensation proceeds through the formation of the intermediate (I), and then carbon–carbon bond cleavage results in the formation of the ketone (**2**) and the heteroarene (**5**). The benzyl migration occurs through the same intermediate (I). Two carbon–carbon bond cleavages occur in some cases, such as quinazolines (**4**) and pyrazolopyrimidines (**13**—**15**), where benzyl migration occurs, followed by the release of arenecarbaldehyde (**3**), resulting in the formation of benzylheteroarenes (**8**). The benzyl group easily rearranges because the benzyl anion is very stable. To confirm that the benzyl migration is catalyzed by cyanide ion, compound **13a** was treated with

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**	19	**8d**	44	
5	**13c**	Reflux	1	—		—		**3c**	60	**8d**	68	
6	**14a**	Reflux	1	—		—		**3c**	40	**8e**	99	
7	**15a**	Reflux	1	—		—		**3c**	48	**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**	3	**8h**	31	
13	**17b**	Reflux	2	**2e**	92	**5h**	67	—		—		
14	**18a**	Reflux	3	**2a**	66	**5i**	36	—		—		32
15	**19a**	120	2	**2a**	73	**5j**	75	—		—		

a) Yield of dimer **21**.

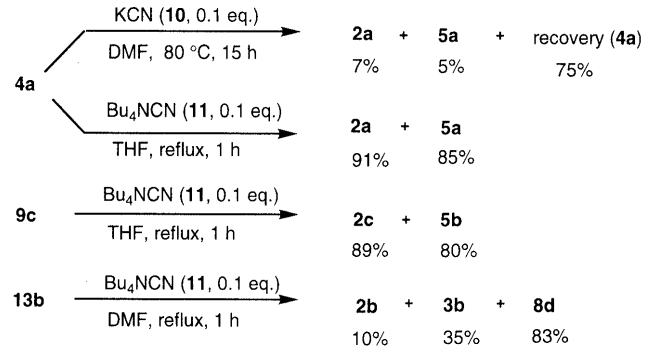
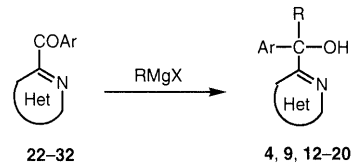


Chart 4



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

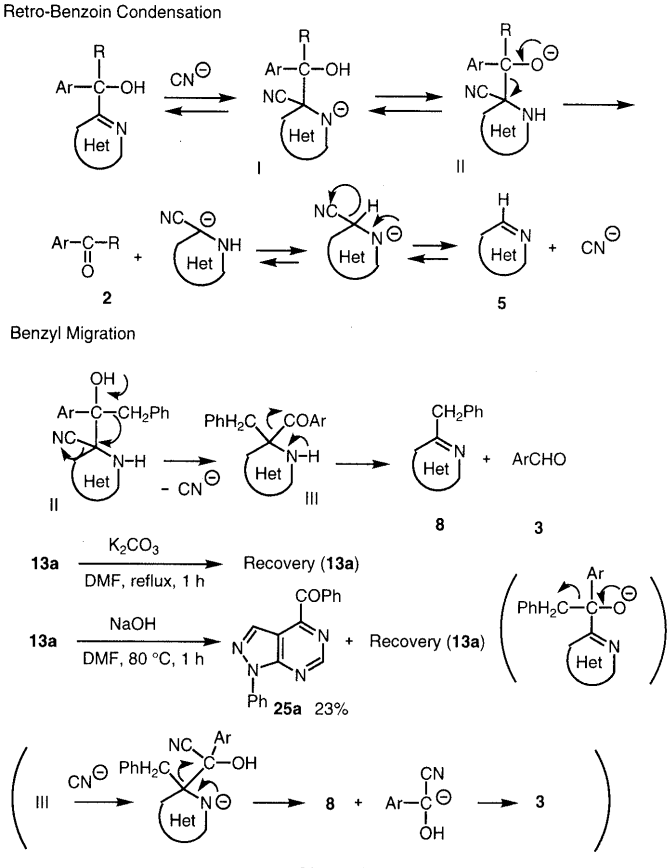


Chart 5

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	$PhCH_2MgBr$	**4a**	76
22b	$PhCH_2MgBr$	**4b**	81
22c	$PhCH_2MgBr$	**4c**	91
22d	$PhCH_2MgBr$	**4d**	70
22c	PhMgBr	**4e**	70
22c	MeMgI	**4f**	79
23c	$PhCH_2MgBr$	**9c**	100
24a	$PhCH_2MgBr$	**12a**	88
24a	PhMgBr	**12b**	83
25a	$PhCH_2MgBr$	**13a**	89
25b	$PhCH_2MgBr$	**13b**	100
25c	$PhCH_2MgBr$	**13c**	73
26c	$PhCH_2MgBr$	**14a**	99
27c	$PhCH_2MgBr$	**15a**	95
27c	PhMgI	**15b**	96
27c	MeMgBr	**15c**	97
28a	$PhCH_2MgBr$	**16a**	86
28c	$PhCH_2MgBr$	**16b**	61
29c	$PhCH_2MgBr$	**17a**	71
29c	PhMgBr	**17b**	100
30a	$PhCH_2MgBr$	**18a**	90
31a	$PhCH_2MgBr$	**19a**	65
32a	$PhCH_2MgBr$	**20a**	75

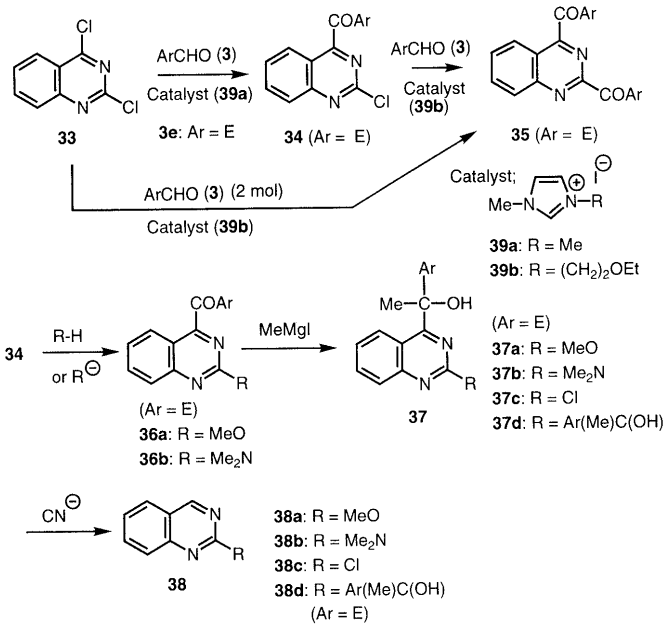


Chart 7

molar *p*-bromobenzaldehyde (**3e**) catalyzed by 1,3-dimethylimidazolium iodide to give 4-(*p*-bromobenzoyl)-2-chloroquinazoline (**34**) in 79% yield. 2,4-Bis(*p*-bromobenzoyl)quinazoline (**35**) was obtained when 2 mol eq of *p*-bromobenzaldehyde (**3e**) was used with 1-(2-ethoxyethyl)-3-methylimidazolium iodide[7] as the catalyst. The chloro group of **34** is easily replaced with nucleophiles to give 2-substituted 4-aroylquinazolines (**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-chloroquinazoline (**38c**) and 2-(α-methyl-α-hydroxy-4-bromobenzyl)quinazoline (**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 benzoins (**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. ^{1}H-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)quinazoline (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–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 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-quinazolinecarbonitrile (**6**)[8] in 3% yield (4 mg). The fraction eluted with *n*-hexane–AcOEt (5 : 1) gave quinazoline (**5a**) in 35% yield (45 mg), and the fraction eluted with *n*-hexane–AcOEt (1 : 1) gave 4-quinazolinecarboxamide (**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 quinazoline (**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 quinazoline (**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–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and AcOEt. In the cases of **4b** and **4d**, 4-benzylquinazoline (**8a**)[9] was obtained. These results are shown in Table 1.

Retro-Benzoin Condensation of 4-(α-Benzyl-α-hydroxy-4-methoxybenzyl)-2-phenylquinazoline (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–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and AcOEt. The first fraction eluted with *n*-hexane–AcOEt (50 : 3) gave 4-benzyl-2-phenylquinazoline (**8b**) in 6% yield (17 mg), the second fraction gave 2-phenylquinazoline (**5b**) in 68% yield (141 mg), and the third fraction gave 4-methoxydeoxybenzoin (**2c**) in 77% yield (174 mg).

4-Benzyl-2-phenylquinazoline (**8b**): Slightly yellow granules (acetone

n-hexane), mp 61—63 °C. *Anal.* Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 84.71; H, 5.57; N, 9.33. ^{1}H-NMR ($CDCl_3$) δ: 4.68 (2H, s, CH_2), 7.20—7.53 (9H, m, aromatic H), 7.78—7.84 (1H, m, aromatic H), 8.07 (1H, d, J=9.8 Hz, C^5-H or C^8-H), 8.12 (1H, d, J=9.8 Hz, C^5-H or C^8-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.[1)]

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–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane, AcOEt and/or CH_2Cl_2. 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). ^{1}H-NMR ($CDCl_3$) δ: 4.43 (2H, s, CH_2), 7.20—7.67 (8H, m, aromatic H), 7.82 (1H, s, C^3-H), 8.04—8.28 (2H, m, aromatic H), 9.00 (1H, s, C^6-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 $C_{19}H_{16}N_4$: C, 75.98; H, 5.37; N, 18.65. Found: C, 75.95; H, 5.22; N, 18.87. ^{1}H-NMR ($CDCl_3$) δ: 2.71 (3H, s, Me), 4.51 (2H, s, CH_2), 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, C^6-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 $C_{24}H_{18}N_8$: C, 68.89; H, 4.34; N, 26.78. Found: C, 68.53; H, 4.42; N, 26.54. ^{1}H-NMR ($CDCl_3$) 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, C^6-H). ^{13}C-NMR ($CDCl_3$) 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–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 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–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 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 Bu_4NCN (11) A solution of **4a** (326 mg, 1.0 mmol) and Bu_4NCN (27 mg, 0.1 mmol) in tetrahydrofuran (THF) (10 ml) was refluxed for 1 h. The reaction mixture was poured into ice–H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 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 Bu_4NCN (11) A solution of **9c** (432 mg, 1.0 mmol) and Bu_4NCN (**11**, 27 mg, 0.1 mmol) in THF (10 ml) was refluxed for 1 h. The reaction mixture was poured into ice–H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 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 Bu_4NCN A solution of **13b** (427 mg, 1.0 mmol) and Bu_4NCN (27 mg, 0.1 mmol) in DMF (10 ml) was refluxed for 1 h. The reaction mixture was poured into ice–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 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–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 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 K_2CO_3 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 Et_2O) 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 NH_4Cl–NH_3–H_2O, and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane, AcOEt and/or $CHCl_3$. 4-Aroylquinazolines (**22a—d**), 4-aroyl-2-phenylquinazoline (**23c**), 7-aroyltriazolopyrimidine (**24a**), 4-aroylpyrazolopyrimidines (**25a—c**, **26c**, **27c**), 2-aroylquinoxalines (**28a**, **28c**), 1-aroylphthalazine (**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–H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and $CHCl_3$. The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 1) gave **34** in 79% yield (6.89 g). Colorless needles (*n*-hexane–CH_2Cl_2), mp 180—181 °C. *Anal.* Calcd for $C_{15}H_8BrClN_2O$: 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). ^{1}H-NMR ($CDCl_3$) 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 iodide[7)] (**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 (*m/z*)
				C	H	N	
4a	117—118	Colorless prisms (MeOH)	$C_{22}H_{18}N_2O$	80.96 (80.80)	5.56 (5.55)	8.58 (8.44)	
4b	156	Yellow needles (MeOH)	$C_{22}H_{17}N_2OCl$	73.23 (73.05)	4.75 (4.64)	7.76 (7.64)	
4c	145—146	Colorless needles (acetone–MeOH)	$C_{23}H_{20}N_2O_2$	77.51 (77.46)	5.66 (5.65)	7.86 (7.85)	
4d	139—140	Colorless columns (MeOH)	$C_{20}H_{16}N_2O_2$	75.93 (75.81)	5.10 (5.08)	8.86 (8.88)	
4e	195—196	Colorless needles (CH_2Cl_2–MeOH)	$C_{22}H_{18}N_2O_2$	77.17 (77.04)	5.30 (5.34)	8.18 (7.92)	
4f	141—142	Colorless needles (acetone–*n*-hexane)	$C_{17}H_{16}N_2O_2$	72.84 (72.98)	5.75 (5.85)	9.99 (10.03)	
9c	146.5—147.5	Colorless needles (acetone–*n*-hexane)	$C_{29}H_{24}N_2O_2$	80.53 (80.34)	5.59 (5.58)	6.48 (6.47)	
12a	130	Colorless needles (acetone–*n*-hexane)	$C_{24}H_{19}N_5O$	73.27 (73.21)	4.87 (4.83)	17.80 (17.94)	
12b	203—205	Yellow prisms (acetone–*n*-hexane)	$C_{23}H_{17}N_5O$	72.81 (72.63)	4.52 (4.41)	18.46 (18.69)	
13a	113—114	Colorless granules (acetone–*n*-hexane)	$C_{25}H_{20}N_4O$	76.51 (76.52)	5.14 (5.02)	14.28 (14.26)	
13b	91—92	Colorless prisms (Et2O–*n*-hexane)	$C_{25}H_{19}N_4OCl$	70.34 (70.16)	4.49 (4.37)	13.12 (13.05)	
13c	106—107	Colorless columns (acetone–*n*-hexane)	$C_{26}H_{22}N_4O_2$	73.92 (73.88)	5.25 (5.22)	13.26 (13.15)	
14a	79—80	Colorless needles (acetone–*n*-hexane)	$C_{21}H_{20}N_4O_2$				FAB-MS; 361 ($M^+ + 1$)
15a	170	Colorless prisms (acetone–*n*-hexane)	$C_{27}H_{24}N_4O_2$	74.29 (74.10)	5.54 (5.44)	12.84 (12.96)	
15b	124—125.5	Colorless granules (Et_2O–*n*-hexane)	$C_{26}H_{22}N_4O_2$	73.92 (73.92)	5.25 (5.20)	13.26 (13.17)	
15c	118—119	Slightly yellow needles (acetone–MeOH)	$C_{21}H_{20}N_4O_2$	69.98 (69.90)	5.59 (5.68)	15.55 (15.48)	
16a	170	Colorless prisms (acetone–*n*-hexane)	$C_{28}H_{22}N_2O$	83.56 (83.49)	5.51 (5.48)	6.96 (6.86)	
16b	165—166.5	Colorless prisms (acetone–*n*-hexane)	$C_{29}H_{24}N_2O_2$	80.53 (80.44)	5.59 (5.82)	6.48 (6.23)	
17a	163—164	Colorless prisms (acetone–*n*-hexane)	$C_{29}H_{24}N_2O_2$	80.53 (80.56)	5.59 (5.87)	6.48 (6.43)	
17b		Amorphous powder	$C_{28}H_{22}N_2O_2$				FAB-MS; 419 ($M^+ + 1$)
18a	136—139	Colorless needles (benzene)	$C_{22}H_{20}N_2O$	EI-MS (HR): Calcd, 328.15756 (M^+) Observed, 328.15751			
19a	105—115	Colorless needles (acetone–*n*-hexane)	$C_{21}H_{17}NOS$				FAB-MS; 332 ($M^+ + 1$)
20a	104—105	Colorless needles (acetone–*n*-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–H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and $CHCl_3$. The fraction eluted with $CHCl_3$ gave **35** in 86% yield (1.27 g). Yellow needles (*n*-hexane–acetone), mp 184—186 °C. *Anal.* Calcd for $C_{22}H_{12}Br_2N_2O_2$: 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). ^{1}H-NMR ($CDCl_3$) 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, C^5-H), 8.30 (1H, d, J=8.3 Hz, C^8-H). ^{13}C-NMR ($CDCl_3$) 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).

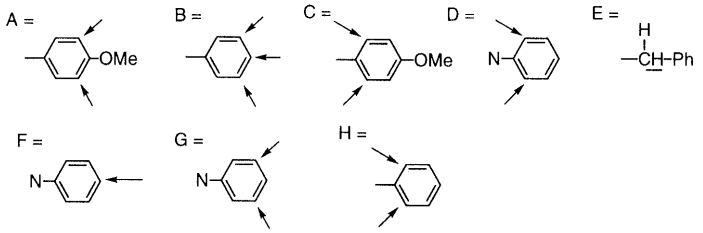
Compound **35** was also obtained by aroylation of **34** with **3e** catalyzed by imidazolium salt **39b**. However, the diaroylated compound **35** could not be obtained by aroylation of **33** or **34** with **3e** catalyzed by the imidazolium salt **39a**.

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 H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and $CHCl_3$. The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 2) gave **36a** in 71% yield (1.50 g). Colorless needles (MeOH), mp 166—167 °C. *Anal.* Calcd for $C_{16}H_{11}BrN_2O_2$: 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). ^{1}H-NMR ($CDCl_3$) 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 H_2O, 20 ml) was refluxed for 100 min. The reaction mixture was poured into ice–H_2O, and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and $CHCl_3$. The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 1) gave **36b** in 96% yield (816 mg). Colorless plates (*n*-hexane–CH_2Cl_2), mp 183—185 °C. *Anal.* Calcd for $C_{17}H_{14}Br$-

Table 5. IR and ^{1}H-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, J=13 Hz, E), 3.98 (1H, d, J=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, J=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, J=14 Hz, E), 4.43 (1H, d, J=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, J=14 Hz, E), 4.05 (1H, d, J=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, J=14 Hz, E), 3.96 (1H, s, OH), 4.03 (1H, d, J=14 Hz, E), 6.96—7.54 (10H, m, aromatic H), 7.66 (2H, d, J=9 Hz, aromatic H), 8.16 (2H, d, J=8 Hz, D), 8.34 (1H, s, C^3-H), 9.01 (1H, s, C^6-H)
13c	3400 (OH)	3.71 (1H, d, J=14 Hz, E), 3.76 (3H, s, OMe), 4.02 (1H, d, J=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, J=13 Hz, E), 3.77 (3H, s, OMe), 3.96 (1H, d, J=13 Hz, E), 4.06 (3H, s, NMe), 4.41 (1H, s, OH), 6.85 (2H, d, J=9 Hz, A), 6.90—6.93 (2H, m, H), 7.09—7.12 (3H, m, B), 7.57 (2H, d, J=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, J=9 Hz, A), 7.13—7.67 (10H, m, aromatic H), 8.13 (2H, d, J=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, J=9 Hz, A), 7.25 (2H, d, J=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, J=14 Hz, E), 3.78 (1H, d, J=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, J=14 Hz, E), 3.73 (1H, d, J=14 Hz, E), 3.79 (3H, s, OMe), 4.99 (1H, s, OH), 6.69 (2H, d, J=9 Hz, A), 6.83 (2H, d, J=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, J=13.2 Hz, E), 4.11 (1H, d, J=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, J=8.8 Hz, C), 7.53—7.56 (3H, m, aromatic H), 7.64—7.75 (4H, m, aromatic H), 8.04 (1H, dd, J=8.3, 2.0 Hz, C^5-H or C^8-H), 8.24 (1H, dd, J=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, J=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, Cd, J= 8.3 Hz, C^5-H or C^8-H), 8.08 (1H, d, J=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, J=14 Hz, E), 4.08 (1H, d, J=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)



N_3O: 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). ^{1}H-NMR ($CDCl_3$) 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 Et_2O) 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 NH_4Cl–NH_3–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and $CHCl_3$. The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 2) gave **37a** in 88% yield (1.30 g). Slightly yellow needles ($CHCl_3$–*n*-hexane), mp 123—125 °C. MS *m/z*: 359, 361 ($M^+ + 1$). IR (KBr) cm^{-1}: 3150—3500 (OH). ^{1}H-NMR ($CDCl_3$) δ: 2.08 (3H, s, Me), 4.20 (3H, s, OMe), 5.80 (1H, s, OH), 7.22—7.15 (1H, m, C^6-H or C^7-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, C^8-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 NH_4Cl–NH_3–H_2O and extracted with AcOEt.

The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and $CHCl_3$. The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 2) gave **37b** in 85% yield (1.26 g). Slightly yellow needles ($CHCl_3$–*n*-hexane), mp 210—212 °C. *Anal.* Calcd for $C_{18}H_{18}BrN_3O$: 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). ^{1}H-NMR ($CDCl_3$) 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, C^5-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, C^8-H).

4-(α-Methyl-α-hydroxy-*p*-bromobenzyl)-2-chloroquinazoline (37c) A solution of MeMgI (9.4 mmol in 10 ml of Et_2O) 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 NH_4Cl–NH_3–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and $CHCl_3$. The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 2) gave **37c** in 64% yield (1.09 g). Colorless needles (acetone–*n*-hexane), mp 165—166 °C. *Anal.* Calcd for $C_{16}H_{12}BrClN_2O$: 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). ^{1}H-NMR ($CDCl_3$) 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, C^8-H).

2,4-Bis(α-methyl-α-hydroxy-*p*-bromobenzyl)quinazoline (37d) A solution of MeMgI (6 mmol in 10 ml of Et_2O) 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 NH_4Cl–NH_3–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and $CHCl_3$. The fraction eluted with *n*-hexane–$CHCl_3$ (10 : 1) gave **37d** in 64% yield (678 mg). Recrystallization of **37d** from MeOH gave the epimers (A, B).

A (38%): Colorless granules (Et_2O–*n*-hexane), mp 126—127 °C. FAB-MS *m/z*: 529 (M^++1, $C_{24}H_{20}{}^{79}Br^{81}BrN_2O_2$). IR (KBr) cm^{-1}: 3400 (OH). ^{1}H-NMR ($CDCl_3$) 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, C^8-H). ^{13}C-NMR ($CDCl_3$) 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 $C_{24}H_{20}Br_2N_2O_2$: 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). ^{1}H-NMR ($CDCl_3$) 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, C^8-H). ^{13}C-NMR ($CDCl_3$) 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–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and $CHCl_3$. The fraction eluted with *n*-hexane–$CHCl_3$ (2 : 1) gave *p*-bromoacetophenone (**2h**) in 83% yield (332 mg). Colorless needles (*n*-hexane). ^{1}H-NMR ($CDCl_3$) 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–$CHCl_3$ (1 : 1) gave **38a** in 86% yield (275 mg). Colorless needles (CH_2Cl_2–*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–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and $CHCl_3$. The fraction eluted with *n*-hexane–$CHCl_3$ (2 : 1) gave *p*-bromoacetophenone (**2h**) in 56% yield (112 mg). The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 1) gave **38b** in 93% yield (161 mg). Colorless oil. ^{1}H-NMR ($CDCl_3$) 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, C^4-H). Picrate of **38b**: Orange columns (MeOH), mp 240 °C. *Anal.* Calcd for $C_{16}H_{14}N_6O_7$: C, 47.77; H, 3.51; N,20.89. Found: C, 47.58; H, 3.55; N, 20.78. The same reaction using Bu_4NCN (**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 Bu_4NCN (80 mg, 0.3 mmol) in THF (8 ml) was refluxed for 2.5 h. The reaction mixture was poured into ice–H_2O and extracted with AcOEt. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 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 Bu_4NCN (27 mg, 0.1 mmol) in THF (10 ml) was refluxed for 20 min. The reaction mixture was poured into ice–H_2O and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on SiO_2 with *n*-hexane and $CHCl_3$. The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 1) gave *p*-bromoacetophenone (**2h**) in 89% yield (177 mg). The fraction eluted with *n*-hexane–$CHCl_3$ (1 : 2) gave **38d** in 98% yield (324 mg). Yellow prisms (acetone–*n*-hexane), mp 94—94.5 °C. *Anal.* Calcd for $C_{16}H_{13}BrN_2O$: 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). ^{1}H-NMR ($CDCl_3$) 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

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